e-ISSN:2602-2079

Volume 7
Issue 8
2023

# JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

# Editorial Team

**Editor-in-Chief**

Yahya Kemal Çalışkan, MD
University of Health Sciences, Kanuni Sultan Suleiman Training And Research Hospital, Istanbul, Turkey
Research areas: Surgical science, Medical science
Email

**Editors & Editorial Board**

Selman Uranues, Prof., MD, FACS, FEBS
Sektion für Chirurgische Forschung
Medical University of Graz
Graz, Austria
Website

Kafil Akhtar, Prof., MD
Department of Pathology
JNMC, AMU, Aligarh-India
Website

Eric Revue, MD
Clinical Practice Committee
IFEM International Federation of Emergency Medicine
West Melbourne, Victoria, Australia
Website

Boris Sakakushev, Prof., MD
Division of General and Operative Surgery with Coloproctology
Medical University of Plovdiv
Plovdiv, Bulgaria
Website

Dimitrios Giakoustidis, Assoc. Prof., MD

First Department of Surgery, General Hospital Papageorgiou
Aristotle University of Thessaloniki
Thessaloníki, Greece
Website

Nancy Berenice Guzmán Martínez, MD
Department of Radiology and Molecular Imaging
Centro Médico ABC (The American British Cowdray Medical Center)
Mexico City, Mexico
Website

Sapana Verma, MD, PhD
Center for Liver and Biliary Sciences
New Delhi, India
Website

Wandong Hong, Assist. Prof., MD, PhD
Department of Gastroenterology and Hepatology
The First Affiliated Hospital of Wenzhou Medical University
Wenzhou, Zhejiang, China
Website

Mingyu Sun, Prof., MD, PhD
Institute of Liver Diseases
ShuGuang Hospital, Shanghai University of TCM.
Shanghai, China
Website

Moshiur Rahman, Assist. Prof., MD
Neurosurgery Department
Holy Family Red Crescent, Medical College,
Dhaka, Bangladesh
Website

Mauro Zago, MD
Policlinico San Pietro, Ponte San Pietro
BG, Italy
Website

Gouda Ellabban, Prof., MD
Faculty of Medicine, Suez Canal University

Ismailia, Egypt
Website

Juan Asensio, MD
Department of Surgery, Creighton University
Omaha, United States
Website

Antonio Sommariva, MD
Surgical Oncology Department, Istituto Oncologico Veneto
Padova, Italy
Website

Mehmet Serhan Er, Prof., MD
University of Akdeniz, Antalya, Turkey
Subjects: Orthopedics, Surgical science
Website

Fatih Sap, Prof., MD
MEDİPOL MEGA, Academic Medical Center Hospital
Pediatric Cardiology, Istanbul, Turkey
Subjects: Pediatry, Medical science
Website

Yıldız Büyükdereli Atadag, MD
Sahinbey Baglarbasi Family Health Centre, Gaziantep, Turkey
Subjects: Medical sciences, Internal medicine, Family medicine
Website

Abdulkadir Aydin, MD
Family Medicine
Sakarya University, Education and Research Hospital, Sakarya, Turkey
Subjects: Medical sciences, Internal medicine, Family medicine
Website

Didem Kaya, MD
Uskudar Number 23. Family Health Centre, Istanbul, Turkey
Subjects: Medical sciences, Internal medicine, Family medicine

Ilyas Kudas, MD
University of Health Sciences, Sarıyer Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey
Subjects: Hepatobiliary – Renal transplantation, General Surgery

Burak Turan, MD
University of Health Sciences, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey
Subjects: Cardiology, Medical science

Burak Guler, MD
Buyukcekmece Mimarsinan State Hospital, Istanbul, Turkey
Subjects: Otolaryngology - Head and neck surgery

Suleyman Kalcan, Assis. Prof., MD
Recep Tayyip Erdogan University, Department of Surgery, Rize, Turkey
Subjects: Surgical science
Website

**Editorial Advisory Board**

Hussein Faour, MD, FACS, FASMBS, SOEMBS
Department of Surgery
Royale Hayat Hospital
Kuwait City, Hawally, Kuwait
Website

Fahmi Khan, MB, BS, CABMs
Hamad Medical Corporation | HMC
Department of Medicine (Hamad General Hospital)
Doha, Qatar
Website

Elroy Patrick Weledji, Professor, BSc, MBBChBAO, MSc, FRCS(Edinburgh)
Department of Medicine
University of Buea
Buea, Cameroon
Website

Prasenjit Das, Professor, MD, DNB, MNAMS, MNASc
Department of Pathology
All India Institute of Medical Sciences
New Delhi, India
Website

Seyed Vahid Hosseini, Professor
Shiraz University of Medical Sciences, Shiraz, Iran
Website

This is an open-access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY NC ND) license.

Powered By SelSistem®

# Vol. 7 No. 8 (2023):


**Published:** 2023-08-31

## Research Article

## Renal dysfunction due to surgical stress and its effects on survival in patients aged 90 and over

Risk of renal dysfunction in patients aged 90 years and older

Sevgi Kutlusoy, Erdinç Koca, Ahmet Aydın

486-490

PDF 19 21 Citations 0

## The etiology, risk factors, and clinical features of anaphylaxis: The single-center retrospective cohort study of the tertiary university hospital

The etiology, risk factors, and clinical features of anaphylaxis

Ceyda Tunakan Dalgıç

491-497

PDF 19 13 Citations 0

## 25-hydroxy vitamin D levels in patients with myelofibrosis and potential relationships with disease severity: A case-control study

Vitamin D levels in myelofibrosis patients

Yildiz Ipek

498-503

PDF 10 9 Citations ?

## Aortic arch repair with extended end-to-side anastomosis in neonates and infants with transverse arch hypoplasia

Aortic arch repair in neonates and infants

Onur Doyurgan, Hasan Balık

504-508

PDF 6 8 Citations ?

## Effect of macrocytosis on erlotinib response in metastatic non-small cell lung cancer

Macrocytosis with erlotinib in non-small cell lung cancer

Seher Nazlı Kazaz , Mustafa Emre Duygulu

509-513

PDF 5 9 Citations ?

## Predisposal factors leading to early re-amputation among diabetic patients who underwent minor amputation

Underlying factors for early subsequent amputations

Onur Gürsan, Mustafa Çeltik, Cihangir Türemiş

514-517

PDF 19 9 Citations ?

## Case Report

### Inguinal herniation associated with hydrocele

Inguinal herniation associated with hydrocele

Mladen Kasalovic, Igrutinović Gojko , Jakovljević Aleksandar , Miljković Nikola , Milentijević Milica

518-520

PDF 32 21 Citations 0

### Pediatric ANCA-associated vasculitis presented with various clinical findings mimicking IgA Vasculitis and IgG4-related disease: Two cases

Pediatric ANCA-associated vasculitis

Mehmet Ali Oktay, Selin Akyuz Oktay, Bahriye Uzun Kenan, Emine Nur Sunar Yayla, Betül Öğüt, Bahar Büyükkaragöz, Deniz Gezgin Yıldırım, Sevcan A. Bakkaloğlu

521-523

PDF 19 17 Citations 0

This is an open-access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY NC ND) license.

Powered By SelSistem®

J Surg Med. 2023;7(8):434-440.
DOI: 10.28982/josam.7812

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Does flaxseed and chia use affect postprandial glucose, insulin and subjective saturation response in healthy individuals?

**Özlem Özpak Akkuş [1], Yüksel Özdemir [1], Çağla Özbek [2], Başak Öncel [3], Betül Yapıcı Nane [2]**

[1] Department of Nutrition and Dietetics, Toros University, Mersin, Turkey
[2] Department of Gastronomy and Culinary Arts, Toros University, Mersin, Turkey
[3] Department of Culinary, Toros University, Mersin, Turkey

**ORCID ID of the author(s)**

ÖÖA: 0000-0002-1471-8000
YÖ: 0000-0001-7089-3690
ÇÖ: 0000-0002-3577-1599
BÖ: 0000-0001-7372-0138
BYN: 0000-0001-5532-8749

**Corresponding Author**
Özlem Özpak Akkuş
Toros University, Faculty of Health Science, Department of Nutrition and Dietetic
33140 Mersin, Turkey
E-mail: dytozlemozpak@hotmail.com

**Ethics Committee Approval**
The study was approved by the Toros University Clinical Research Ethics Committee on February 5, 2020 (number: 2020/80).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
This work was supported by the Toros University under Grant number 2020-SBYO-ÖÖA-1.

**Published**
2023 July 21

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** In recent years, there has been an increase in the prevalence of obesity and its complications, along with a growing awareness of healthy nutrition. As a result, consumers are seeking to incorporate more functional foods into their diets. Chia and flax seeds have gained popularity due to their soluble fiber and antioxidant capacity. This study aims to compare the effects of consuming cakes made with the addition of chia and flax seeds on blood glucose and insulin levels, as well as evaluate their impact on post-consumption satiety response in individuals.

**Methods:** This randomized, double-blind, self-controlled experimental study involved 12 volunteers (19–64 years old) who were free from acute or chronic diseases. The participants had a body mass index (BMI) value between 18.5 and 24.9 kg/m$^2$ and a Beck Depression Inventory score of 8 or below. The study investigated the effects of standard and test cakes containing 50 g of digestible carbohydrates, including chia-added cake, flaxseed-added cake, and chia+flaxseed-added cake. Postprandial blood sugar, insulin, and subjective satiety responses were assessed. A standard nutrition program (diet: 60% carbohydrates, 20% protein, 30% fat) was implemented at least one week before the study, and participants were asked to maintain 24-h food consumption records the day before the test days. Throughout the study period, individuals were instructed to avoid caffeine, medication, nutritional supplements, and heavy physical activity. Cake consumption sessions were conducted at the research center, with participants visiting four times in total, with at least 1-week intervals. Fasting for 10–12 h prior to each visit, saturation responses were measured using a visual analog scale at 0, 15, 30, 60, 90, 120, and 180 min. Blood samples were also collected to assess blood glucose and insulin levels.

**Results:** The study revealed that cakes containing chia and flaxseeds, compared to the standard cake, as well as flaxseed-added cake compared to chia-added cake, resulted in higher plasma glucose under-curve values and saturation responses and lower hunger responses ($P$=0.038, $P$=0.016, $P$=0.004, respectively).

**Conclusion:** The findings indicate that both chia and flax seeds impact glycemic control and the sensation of satiety, with flaxseed exhibiting greater effectiveness than chia.

**Keywords:** chia, flaxseed, blood glucose, insulin, appetite

How to cite: Özpak Akkuş O, Özdemir Y, Özbek C, Öncel B, Yapıcı Nane B. Does flaxseed and chia use affect postprandial glucose, insulin and subjective saturation response in healthy individuals? J Surg Med. 2023;7(8):434-440.

## Introduction

In recent years, there has been a rise in the prevalence of obesity and its associated complications. Concurrently, there has been an increased awareness of healthy nutrition and a growing desire among consumers to lead healthy lives. As a result, individuals seek to obtain essential nutrients and health benefits from their food choices. This has led to a greater demand for functional foods in their diets [1].

Chia seeds (*Salvia hispanica* L.) and flaxseeds *(Linum usitatissimum*) are edible oilseeds/grains. The United States Nutrition Guidelines, published in 2000, recommend a daily consumption limit of 48 g for chia seeds in adults, considering potential gastrointestinal complaints. The recommended daily consumption amount for flaxseeds is less than 40 g [2,3].

According to data from the United States Department of Agriculture Research Service (USDA) in 2017, chia seeds contain 30.7% lipid, 16.5% protein, and 34.4% fiber, while flaxseeds contain 30–45% lipid, 20–25% protein, and 28% fiber [4-6]. Functional fibers are plant-based components that exhibit specific properties and undergo partial or complete fermentation in the colon. These fibers can be classified into two groups based on their water solubility: soluble and insoluble [7]. Most fibers found in chia and flaxseeds belong to the soluble fraction [8]. These seeds have gained popularity as functional foods due to their antioxidant capacity, particularly their soluble fiber content, and the presence of omega-three fatty acids [9,10].

The soluble fibers present in these seeds contribute to delayed gastric emptying by increasing the viscosity of gastric content and prolonging gastrointestinal transit time. As a result, carbohydrate absorption is slowed, the glycemic index is reduced, insulin release is slowed, and feelings of satiety are enhanced by the increased viscosity of the small intestine contents. These properties make these seeds useful in the nutritional management of obesity and its related complications [8].

While the most effective approach to combat obesity is long-term energy intake that is lower than energy expenditure, adherence to long-term energy-restricted diets is often low [11]. Foods enriched with chia and flax seeds offer an alternative option in the battle against weight loss. They contain increased amounts of soluble fiber, protein, and minerals, as well as α-linolenic acid and phytochemicals, which can aid in treating obesity and its complications, including inflammation [11].

Although using chia and flax seeds in the food industry, particularly in heat-treated products, is uncommon, these seeds have various commercial applications [12].

While studies investigating the impact of consuming products incorporating these seeds, which are gaining popularity as functional foods, on biochemical parameters are not widely available in the literature, a recent study examined the effect of chia seeds on body weight in mildly overweight and obese individuals with type 2 diabetes. The results indicated that the group consuming chia seeds demonstrated improved glycemic control, greater weight loss, and reduced waist circumference [13].

In another study, which assessed the effects of supplementing 10 g/day of flaxseed for one month in individuals with type 2 diabetes, it was found that flaxseed significantly reduced fasting and three-month blood glucose levels [14]. However, a contrasting study conducted in the United States reported that flaxseed improved glycemic control [15].

In this study, we aim to investigate the impact of chia and flax seeds on glycemic control, insulin levels, and satiety response. By examining these effects, we aim to promote the use of alternative products incorporating these seeds in obesity management, as well as weight loss programs and the prevention of obesity-related complications. Specifically, this study aims to evaluate the effects of cakes supplemented with chia and flax seeds, which can be easily prepared at home and are regarded as popular and healthy snack alternatives, on postprandial blood glucose, insulin levels, and individuals' satiety responses.

## Materials and methods

### Study design

This randomized, double-blind, self-controlled experimental study was conducted at Mersin Forum Yaşam Hospital between May and June 2022. The study included 12 individuals aged 19 to 64 who were free from acute or chronic diseases, had a body mass index (BMI) value between 18.5 and 24.9 $kg/m^2$, and had a Beck Depression Inventory score of 8 or below. Participants who were using prescription drugs and/or fiber supplements, following a specific diet, pregnant or lactating, consuming excessive alcohol (more than two drinks per day), experiencing menstruation, diagnosed with gluten enteropathy, or had previously experienced an allergic reaction to chia and flax seeds were excluded from the study.

To establish the nutritional standard for the study, a standardized nutrition program was implemented at least one week before the study. The program included a diet comprising 60% carbohydrates, 20% protein, and 30% fat. Participants were provided with this program, and their 24-h food consumption records from the day before the test days were evaluated using the Nutrition Information System (BEBIS) 8.2 software [16]. Throughout the study period, participants were instructed to refrain from consuming caffeine, medication, or any nutritional supplements and to avoid engaging in strenuous physical activity, as these factors could potentially affect the results.

To determine the sample size, a power analysis was conducted using G*Power software. The analysis utilized alpha (α) set at 0.05, power (1-β) set at 0.80, and a medium effect size (d) of 0.50. The results indicated that a minimum of six individuals per group were required. To account for potential issues such as withdrawals and irregular participation, the study initially enrolled 14 volunteers. However, two individuals withdrew voluntarily in the subsequent weeks. Random assignment of participants who met the inclusion and exclusion criteria was performed by the principal researcher using the R programming language in a computerized environment. Ethical approval for this study was obtained from the Mersin University Clinical Research Ethics Committee on February 5, 2020 (number: 2020/80), and written informed consent was obtained from all participants before their participation. This study has been registered at ClinicalTrials.gov under the identifier NCT05358561.

The study consists of two stages. The first stage involved conducting sensory analyses on the standard and test cakes, which were integral to the background study. Based on the results of this analysis, the selection of cereal-like products to be used in the test cakes was determined. Additionally, nutritional analyses were performed during this stage to ascertain the quantities of the standard and test cakes that contained 50 g of digestible carbohydrates (cakes with added chia seeds, cakes with added flaxseeds, and cakes with added chia and flaxseeds). These cake variations were finalized based on the sensory analysis results. The second stage of the study aimed to investigate the effects of these cakes on postprandial blood glucose, insulin, and subjective satiation response in the participants.

**Making the cakes and their contents**

To determine the quantities of the standard cake (with ingredients: egg 30 g, sugar 19.3 g, sunflower oil 36 g, vanilla 0.75 g, baking powder 0.75 g, wheat flour 40 g, cow's milk 28.5 g) and the test cakes prepared in addition to the standard recipe (chia seed-added cake 15 g, flaxseed-added cake 22.5 g, chia and flaxseed-added cake 9 g each) that would contain 50 g of carbohydrates, various analyses were conducted on samples taken from each of the four cake types in the Food Chemistry Laboratory at Toros University. These analyses included protein, fat, moisture, ash, total fiber, and soluble fiber analyses. Based on the obtained results, the amounts of cakes containing 50 g of digestible carbohydrates were calculated. The cakes were then weighed and prepared for individual consumption one day before the study (Table 1).

The quantities of chia and flax seeds added to the cakes for the study were calculated to ensure that the total fiber content remained consistent and within the recommended daily consumption limits, as stated in the literature [2, 3]. Both chia seeds (Köryusuflar, Mersin) and flax seeds (Köryusuflar, Mersin) were sourced from local markets.

**Nutritional analysis of cakes**

**Moisture Analysis:** The moisture analysis of cake samples will be performed after the cakes have been baked and cooled for one hour. The moisture content (%) will be calculated based on the weight difference resulting from drying in an oven at 105ºC until a constant weight is achieved [17].

**Ash Analysis:** The ash analysis of cakes will be carried out according to Association of Official Analytical Chemists (AOAC) 1990 [18]. The samples will be weighed in porcelain crucibles that have been previously brought to a constant weight and burned in a muffle furnace (Elektro-mag M1813, Turkey) at 550 ± 5ºC until the residue turns white. The ash content (%) of the cakes will be calculated by proportioning the sample mass remaining in the crucibles at the end of the incineration process to the initial sample mass.

**Protein Analysis:** In the protein determination by the Kjeldahl method, the total amount of nitrogen contained in the food is determined. The protein content (%) will be determined by multiplying the total nitrogen amount determined by the nitrogen factor, which is determined according to the total organic nitrogen ratio in the protein molecule [19,20].

**Fat Analysis:** The fat analysis will be carried out using the Soxhlet method according to AOAC 1990 [17]. For fat determination, approximately 4 g of cake sample will be weighed into a cellulose cartridge, covered with cotton wool, and placed in the Soxhlet apparatus. At the end of the extraction using petroleum ether, the ether in the balloons will be evaporated, and the fat content in the sample will be calculated.

**Fiber Analysis:** The dietary fiber content of the cakes will be determined according to American Association of Cereal Chemists (AACC) 2000 [21]. Samples for dietary fiber analysis will be subjected to enzymatic digestion with heat-resistant enzymes α-amylase, protease, and amyloglucosidase (Sigma-Aldrich, St. Louis, MO, USA) to remove starch and protein. The enzyme-digested material will then be treated with alcohol to precipitate soluble dietary fiber before filtration. The dietary fiber residue will be washed with water, then acetone, dried, and weighed.

**Soluble Fiber Analysis:** The dietary fiber contents of cake samples were determined according to AOAC 991.43 [22] using the Megazyme analysis kit. The samples were treated with α-amylase (30 min, 100°C), protease (30 min, 60°C), and amyloglucosidase (30 min, 60°C) enzymes, respectively, to remove starch and protein molecules from the structure. The resulting mixture was filtered with a Gooch crucible. The solid portion remaining at the top of the crucible was washed with distilled water, ethanol (95%), and acetone (99%) and then dried at 105 °C for 3 h. The ash and protein contents of the dried samples were determined, and the insoluble dietary fiber was calculated. Soluble dietary fibers were precipitated and filtered by adding four times the volume of ethanol (95%) to the filtrate obtained from the filtration process. The precipitate was washed with 78% and 95% ethanol and acetone, respectively, and dried to a constant weight, and the residue was analyzed for ash and protein to determine the amount of soluble dietary fiber.

The soluble fiber analysis of the cake samples, using 100 g portions, revealed the following findings: the standard cake made with 40 g of wheat flour (100% wheat flour) contained 2.32 g of soluble fiber, while the cake prepared with 64.0 g of wheat flour and 36% flaxseed (equivalent to 22.5 g of flaxseed) contained 2.95 g of soluble fiber. Furthermore, when analyzing the cake (15 g) with chia added (composed of 72.4% wheat flour and 27.6% chia), it contained 0.65 g of soluble fiber. Based on these results, it can be concluded that flaxseed exhibits a notably high soluble fiber content, containing approximately 4.5–5 times more soluble fiber than chia (Table 1).

Table 1: Quantity and nutritional value of test cakes.

| Nutritional values | Standard cake | Chia-added cake | Flaxseed-added cake | Chia+flaxseed-added cake |
|---|---|---|---|---|
| **Quantities of cakes** | 142.3 | 114.9 | 140.2 | 120.8 |
| **Carbohydrate (g)** | 50.0 | 50.0 | 50.0 | 50.0 |
| **Total fiber (g)** | 1.7 | 6.8 | 6.8 | 6.8 |
| **Soluble fiber (g)** | 2.32 | <0.65 | 2.95 | <0.65 |
| **Protein (g)** | 11.6 | 11.5 | 12.9 | 10.9 |
| **Lipid (g)** | 34.2 | 16.7 | 40.4 | 28.5 |
| **Moisture (g)** | 43.4 | 36.5 | 36.2 | 30.4 |
| **Ash (g)** | 3.12 | 0.33 | 1.16 | 1.06 |
| **TPC (mg gallic acid/L)** | 271 | 289 | 328 | 334 |
| **Aox (mmol trolox/g)** | 0.151 | 0.155 | 0.247 | 0.200 |

Aox: Antioxidant; TPC: Total phenolic content

**Consumption and evaluation of cakes**

The participants involved in the study visited the research center on four separate occasions, with at least 1-week intervals between visits, to consume their assigned cakes. On the test day, the individuals were required to fast for 10–12 h before

they arrived at the research center, during which time they were only permitted to drink water. Furthermore, as the study was conducted double-blind, both the participants and the researchers responsible for cake production and distribution were unaware of the specific cake types. The cakes were identified solely by their assigned codes. Upon arrival, the fasting and appetite responses of the participants were assessed using a 100-mm Visual Analog Scale (VAS), and fasting venous blood samples were collected to measure blood glucose and insulin levels. Subsequently, the participants consumed the cakes within a 10-min timeframe. VAS measurements of appetite responses were recorded at the 15th, 30th, 60th, 90th, 120th, and 180th min following cake consumption, and additional venous blood samples were taken during these 3 h. Throughout this time, the participants were instructed not to leave the research center or consume any other food.

**Biochemical parameters and saturation responses**

Glucose values were analyzed using the glucose hexokinase enzymatic reference method (Cobas 501), while insulin values were analyzed using the electrochemiluminescence (ECL) method (Cobas 601).

The VAS converts certain non-numerical values into digitized measurements. The parameter being assessed is represented by two definitions placed at the ends of a 100 mm line, and participants are instructed to indicate their respective position by assigning corresponding numbers [23]. In this study, the VAS was employed to gauge individual responses to hunger, satiety, desire for prospective food consumption, perception of sweetness, taste satisfaction (deliciousness), saltiness, and fattiness at the 15th, 30th, 60th, 90th, 120th, and 180th minutes. This allowed for the acquisition of numerical values.

**Sensory analysis results**

Panelists evaluated the sensory analyses of the cake samples following the pre-test productions. In the pre-test productions, a total of eight different cakes, along with a standard cake, were produced. These cakes were made using varying proportions of chia seeds, flaxseeds, buckwheat, and combinations thereof. The sensory properties of the samples were assessed based on color, texture, taste, appearance, and overall taste. The analysis revealed that the utilization of cereal-like products did not have a statistically significant impact on any sensory quality of the cake samples.

Consequently, it was concluded that all cake samples were equivalent in terms of sensory quality, and the inclusion of cereal-like products did not adversely affect the overall quality. However, it was noted that cake samples containing buckwheat were preferred in terms of volume, although the panelists described the presence of hard particles in their mouths when consuming the buckwheat-added samples as a negative experience. Therefore, the effect of buckwheat was not further examined in the study. While no statistical differences were observed among the samples, the first three samples, excluding the control sample, were selected for further investigation based on their general taste. The study aimed to explore the effects of chia and flax seeds used in these selected samples.

Regarding general taste, the cakes that incorporated both chia and flax seeds received the same score as those that solely used chia seeds. However, the samples that utilized both seeds together were the most preferred in terms of color. In a study conducted by Shaikh et al. [24], it was stated that cupcake samples containing a 10% mixture of chia and flax seeds achieved a color and appearance similar to that of the control sample. These samples also exhibited comparable texture, taste, smell, and general acceptability. Lipilina and Ganji [25] reported that using flaxseed improved the color of muffin samples, with higher scores given to samples containing a greater ratio of flax seeds. Cake samples made exclusively with chia seeds received higher scores for their porous structure and taste characteristics than the other samples. Chelladurai et al. [26] indicated that incorporating chia seeds into cookie recipes, with increasing concentrations, enhanced sensory properties such as color, appearance, texture, taste, smell, and overall acceptability. Steffolani et al. [27] demonstrated that including chia seeds enhanced the taste, texture, and appearance of gluten-free bread. Regarding texture, cake samples using only flaxseed received the highest score. Pohjanheimo et al. [28] reported that flaxseed bread was softer and more elastic than the control samples. Consistent with the findings of this study (Table 2), several researchers have reported that the inclusion of chia and flax seeds in bakery and pastry products does not significantly impact the overall acceptability of the samples in terms of sensory evaluation [25,27,29-32].

Table 2: Sensory parameters of cake samples.

| Cakes | Color | Texture | Flavor | Appearance | | General taste |
|---|---|---|---|---|---|---|
| | | | | Volume | Porous structure | |
| **Standard** | 3.9 (1.1)† | 4.0 (1.0)† | 3.6 (1.1)† | 3.3 (0.9)† | 3.9 (0.4)† | 3.9 (0.4)† |
| **Chia-added** | 3.7 (1.3)† | 4.1 (0.7)† | 3.9 (0.9)† | 4.1 (1.2)† | 4.0 (0.6)† | 4.0 (0.6)† |
| **Flaxseed-added** | 4.0 (1.4)† | 4.3 (0.9)† | 2.9 (1.3)† | 4.1 (0.4)† | 3.9 (1.1)† | 3.9 (1.1)† |
| **Chia+Flaxseed-added** | 4.6 (0.5)† | 4.1 (1.5)† | 3.0 (1.3)† | 4.1 (1.1)† | 4.0 (1.2)† | 4.0 (1.2)† |

† There is no difference between the groups with the same letter

**Statistical analysis**

During the hypothesis testing phase of the study, the suitability of variables for normal distribution was determined using the Shapiro-Wilk test. For variables that met the assumption of normal distribution, the analysis of variance (ANOVA) test was employed for comparisons among three or more independent groups. When the assumption of sphericity was met, the Sphericity Assumed test statistic was utilized. In cases where the sphericity assumption was not met, the Greenhouse-Geisser test statistic was employed. The Bonferroni correction paired t-test, and Tukey test were used for multiple comparisons between groups and yielded significant results. A margin of error of 5% was set for statistical analysis. Graphs and the calculation of the area under the curve (AUC) were performed using the R-Project program [33], while all other analyses were conducted using SPSS (IBM SPSS Statistics 26). The significance level was set at $P$-value <0.05.

## Results

Table 3 presents the AUC values for time-based plasma glucose and insulin levels following the consumption of the test cakes by study participants. Upon examining the results, it was observed that the AUC values for plasma glucose were higher after consuming cakes with added chia and flaxseeds compared to the standard cake ($P$=0.038). Furthermore, it was found that the AUC values for plasma glucose were significantly higher after consuming flaxseed-added cake compared to chia-added

cake. However, there was no significant difference in plasma insulin levels and AUC values ($P$=0.237).

Table 3: Comparison of the area under the curve of plasma glucose and insulin levels of individuals consuming cake based on time.

| AUC values | Flaxseed-added cake n=12 | Chia-added cake n=12 | Chia+flaxseed-added cake n=12 | Standard cake n=12 | *P*-value |
|---|---|---|---|---|---|
| **Glucose** | 2992.7¶ | 2681.4 ¶†† | 2724.1 ¶†† | 2637.1†† | 0.038 †§* |
| **Insulin** | 954.2 | 1118.9 | 1035.9 | 1167.2 | 0.237 †‡ |

AUC: Area Under the Curve, †: ANOVA, ‡: Sphericity Assumed, §: Greenhouse-Geisser, ¶††: No difference between groups with the same symbol; *$P$<0.05; **$P$<0.001

Figure 1 illustrates a line chart depicting the changes in plasma glucose and insulin levels over time following cake consumption by the participants.

Figure 1: Plasma glucose and insulin levels based on time after cake consumption of individuals.

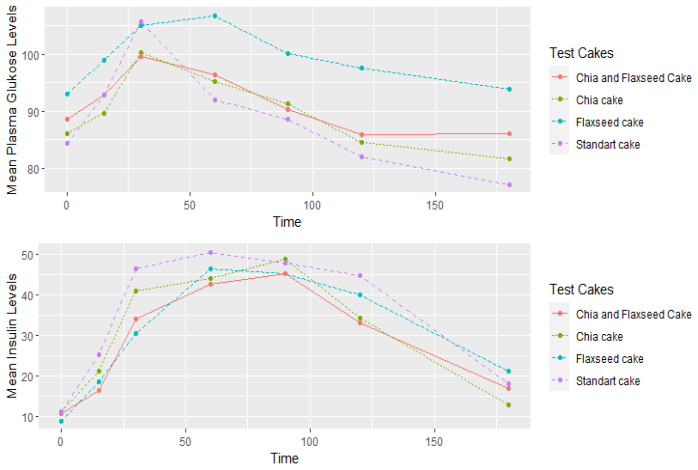



Table 4 presents the AUC values on the VAS for different aspects related to cake consumption by the study participants. Statistical analysis revealed significant differences in hunger, satiation, and craving for sugary, delicious, salty, and fatty foods after cake consumption ($P$=0.004, $P$=0.016, $P$=0.007, $P$=0.027, $P$=0.028, $P$=0.035, respectively). Hunger levels were found to be lower ($P$=0.004), and satiation levels were higher ($P$=0.016) after consuming flaxseed and chia-added cakes compared to the standard cake. Furthermore, when comparing the individuals who consumed flaxseed cake with those who consumed chia-added cake, it was observed that the former group experienced less hunger ($P$=0.004) and greater satiation ($P$=0.016).

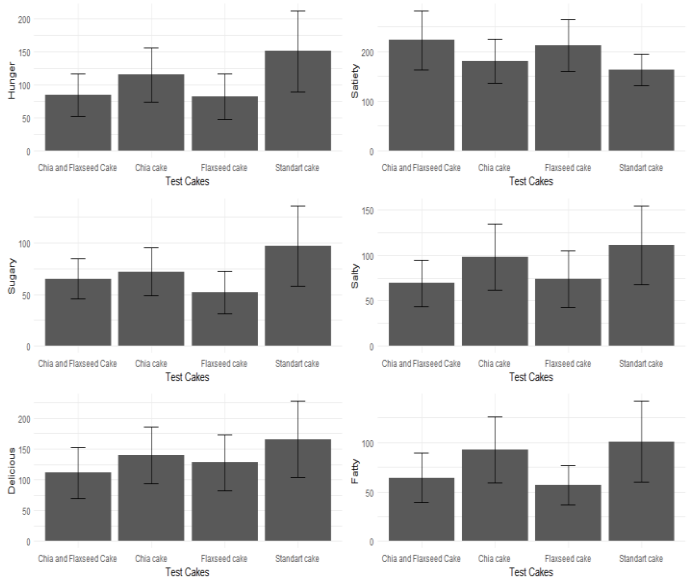
Table 4: Comparison of VAS area under the curve values of individuals consuming cake.

| AUC values | Flaxseed-added cake n=12 | Chia-added cake n=12 | Chia+flaxseed-added cake n=12 | Standard cake n=12 | *P*-value |
|---|---|---|---|---|---|
| **Feeling of Hunger** | 82.083†† | 114.792¶†† | 84.792¶†† | 150.521¶ | 0.004†‡* |
| **Feeling of Saturation** | 223.438†† | 180.417¶†† | 212.396¶†† | 163.438¶ | 0.016†‡* |
| **Desire to eat** | 114.896 | 121.771 | 82.708 | 129.688 | 0.064†§ |
| **The level of desire to eat** | 100.413 | 121.667 | 79.688 | 133.542 | 0.089†§ |
| **Desire to consume sugary foods** | 65.208¶†† | 71.979¶†† | 51.979†† | 96.979¶ | 0.007†‡* |
| **Desire to consume salty foods** | 69.167†† | 98.125¶ | 73.646¶†† | 111.042¶†† | 0.028†§* |
| **Desire to consume delicious foods** | 111.146†† | 139.687¶ | 128.021¶†† | 165.937¶†† | 0.027†§* |
| **Desire to consume fatty foods** | 64.167¶†† | 92.813¶ | 56.771†† | 100.833¶†† | 0.035†§* |

AUC: Area Under the Curve, †: ANOVA, ‡: Sphericity Assumed, §: Greenhouse-Geisser, ¶††: No difference between groups with the same symbol; *$P$<0.05; **$P$<0.001

Figure 2 presents a bar graph representing the AUC measured on the VAS after cake consumption by the individuals.

Figure 2: VAS under-curve area values after cake consumption of individuals.




## Discussion

This study demonstrates that consuming chia and flaxseed positively affects glycemic control and the feeling of satiety. However, its impact on insulin secretion is negligible. Furthermore, it suggests that flaxseed exhibits a stronger effect than chia, which may prompt further investigation into this topic.

Chia and flax seeds are widely consumed in many countries and have gained recognition as functional foods. They are valued for their positive effects on glycemic control, antioxidant content, and anti-inflammatory properties [13,34]. The primary mechanism through which chia and flax seeds influence glycemic control is by virtue of the soluble fibers they contain. These fibers increase stomach and small intestine viscosity, delaying gastric emptying and prolonged gastrointestinal transit time. Consequently, the absorption of carbohydrates is delayed, resulting in reduced glycemic response, delayed insulin release, and increased satiety [8]. Moreover, lignan, one of the three primary phytoestrogens found in these seeds, aids in glycemic control by suppressing the expression of the phosphoenolpyruvate carboxykinase (PEPCK) gene responsible for glucose production through gluconeogenesis, thus inhibiting glucose production [35]. Furthermore, the alpha-linolenic acid (ALA) content of these seeds contributes to glycemic control through improved insulin sensitivity [36,37].

In a study involving mildly overweight and obese individuals with type 2 diabetes, it was observed that daily consumption of 30 g/1000 kcal of chia seeds, along with an energy-restricted diet, resulted in improved weight loss and postprandial glycemia levels [13]. Similarly, a study conducted with healthy individuals found that the consumption of each 1 gram of chia seeds led to a 2% decrease in postprandial glycemia, slowed carbohydrate release, and reduced appetite response [12]. Numerous randomized controlled clinical trials have been carried out to assess the effectiveness of flaxseed or its derivatives in glycemic control and insulin sensitivity [10,38,39]. While some studies have reported the beneficial effects of

flaxseed, others have found no significant benefits [14,40-42]. Inconsistencies in these findings have been attributed to variations in sample sizes and intervention durations among the target populations.

This study observed that the plasma glucose AUC values, measured after consuming cakes with added chia and flaxseeds, were higher than the standard cake. Additionally, the plasma glucose AUC values were higher in the flaxseed-added cake than the chia-added cake. Despite the similar nutritional composition of the chia and flaxseed-added cakes, these differences in postprandial glycemia can be attributed to the higher content of soluble fiber found predominantly in the seeds. This finding aligns with existing literature, as flaxseed contains, on average, five times more soluble fiber than chia on a gram-to-gram basis [42-45].

The consumption of chia and flaxseed also has a positive impact on insulin secretion, supported by several mechanisms. Firstly, the soluble fiber content in these seeds slows down glucose absorption, reducing the need for insulin production. Secondly, their antioxidant content can enhance insulin sensitivity [15,46]. Additionally, the protein content of these seeds has been shown to stimulate insulin secretion, while the ALA content can contribute to increased insulin sensitivity [36,37,47]. A recent meta-analysis demonstrated that flaxseed significantly decreased insulin secretion in interventions lasting 12 weeks or more but not in shorter interventions [48]. These findings were further supported by another study that investigated the effects of flaxseed supplementation on blood glucose and insulin resistance in individuals with obesity and insulin resistance over a 12-week intervention period [49]. Possible explanations for these time-dependent intervention results include a gradual increase in ALA, which can be converted to long-chain fatty acids such as EPA (Eicosapentaenoic acid; 20:5, n-3) and DHA (Docosahexaenoic acid; 22:6, n-3), improving insulin sensitivity and glycemic control. Additionally, improvements in gut flora, brought about by the consumption of soluble fiber, may contribute to enhanced glycemic control [50-53]. This study found no significant difference in the plasma insulin AUC values between individuals consuming cakes with added chia or flaxseeds and those consuming the standard cake. This lack of significant difference can be attributed to the short intervention period in the study design.

Consuming soluble fiber has been linked to a sensation of satiety and its potential impact on food intake [54]. Insufficient satiety significantly contributes to increased caloric intake and the high prevalence of obesity and its associated complications [55]. The effect of consuming soluble fiber on the feeling of satiety is attributed to its ability to form a gel-like structure in the stomach during digestion, leading to increased gastric distension and triggering satiety signals through the afferent vagus nervous system [56,57]. Furthermore, soluble fiber consumption has been shown to modulate the secretion of gastrointestinal (GI) hormones involved in appetite regulation [58]. Several studies have demonstrated that consumption of soluble fiber, typically in doses exceeding 5 g, increases the production of satiety-regulating GI hormones such as glucagon-like peptide 1 (GLP-1) and Peptide YY (PYY) [59-61]. Additionally, it has been suggested that soluble fiber consumption may harm levels of ghrelin, the hormone commonly known as the "hunger hormone," in healthy adults [60,62,63].

In a study assessing the effects of flaxseed on satiety, it was observed that adding 5–15 g of flax mucilage (equivalent to approximately 50–150 g of whole ground flax) to baked goods did not significantly impact satiety parameters. However, adding 2.5 g of flax mucilage (equivalent to 25 g of ground flax) to a beverage resulted in decreased satiety and general appetite [64-66]. Another study involving bread containing 24 g of chia seeds found that chia-added bread led to a greater sense of fullness after 120 min compared to control white bread [67]. While the effect of soluble fiber enrichment on satiety has mainly been studied in cereal derivatives, generally positive associations have been reported in various populations, including obese individuals and those with cardiometabolic risk [68,69]. However, some studies have reported contrasting findings [70,71]. This study observed that the consumption of cakes with added chia and flaxseeds increased the feeling of satiety compared to the standard cake. Additionally, flaxseed consumption was associated with a greater sense of satiety when compared to chia seeds. These results are consistent with the findings of studies conducted by Vuksan et al. [66] and Ibrugger et al. [67], further supporting the positive impact of soluble fibers on satiety.

**Limitations**

This study possesses several strengths. Firstly, the cakes incorporating chia and flax seeds were produced through both laboratory and clinical stages, ensuring robustness in the experimental process. Moreover, the study design allowed individuals to control their variables, thereby minimizing variability. Despite these strengths, certain limitations should be acknowledged. Firstly, all participants were young and healthy individuals, thus limiting the generalizability of the study's findings to older, obese, and chronically ill populations. Furthermore, the absence of a long-term intervention and the lack of monitoring of individuals' plasma antioxidant levels restrict the study's overall impact. Considering the results obtained from this short-term intervention study, future research should encompass diverse populations with varying initial glucose levels and BMI values. Additionally, studies with larger sample sizes and longer intervention periods are required to yield more significant outcomes regarding improved glycemic control, reduced food intake, and effective weight management.

**Conclusions**

This study demonstrates the efficacy of both chia and flax seeds in terms of glycemic control, increased satiety, and reduced hunger, primarily attributed to their soluble fiber content. Furthermore, the findings indicate that flaxseed exhibits a stronger effect compared to chia in these regards. Additionally, although these seeds do not significantly impact insulin responses, they do diminish cravings for sugary, salty, fatty, and indulgent foods. Based on these results, it is suggested that incorporating foods rich in soluble fiber, such as chia and flax seeds, into our consumption habits through healthy and safe products may have a protective role against obesity and its associated complications and potentially prevent its progression.

**Acknowledgments**

The authors would like to thank the individuals who participated in this study for their cooperation.

## References

1. Green M, Arora K, Prakash S. Microbial medicine: prebiotic and probiotic functional foods to target obesity and metabolic syndrome. Int J Mol Sci. 2020;21(8):2890. doi: 10.3390/ijms21082890.
2. Mohd Ali N, Yeap SK, Ho WY, Beh BK, Tan SW, Tan SG. The Promising future of chia, Salvia hispanica L. J Biomed Biotechnol. 2012;2012:171956. doi: 10.1155/2012/171956 .
3. Carraro JCC, Dantas MS, Espeschit ACR, Martino HSD, Ribeiro SMR. Flaxseed and human health: reviewing benefits and adverse effects. Food Reviews International. 2012;28(2):203-30. doi: 10.1080/87559129.2011.595025.
4. Unites States Department of Agriculture Research Service. USDA Food Composition Databese. [Cited 2022/5/8]; Available from: https://fdc.nal.usda.gov/
5. Ramcharitar A, Badrie N, Mattfeldt-Beman M, Matsuo H, Ridley C. Consumer acceptability of muffins with flaxseed (Linum usitatissimum). Journal of Food Science. 2005;70(7):504-7. doi: 10.1111/j.1365-2621.2005.tb11499.x.
6. Rashed MM, Shallan M, Mohamed D, Fouda K, Hanna L. Biological evaluation of anti-androgenic effect of some plant foods. J Food Nutr Res. 2014;2(9):645-51. doi: 10.12691/jfnr-2-9-19.
7. Malkki Y. Physical properties of dietary fiber as keys to physiological functions. Cereal Foods World. 2001;46(5):196-9.
8. Klotzbach-Shimomura K. Functional foods: The role of physiologically active compounds in relation to disease. Topics in Clinical Nutrition. 2001;16(2):68-78.
9. Marcinek K, Krejpcio Z. Chia seeds (Salvia hispanica): health promoting properties and therapeutic applications – a review. Rocz Panstw Zakl Hig. 2017;68(2):123-9.
10. Pan A, Yu D, Demark-Wahnefried W, Franco O, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. Am J Clin Nutr. 2009;90(2):288-97. doi: 10.3945/ajcn.2009.27469.
11. Nieman DC, Cayea EJ, Austin MD, Henson DA, McAnulty SR, Jin F. Chia seed does not promote weight loss or alter disease risk factors in overweight adults. Nutr Res. 2009;29(6):414-8. doi: 10.1016/j.nutres.2009.05.011.
12. Vuksan V, Jenkins AL, Brissette C, Choleva L, Jovanovski E, Gibbs AL, et al. Salba-chia (Salvia hispanica L.) in the treatment of overweight and obese patients with type 2 diabetes: A double-blind randomized controlled trial. Nutr Metab Cardiovasc Dis. 2017;27(2):138-46. doi: 10.1016/j.numecd.2016.11.124.
13. Vuksan V, Choleva L, Jovanovski E, Jenkins AL, Au-Yeung F, Dias AG, et al. Comparison of flax (Linum usitatissimum) and Salba-chia (Salvia hispanica L.) seeds on postprandial glycemia and satiety in healthy individuals: a randomized, controlled, crossover study. Eur J Clin Nutr. 2017;71(2):234-8. doi: 10.1038/ejcn.2016.148.
14. Mani UV, Mani I, Biswas M, Kumar SN. An open-label study on the effect of flax seed powder (Linum usitatissimum) supplementation in the management of diabetes mellitus. J Diet Suppl. 2011;8(3):257-65. doi: 10.3109/19390211.2011.593615.
15. Hutchins AM, Brown BD, Cunnane SC, Domitrovich SG, Adams ER, Bobowiec CE. Daily flaxseed consumption improves glycemic control in obese men and women with pre-diabetes: a randomized study. Nutr Res. 2013;33(5):367-75. doi: 10.1016/j.nutres.2013.02.012.
16. Schmind M. Beslenme Bilgi Sistemi BEBİS 8.2 Paket programı Entwickelt an der Universital Hohenheim, Struttgart, Germany. 2011. Available at:https://www.bebis.com.tr
17. AACC. International Approved Methods of Analysis, American Association of Cereal Chemists (11 th Edition), USA: St. Paul MN; 2010.
18. A.O.A.C. Official methods of analysis (15 th Edition), USA: Arlington VA; 1990.
19. Anonim. T.C. Gıda, Tarım ve Hayvancılık Bakanlığı, Ulusal Gıda Kompozisyonu Veri Tabanı (Türkomp); 2018.
20. A.O.A.C. Official Methods for Analysis, Association of Official Analytical Chemists (17 th Edition), USA: Arlington VA; 2000.
21. A.A.C.C. American Association of Cereal Chemists International, Approved Methods of the AACC the Association (8 th Edition), USA: St. Paul MN; 2000.
22. A.O.A.C Official Method 991.43. Total, soluble and insoluble dietary fiber in foods. In: Official methods of analysis of AOAC international. 16 th Ed. Cunniff P, eds. Gaithersburg, AOAC International Chapter 32; 1999. pp. 7-9.
23. Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes Relat Metab Disord. 2000;24(1):38-48. doi: 10.1038/sj.ijo.0801083.
24. Shaikh RP, Gadhe K. Studies on development and quality evaluation of cupcake fortified with flaxseed and chia seed flour. Pharma Innov. 2020;9:214-7.
25. Lipilina E, Ganji V. Incorporation of ground flaxseed into bakery products and its effect on sensory and nutritional characteristics – a pilot study. Journal of Foodservice. 2009;20(1):52-9. doi: 10.1111/j.1748-0159.2008.00124.x.
26. Chelladurai C, Pandey A, Panmand SA, Nikam S. Development of innovative bakery product chia seed enriched cookies. Int J Food Sci Nutr. 2019;4:19-23.
27. Steffoloni E, De La Hera E, Perez G, Gomez M. Effect of chia (Salvia Hispanica L) addition on the quality of gluten-free bread. Journal of Food Quality. 2014;37(5):309-17. doi: 10.1111/jfq.12098.
28. Pohjanheimo T, Hakala M, Tahvonen R, Salminen S, Kallio H. Flaxseed in breadmaking: effects on sensory quality, aging, and composition of bakery products. Journal of Food Science. 2006;71(4):343-8. doi: 10.1111/j.1750-3841.2006.00005.x.
29. Dündar AN, Aydın E, Yıldız E, Parlak O. Effects of chia seed properties and quality characteristics of regular and low-fat crackers. Food Science and Technology. 2021;41:4. doi: 10.1590/fst.26120.
30. Zhu F, Chan C. Effect of chia seed on glycemic response, texture, and sensory properties of Chinese steamed bread. LWT. 2018;98:77-84. doi: 10.1016/J.LWT.2018.08.016.
31. Koca A, Anil M. Effect of flaxseed and wheat flour blends on dough rheology and bread quality. J Sci Food Agric. 2007;87(6):1172-5. doi: 10.1002/jsfa.2739.
32. Merenkova SP, Lukin AA, Klejman DA. Influence of flaxseed flour additives on quality parameters of bakery products. News of institutes of higher education Food Technology. 2016;5;10-3.
33. R Core Team. R: A language and environment for statistical computing. In: Computing. RFfS, editor. Vienna, Austria. 2019. Available at: https://www.R-project.org/
34. Au MMC, Goff H, Kisch J, Coulson A, Wright A. Effects of soy-soluble fiber and flaxseed gum on the glycemic and insulinemic responses to glucose solutions and dairy products in healthy adult males. J Am Coll Nutr. 2013;32(2):98-100. doi: 10.1080/07315724.2013.767579.
35. Pan A, Sun J, Chen Y, et al. Effects of a flaxseed-derived lignan supplement in type 2 diabetic patients: a randomized, double-blind, cross-over trial. PLoS One. 2007;2(11):1148. doi: 10.1371/journal.pone.0001148.
36. Karakas SE, Perroud B, Kind T, Palazoglu M, Fiehn O. Changes in plasma metabolites and glucose homeostasis during omega-3 polyunsaturated fatty acid supplementation in women with polycystic ovary syndrome. BBA Clin. 2016;5:179-85. doi: 10.1016/j.bbacli.2016.04.003.
37. Nettleton JA, Katz R. n-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. J Am Diet Assoc. 2005;105(3):428-40. doi: 10.1016/j.jada.2004.11.029.
38. Machado AM, de Paula H, Cardoso LD, Costa NMB. Effects of brown and golden flaxseed on the lipid profile, glycemia, inflammatory biomarkers, blood pressure and body composition in overweight adolescents. Nutrition. 2015;31(1):90-6. doi: 10.1016/j.nut.2014.05.002.
39. Stuglin C, Prasad K. Effect of flaxseed consumption on blood pressure, serum lipids, hemopoietic system and liver and kidney enzymes in healthy humans. J Cardiovasc Pharmacol Ther. 2005;10(1):23-7. doi: 10.1177/107424840501000103.
40. Dahl WJ, Lockert EA, Cammer AL, Whiting SJ. Effects of flax fiber on laxation and glycemic response in healthy volunteers. J Med Food. 2005;8(4):508-11. doi: 10.1089/jmf.2005.8.508.
41. Barre DE, Mizier-Barre KA, Griscti O, Hafez K. High dose flaxseed oil supplementation may affect fasting blood serum glucose management in human type 2 diabetics. J Oleo Sci. 2008;57(5):269-73. doi: 10.5650/jos.57.269.
42. Cornish SM, Chilibeck PD, Paus-Jennsen L, Biem HJ, Khozani T, Senanayake V, et al. A randomized controlled trial of the effects of flaxseed lignan complex on metabolic syndrome composite score and bone mineral in older adults. Appl Physiol Nutr Metab. 2009;34(2):89-98. doi:10.1139/H08-142.
43. Bernacchia R, Preti R, Vinci G. Chemical composition and health benefits of flaxseed. Austin J Nutr Food Sci. 2014;2(8):1045.
44. Coorey R, Tjoe A, Jayasena V. Gelling properties of chia seed and flour. J Food Sci. 2014;79(5):859-66. doi: 10.1111/1750-3841.12444.
45. da Silva BP, Anunciação PC, Matyelka JCDS, Della Lucia CM, Martino HSD, Pinheiro-Sant'Ana HM. Chemical composition of Brazilian chia seeds grown in different places. Food Chemistry. 2017;221:1709-16. doi: 10.1016/j.foodchem.2016.10.115.
46. Morisset AS, Lemieux S, Veilleux A, Bergeron J, John Weisnagel S, Tchernof A. Impact of a lignan-rich diet on adiposity and insulin sensitivity in post-menopausal women. Br J Nutr. 2009;102(2):195-200. doi: 10.1017/s0007114508162092.
47. Clarke ST, Sarfaraz S, Qi X, Ramdath DG, Fougere GC, Ramdath DD. A Review of the Relationship between lentil serving and acute postprandial blood glucose response: effects of dietary fibre, protein and carbohydrates. Nutrients. 2022;14(4);849. doi: 10.3390/nu14040849.
48. Mohammadi-Sartang M, Sohrabi Z, Barati-Boldaji R, Raeisi-Dehkordi H, Mazloom Z. Flaxseed supplementation on glucose control and insulin sensitivity: a systematic review and meta-analysis of 25 randomized, placebo-controlled trials. Nutr Rev. 2018;76(2):125-39. doi: 10.1093/nutrit/nux052.
49. Khalesi S, Irwin C, Schubert M. Flaxseed consumption may reduce blood pressure: a systematic review and meta-analysis of controlled trials. J Nutr. 2015;145(4):758-65. doi: 10.3945/jn.114.205302.
50. Albert BB, Derraik JGB, Brennan CM, Biggs JB, Smith GC, Garg ML, et al. Higher omega-3 index is associated with increased insulin sensitivity and more favourable metabolic profile in middle-aged overweight men. Sci Rep. 2014;4:6697. doi: 10.1038/srep06697.
51. Wien M, Rajaram S, Oda K, Sabaté J. Decreasing the linoleic acid to alpha-linolenic acid diet ratio increases eicosapentaenoic acid in erythrocytes in adults. Lipids. 2010;45(8):683-92. doi: 10.1007/s11745-010-3430-3.
52. Karlsson FHh, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg BF, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature. 2013;498(7452):99-103. doi: 10.1038/nature12198.
53. Kuo SM. The interplay between fiber and the intestinal microbiome in the inflammatory response. Adv Nutr. 2013;4(1):16-28. doi: 10.3945/an.112.003046.
54. Hervik AK, Svihus B. The role of fiber in energy balance. J Nutr Metab. 2019;2019:4983657. doi: 10.1155/2019/4983657.
55. Tremblay A, Bellisle F. Nutrients, satiety, and control of energy intake. Appl Physiol Nutr Metab. 2015;40(10):971-9. doi: 10.1139/apnm-2014-0549.
56. Capuano E. The behavior of dietary fiber in the gastrointestinal tract determines its physiological effect. Crit Rev Food Sci Nutr. 2017;57(16):3543-64. doi: 10.1080/10408398.2016.1180501.
57. Ho IH, Matia-Merino L, Huffman LM. Use of viscous fibres in beverages for appetite control: a review of studies. Int J Food Sci Nutr. 2015;66(5):479-90. doi: 10.3109/09637486.2015.1034252.
58. Sánchez D, Miguel M, Aleixandre A. Dietary fiber, gut peptides, and adipocytokines. J Med Food. 2012;15(3):223-30. doi: 10.1089/jmf.2011.0072.
59. Rahman S, Zhao A, Xiao D, Park E, Edirisinghe I, Burton-Freeman B. A randomized, controlled trial evaluating polydextrose as a fiber in a wet and dry matrix on glycemic control. J Food Sci. 2017;82(10):2471-8. doi: 10.1111/1750-3841.13855.
60. Tarini J, Wolever TM. The fermentable fibre inulin increases postprandial serum short-chain fatty acids and reduces free-fatty acids and ghrelin in healthy subjects. Appl Physiol Nutr Metab. 2010;35(1):9-16. doi: 10.1139/H09-119.
61. Ye Z, Arumugam V, Haugabrooks E, Williamson P, Hendrich S. Soluble dietary fiber (Fibersol-2) decreased hunger and increased satiety hormones in humans when ingested with a meal. Nutr Res. 2015;35(5):393-400. doi: 10.1016/j.nutres.2015.03.004.
62. Lumaga RB, Azzali D, Fogliano V, Scalfi L, Vitaglione P. Sugar and dietary fibre composition influence, by different hormonal response, the satiating capacity of a fruit-based and a β-glucan-enriched beverage. Food Funct. 2012;3(1):67-75. doi: 10.1039/c1fo10065c.
63. Rahat-Rozenbloom S, Fernandes J, Cheng J, Wolever TMS. Acute increases in serum colonic short-chain fatty acids elicited by inulin do not increase GLP-1 or PYY responses but may reduce ghrelin in lean and overweight humans. Eur J Clin Nutr. 2017;71(8):953-8. doi: 10.1038/ejcn.2016.249.
64. Cohen L, Meira J, Cosendey GM, de Souza AF, Mattos F, Carneiro JRI, et al. Evaluation of the influence of whole and defatted flaxseed on satiety, glucose, and leptin levels of women in the late postoperative stage of bariatric surgery. Obes Surg. 2013;23(2):157-66. doi: 10.1007/s11695-012-0733-x.
65. Lafond DW, Greaves KA, Maki KC, Leidy HJ, Romsos DR. Effects of two dietary fibers as part of ready-to-eat cereal (RTEC) breakfasts on perceived appetite and gut hormones in overweight women. Nutrients. 2015;7(2):1245-66. doi: 10.3390/nu7021245.
66. Vuksan V, Jenkins AL, Dias AG, Lee AS, Jovanovski E, Rogovik AL, et al. Reduction in postprandial glucose excursion and prolongation of satiety: possible explanation of the long-term effects of whole grain Salba (Salvia Hispanica L.). Eur J Clin Nutr. 2010;64(4):436-8. doi: 10.1038/ejcn.2009.159.
67. Ibrügger S, Kristensen M, Mikkelsen MS, Astrup A. Flaxseed dietary fiber supplements for suppression of appetite and food intake. Appetite. 2012;58(2):490-5. doi: 10.1016/j.appet.2011.12.024.
68. Reimer RA, Pelletier X, Carabin IG, Lyon M, Gahler R, Parnell JA, et al. Increased plasma PYY levels following supplementation with the functional fiber PolyGlycopleX in healthy adults. Eur J Clin Nutr. 2010;64(10):1186-91. doi:10.1038/ejcn.2010.141.
69. Sandberg JC, Björck IME, Nilsson AC. Effects of whole grain rye, with and without resistant starch type 2 supplementation, on glucose tolerance, gut hormones, inflammation and appetite regulation in an 11-14.5 hour perspective; a randomized controlled study in healthy subjects. Nutr J. 2017;16:25. doi: 10.1186/s12937-017-0246-5.
70. Juvonen KR, Salmenkallio-Marttila M, Lyly M, Liukkonen KH, Lahteenmaki L, Laaksonen DE, et al. Semisolid meal enriched in oat bran decreases plasma glucose and insulin levels, but does not change gastrointestinal peptide responses or short-term appetite in healthy subjects. Nutr Metab Cardiovasc Dis. 2011;21(9):748-56. doi: 10.1016/j.numecd.2010.02.002.
71. Karhunen LJ, Juvonen KR, Flander SM, Luikkonen KH, Lahteenmaki L, Siloaho M, et al. A psyllium fiber-enriched meal strongly attenuates postprandial gastrointestinal peptide release in healthy young adults. J Nutr. 2010;140(4):737-44. doi: 10.3945/jn.109.115436.

J Surg Med. 2023;7(8):441-445.
DOI: 10.28982/josam.7858

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# HPV vaccinations in males; Knowledge, attitudes, and practices of physicians on human papilloma virus vaccinations for their sons

**Sevtap Seyfettinoglu,[1] Betul Dagoglu Hark [2]**

[1] University of Health Sciences, Adana City Training and Research Hospital, Department of Obstetrics and Gynecology, Adana, Turkey
[2] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Fırat University Elazıg, Turkey

**ORCID ID of the author(s)**

SS: 0000-0001-8607-6628
BDH: 0000-0002-5189-1929

**Corresponding Author**
Sevtap Seyfettinoglu
Adana City Training and Research Hospital, Department of Obstetrics and Gynecology, Adana, Turkey
E-mail: sevtaponcul@gmail.com

**Ethics Committee Approval**
The study was approved by the Institutional Review Board of Adana City Training and Research Hospital (No: 76-1320).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 3

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** The Human Papilloma Virus (HPV) infection is the most common sexually transmitted disease and has been shown to cause cancer. Both sexes have a lifetime risk of at least 50% of exposure to HPV. Male HPV vaccinations can yield advantages for both the individual and community, including reduced transmission of HPV and protection of male and female health. The approval of vaccinations is mainly influenced by parental perspectives on this matter. It is essential to examine the subject in terms of physicians, who have the highest knowledge about HPV in society. This cross-sectional study aims to investigate physicians' attitudes and knowledge about vaccinating their male children against the human papillomavirus.

**Methods:** A total of 1670 physicians were included in this study. Working as a physician and having a son were determined as inclusion criteria. A digital questionnaire was given to the physicians participating in the study. The answers to the survey questions were rated on a 4-point Likert scale (agree, do not know, disagree, strongly disagree). The responses were compared with the variables, and statistical analysis was performed.

**Results:** Of the physicians participating in the study, 34.4% were male and 65.6% were female. A small percentage of the physicians (6.2%) reported that they would vaccinate their boys against HPV, and 59.9% of them indicated that they would not but they would consider it. The physicians' who were most likely to vaccinate their sons worked in the fields of radiology (97.3%), orthopedics (80%), and gynecology (78.8%). It was determined that the physicians who said they would never have their sons vaccinated against HPV were most frequently specialists in anesthesiology and reanimation, infectious diseases, and clinical microbiology.

**Conclusions:** This study determined that physicians in some specialties hesitated to give the HPV vaccine to their sons. The HPV vaccine is crucial for boys, and it is essential to point out the significance of providing seminars to physicians, particularly in developing nations like Turkey, regarding this issue and its consequences.

**Keywords:** HPV vaccine, immunization, male, physician, cancer

How to cite: Seyfettinoglu S, Hark BD. HPV vaccinations in males; Knowledge, attitudes, and practices of physicians on human papilloma virus vaccinations for their sons. J Surg Med. 2023;7(8):441-445.

## Introduction

Human papillomavirus (HPV) infection is a sexually transmitted virus that plays an essential role in cancer development. HPV infection is prevalent in both women and men [1]. Lesions caused by HPV considered high risk for cancer development can progress to cervical cancer, the second most common malignancy in young women. HPV causes gynecological cancers and lesions that can lead to cancer in the head and neck region, anus, and penis. Therefore, women and men are at risk of HPV-related cancer [2,3].

Vaccination is the most effective way to prevent HPV. Unfortunately, recent posts, primarily through digital platforms, have increased vaccine hesitancy in society. Anti-vaccination sentiment was listed by the World Health Organization (WHO) as one of the top ten global public health threats in 2019. WHO aims to achieve 90% worldwide HPV vaccine coverage, but misunderstandings, lack of information, and fake news are the main obstacles to achieving this goal [4–6].

Today, 146 countries worldwide have included the HPV vaccine in their vaccination program. In Turkey, the HPV vaccine is not included in the vaccination program, and there is insufficient awareness about this vaccine. According to the 2019 data from UNICEF and WHO, all doses of the HPV vaccine were administered to approximately 4% of males and 15% of females globally [7]. This vaccine, which can be administered to both sexes, is the only way to eradicate HPV-related cancer [8].

When we look at the way HPV infection is transmitted and the disease it causes, it is apparent that this is not only a women's problem but also a significant health problem that threatens men. Therefore, it is necessary to vaccinate boys for both individual and public health reasons [9].

The success of HPV vaccine application depends on physicians' belief in the efficacy and safety of this vaccine. Physicians in different specialties may differ in opinion on the effectiveness of vaccines. This situation creates hindrances to the success of immunization programs [10,11]. For the success of HPV vaccination in Turkey, it is necessary to increase physicians' belief in all specialties in the efficacy and safety of this vaccine [11]. This study aims to evaluate physicians' awareness of HPV vaccination and to show their attitudes toward the immunization of their sons. Their perspectives as parents and physicians will mirror society's consciousness.

## Materials and methods

This national descriptive study was conducted online between May 2022 and December 2022. Ethics committee approval of the study was obtained from Adana City Training and Research Hospital Clinical Research Ethics Committee (No: 76-1320). The questionnaire was designed to determine the knowledge level of the participants about the HPV vaccine and their attitudes regarding vaccinations for their sons. Participants were required to read the fact sheet and declare that they agreed to take part in the survey before participating. The inclusion criteria for the study were that the participant had to be an active physician and have at least one son. A total of 1670 physicians met these criteria and answered all the survey questions. Physicians who were not actively working and did not have at least one son were excluded from the study.

Using the questionnaire, data were collected about the demographics of the participating physicians, their knowledge of HPV, and their attitudes toward vaccinating their sons against the virus. The answers to the survey questions were yes, no, and I do not know, and these responses were ranked on a 4-point Likert scale (agree, do not know, disagree, strongly disagree). Since the data were generally categorical, statistical significance was considered when evaluating the results according to ratios and percentages.

### Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 22.0 statistical software package (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean (standard deviation), and median and minimum-maximum where appropriate. The chi-square test was used to compare categorical variables between the groups. For the comparison of more than two groups, one-way ANOVA was used. The statistical level of significance for all tests was 0.05.

## Results

The mean age of the physicians was 41.6 (8.1). While the number of male physicians was 564 (34.4%), the number of female physicians was 1096 (65.6%). When the frequency of the physicians were examined according to their specialties, the highest rate of participants worked in obstetrics and gynecology (27.9%). Following obstetrics and gynecology, other fields included family physicians (21.8%), pediatrics (7.8%), anesthesiology and reanimation (6.7%), orthopedics (4.8%), and radiology (4.4%). The number of physicians working in public hospitals totaled 704 (42.6%); followed by those working in the university hospital, 422 (25.5%); and clinics, 280 (16.9%). Table 1 shows descriptive statistics for the demographic characteristics of the physicians participating in the research.

Table 1: Demographic characteristics of the participants

| Variables | | n (%) |
|---|---|---|
| **Age**[ŧ] | | 41.65(8.07) |
| **Gender** | Male | 574 (34.4) |
| | Female | 1096 (65.6) |
| **Department** | Family physician | 364 (21.8) |
| | Obstetrics and gynecology | 466 (27.9) |
| | Orthopedics | 80 (4.8) |
| | Radiology | 74 (4.4) |
| | Pediatrics | 130 (7.8) |
| | Internal medicine | 70 (4.2) |
| | Anesthesiology and reanimation | 112 (6.7) |
| | Infectious disease and clinical microbiology | 72 (4.3) |
| | Others | 344 (18.1) |
| **Hospital** | University hospital | 422 (25.5) |
| | Public hospital | 704 (42.6) |
| | Private hospital | 96 (5.7) |
| | Family health center | 152 (9.1) |
| | Own clinic | 280 (16.8) |
| **Male child number**[ŧŧ] | | 1.0 (1-4) |
| **Number of boys aged 0-9** | 1 | 720 (78.3) |
| | 2 | 198 (21.5) |
| | 3 | 2 (0.2) |
| **Number of boys aged 9-18** | 1 | 496 (87.3) |
| | 2 | 72 (12.7) |
| **Number of boys over the age of 18** | 1 | 184 (71.9) |
| | 2 | 72 (28.1) |

[ŧ] mean (SD), SD: standard deviation, [ŧŧ] median(min-max)

Participants' HPV knowledge and HPV vaccine awareness are documented in Table 2. The number of physicians reporting that HPV infection is a rare sexually transmitted disease was 1070 (64.1%). Those physicians who correctly reported the cancer types associated with HPV infection totaled 332 (19.9%), while 1278 (76.5) did not answer this question. While 780 (46.8%) of the participants responded "intramuscularly," about the application of the HPV vaccine, 600 (36.0%) did not have an answer to this question. A total of 664 (39.8%) physicians stated that three doses of HPV vaccine should be administered; however 546 (32.7%) reported two doses as the correct answer, and 388 (23.2%) did not respond. Of the participants, 1596 (95.6%) believed that including the vaccine in the routine vaccination program for girls was necessary. The number of physicians indicating that there were two types of vaccines in Turkey was 844 (50.6%). Furthermore, the number of physicians who knew whether the bivalent or quadrivalent vaccine was approved for use in men was high (54.4% and 54.7%, respectively). It was found to be accurate by all participants that the vaccine would significantly reduce HPV infection and reduce high-grade lesions and genital warts in both sexes and that infection in men causes penile cancers. A total of 1218 (72.9%) physicians approved the necessity of a booster dose application. One hundred four (6.2%) of the physicians stated that they had their sons get the HPV vaccine; 1000 (59.9%) did not, but they thought about getting it, and 72 (4.3%) indicated that they would definitely not have their sons vaccinated. The reason why most of these 72 participants would not have their boys vaccinated with HPV is that the long-term results are not precise (55.6%).

We compared the vaccination status of the participants according to their other demographic characteristics (Table 3). The mean age did not show a statistically significant difference according to HPV vaccination status (*P*=0.073). However, the difference according to gender was substantial, and this significant difference was that the percentage of women being undecided about getting vaccinated (33.0%) was higher than men (23.0%). In comparison, the rate of men thinking of getting vaccinated (65.9%) was higher than women (56.8%) (p=0.024). When the vaccine preferences of the physicians were examined according to hospital information, it was seen that none of the physicians working in the university hospital had the vaccine. In addition, one finding showed that the physicians working in the private hospitals had the highest vaccination rate (25.0%), and the number of physicians who considered not vaccinating was 0 (0.0%). It was further seen that most of the physicians working in the family physician department were in favor of vaccination, and the number of physicians who did not have the vaccination was 0 (0.0%). Physicians working in the obstetrics and gynecology department and those working in the family physician department mostly opted to have it done. However, 16 (6.9%) of the obstetrics and gynecology department physicians considered not having the vaccine. When the vaccination percentages of physicians working in infectious diseases and clinical microbiology were examined, the number of physicians who vaccinated their sons was 0 (0.0%). Among the physicians working in this field, the number of undecided and planning physicians was the same at 32 (44.4%).

Table 2: Participants' HPV knowledge and HPV vaccine awareness

| Variables | | n (%) |
|---|---|---|
| **HPV infection is a rare sexually transmitted disease.** | True | 1070 (64.1) |
| | False | 600 (35.9) |
| **Cancers associated with HPV infection** | Vaginal, vulvar, cervical, anal, lung, penile, oropharynx, | 332 (19.9) |
| | Incomplete answer | 1278 (76.5) |
| | All of them | 58 (3.5) |
| **HPV vaccine administration route** | İntramuscularly | 780 (46.8) |
| | Subcutaneous | 112 (6.7) |
| | Both intramuscular and subcutaneous | 176 (10.6) |
| | I do not know | 600 (36.0) |
| **How many doses of the HPV vaccine are administered?** | 1 | 48 (2.9) |
| | 2 | 546 (32.7) |
| | 3 | 664 (39.8) |
| | >3 | 24 (1.4) |
| | I do not know | 388 (23.2) |
| **At what age is the HPV vaccine administered to boys?** | 0-9 | 62 (3.7) |
| | 9-13 | 270 (16.2) |
| | 9-15 | 314 (18.8) |
| | 9-26 | 280 (16.8) |
| | 11-12 | 72 (4.3) |
| | <15 | 112 (6.7) |
| | 15-26 | 104 (6.2) |
| | >26 | 0 (0.0) |
| | I do not know | 456 (27.3) |
| **It should be included in the routine vaccination program for girls** | Yes | 1596 (95.6) |
| | No | 74 (4.4) |
| **How many types of HPV vaccines are available in Turkey?** | 1 | 106 (6.4) |
| | 2 | 844 (50.6) |
| | 3 | 152 (9.1) |
| | 4+ | 96 (5.8) |
| | I do not know | 470 (28.2) |
| **The bivalent vaccine is approved for use in men.** | Yes | 634 (38.0) |
| | No | 128 (7.7) |
| | I do not know | 908 (54.4) |
| **The quadrivalent vaccine is approved for use in men.** | Yes | 606 (36.3) |
| | No | 150 (9.0) |
| | I do not know | 914 (54.7) |
| **HPV infection can be reduced to 1% with an effective vaccination program.** | Yes | 1670 (100.0) |
| | No | 0 (0.0) |
| **Rappel dose** | Yes | 1218 (72.9) |
| | No | 452 (27.1) |
| **Reduction in high-grade lesions** | Yes | 1670 (100.0) |
| | No | 0 (0.0) |
| **Genital warts can occur in both men and women.** | Yes | 1670 (100.0) |
| | No | 0 (0.0) |
| **The most common HPV-related penile cancers in men** | Yes | 1670 (100.0) |
| | No | 0 (0.0) |
| **Situation and opinion about getting the HPV vaccine** | I had it done | 104 (6.2) |
| | I haven't done it, but I'm thinking of doing it | 1000 (59.9) |
| | I'm undecided | 496 (29.6) |
| | I don't plan to | 72 (4.3) |
| **The reason you don't want to have your son vaccinated against HPV** | Not helpful | 14 (19.4) |
| | Adverse effect | 8 (11.1) |
| | Don't think HPV infection will be | 10 (13.9) |
| | Don't know long-term outcome | 40 (55.6) |

Table 3: Comparison of the vaccination status of the participants according to their demographic characteristics

| | | HPV Vaccination Status | | | | *P*-value |
|---|---|---|---|---|---|---|
| | | Yes, I did | Yes, I will | Undecided | No | |
| **Age**[t] | | 40.5(7.1) | 42.2(7.9) | 41.1(8.2) | 39.3(9.9) | 0.073 |
| **Gender** | Male | 40(7.0) | 378(65.9) | 132(23.0) | 24(4.2) | 0.024 |
| | Female | 64(5.8) | 622(56.8) | 362(33.0) | 48(4.4) | |
| **Hospital** | University hospital | 0(0.0) | 286(67.8) | 104(24.6) | 32(7.6) | <0.001 |
| | Public hospital | 16(2.3) | 448(63.6) | 208(29.5) | 32(4.5) | |
| | Private hospital | 24(25.0) | 48(50.0) | 24(25.0) | 0(0.0) | |
| | Family health center | 16(10.5) | 80(52.6) | 56(36.8) | 0(0.0) | |
| | Own clinic | 48(17.1) | 128(45.7) | 96(34.3) | 8(2.9) | |
| **Department** | Family physician | 24(6.6) | 200(54.9) | 149(38.5) | 0(0.0) | NA |
| | Obstetrics and gynecology | 24(5.2) | 344(73.8) | 66(14.2) | 32(6.9) | |
| | Orthopedic | 0(0.0) | 64(80.0) | 16(20.0) | 0(0.0) | |
| | Radiology | 0(0.0) | 72(97.3) | 2(2.7) | 0(0.0) | |
| | Pediatric | 24(16.5) | 66(50.8) | 40(30.8) | 0(0.0) | |
| | Internal medicine | 0(0.0) | 22(31.4) | 40(57.1) | 8(11.4) | |
| | Anesthesiology and reanimation | 16(14.3) | 40(35.7) | 48(42.9) | 8(7.1) | |
| | Infectious Disease and Clinical Microbiology | 0(0.0) | 32(44.4) | 32(44.4) | 8(11.1) | |
| | Others | 16(5.3) | 160(53.0) | 110(36.4) | 16(5.3) | |

[t]mean (SD), SD: standard deviation

Vaccination status is shown in Table 4, based on the questions asked to measure vaccination knowledge of the participants. Accordingly, most physicians who knew correctly that HPV infection is a rare disease stated that they were undecided (34.7%) or would not vaccinate (5.3%) (*P*=0.033). While 10.3% of the physicians who answered the application method of HPV vaccine correctly stated that they had been vaccinated, 5.6% and 1.3% of the physicians who responded to the question incorrectly or did not answer the question had the vaccine, respectively. A total of 72% of the incorrectly responding participants said they planned to get vaccinated eventually, while 38.7% of those not answering participants said they could not decide what to do. Only 8.6% of doctors who gave the correct answer about HPV vaccination doses reported being vaccinated themselves. In contrast, 44.4% of the physicians who answered this question incorrectly and 44.8% who stated that they did not know the number of doses administered indicated that they were undecided about vaccination. Eleven percent of the physicians who correctly reported the vaccine age for males stated that they had been vaccinated, and 66.7% said they would vaccinate. Those who did not answer this question were mainly undecided about getting vaccinated (*P*<0.001). Physicians who did not consider it necessary to include it in the routine vaccination program for girls were undecided, with a rate of 56.8%. In comparison, 10.8% said they would not be vaccinated (*P*<0.001).

Table 4: Comparison of the vaccination status of the participants according to their vaccination information

| | | HPV Vaccination Status | | | | *P*-value |
|---|---|---|---|---|---|---|
| | | Yes, I did | Yes, I will | Undecided | No | |
| **HPV infection is rare** | Yes (wrong) | 64(6.0) | 680(63.6) | 286(26.7) | 40(3.1) | 0.033 |
| | No (right) | 40(6.7) | 320(53.3) | 208(34.7) | 32(5.3) | |
| **HPV related cancers** | Vaginal, Vulvar, Cervical, Anal, Lung, Penile, Oropharynx | 10(3.0) | 232(69.9) | 76(22.9) | 14(4.2) | 0.032 |
| | Incomplete answer | 88(6.9) | 726(56.8) | 406(31.8) | 58(4.5) | |
| | All of them | 6(10.3) | 40(69.0) | 12(20.7) | 0(0.0) | |
| **HPV vaccine administration route** | Right | 80(10.3) | 456(58.5) | 204(26.2) | 40(5.1) | <0.001 |
| | False | 16(5.6) | 208(72.2) | 56(19.4) | 8(2.8) | |
| | Don't know | 4(1.3) | 168(56.0) | 116(38.7) | 12(4.0) | |
| **HPV vaccine dose number** | Right | 52(8.6) | 381(63.0) | 144(23.8) | 28(4.6) | <0.001 |
| | False | 0(0.0) | 20(55.6) | 16(44.4) | 0(0.0) | |
| | Don't know | 0(0.0) | 99(51.0) | 87(44.8) | 8(4.1) | |
| **Administration of HPV vaccine in boys** | Right | 4(11.1) | 24(66.7) | 8(22.2) | 0(0.0) | <0.001 |
| | False | 58(8.4) | 380(66.5) | 123(21.5) | 20(3.5) | |
| | Don't know | 0(0.0) | 96(42.1) | 116(50.9) | 16(7.0) | |
| **HPV vaccine should be a routine for girls** | Yes | 44(5.5) | 496(62.2) | 226(28.3) | 32(4.0) | <0.001 |
| | No | 8(21.6) | 4(10.8) | 21(56.8) | 4(10.8) | |
| **Types of HPV Vaccines in Turkey** | Right | 24(5.7) | 269(63.7) | 113(26.8) | 16(3.8) | <0.001 |
| | False | 24(13.6) | 116(65.5) | 33(18.6) | 4 (2.3) | |
| | Don't know | 4(1.7) | 114(48.5) | 101(43.0) | 16(6.8) | |
| **Bivalent vaccine approved in male** | Yes | 32(10.1) | 224(70.7) | 45(14.2) | 16(5.0) | <0.001 |
| | No | 4(6.2) | 58(90.6) | 2(3.1) | 0(0.0) | |
| | Don't know | 16(3.5) | 218(48.0) | 200(44.1) | 20(4.4) | |
| **Quadrivalent vaccine approved in male** | Yes | 31(10.2) | 220(72.6) | 41(13.5) | 11(3.6) | <0.001 |
| | No | 1(1.3) | 54(72.0) | 20(26.7) | 0(0.0) | |
| | Don't know | 20(4.4) | 226(49.5) | 186(40.7) | 25(5.5) | |
| **A booster dose is necessarily** | Yes | 36(5.9) | 349(57.3) | 203(33.3) | 21(3.4) | <0.001 |
| | No | 16(7.1) | 151(66.8) | 44(19.5) | 15(6.6) | |

Physicians who stated they were unaware of the HPV vaccine types available in Turkey were divided into three groups: 48.5% said they would receive the vaccine, 43.0% were undecided, and 6.8% said they would not (*P*<0.001). Stating that the bivalent vaccine is approved for use in men, 90.6% of those who answered incorrectly stated that they would be vaccinated, while 10.1% of those who responded correctly said that they already had the vaccine. On the other hand, 44.1% of those who did not know were undecided about getting vaccinated. Ten percent of the physicians who answered correctly that the quadrivalent vaccine was approved for use in men had been vaccinated. In addition, 40.7% of those who did not know about the approval for use stated that they were undecided about getting the vaccine, while 25.5% stated that they would not. While 33.3% of those who said yes to rappel dosing were uncertain about getting vaccinated, 19.5% of those who said no to rappel dosing were undecided (*P*<0.001).

## Discussion

In the literature, there are no studies evaluating physicians' attitudes toward giving the HPV vaccine to their sons; the current study closes this research gap. More than 90% of anal cancers in men are caused by HPV 16 and HPV 18. In addition, most oropharyngeal and penile cancers are caused by HPV infection. Compared to the incidence of cervical cancer, the incidence of penile cancer is very low. Nevertheless, protecting men with the HPV vaccine is very important in terms of immunization.

The contribution of male immunization to female and community vaccination should be considered, as it is necessary to vaccinate both sexes for a fully immunized population [12]. As previously indicated, a significant barrier to immunization in many developing countries is the lack of public funding [13]. In our study, 95.6% of the participants believed that it is necessary to include the vaccine in the routine vaccination program for girls, while 59.9% reported that they did not vaccinate their boys but planned to do so. In a recent study involving nurses and midwives, it was found that 98% of the respondents did not get vaccinated, and only 34% had recommended the vaccine to someone [14]. This showed that the level of positive awareness among physicians about the vaccination of girls was quite good, but the same was not valid for boys. We believe that with the increase in physicians' knowledge level about the threats posed by HPV infections for boys, similar results will be obtained for both genders.

HPV infections, which causes cancer to develop in women and men, can be prevented by vaccination. However, since the HPV vaccine is not included in the immunization program in Turkey, it is applied in line with the physicians' recommendations. A previous study reported that the most influential factor for families to get the HPV vaccine was the recommendation of the physician [15,16]. Studies have indicated that physicians' attitudes in recommending the HPV vaccine are related to a lack of knowledge [17–19]. In our study, when the answers were given to information questions such as the incidence of HPV infections and which types cause cancer, the number of those who gave correct answers was low. Tasar et al. [20] reported that most of the participants in their study considered themselves to have sufficient knowledge about the HPV vaccine, and only 14.3% of them felt inadequate. According to our study results, the rate of correct answers to the questions about HPV by the participating physicians was low. However, it was confirmed by all participants that the vaccine would drastically reduce HPV infection, and reduce high-grade lesions and genital warts.

There are differences between female and male physicians regarding knowledge and attitudes about the HPV vaccine. In our study, 65.9% of male and 56.8% of female physicians considered vaccinating their sons. In previous studies of physician attitudes toward the HPV vaccine, it was observed that female physicians exhibited more positive attitudes [21,22]. Kartal et al. [23] reported similar results in their study. They attributed this to female physicians' increased sensitivity to HPV infections, primarily because of women's high cancer incidence. We attribute the reason why male physicians show more positive attitudes toward HPV vaccine administration to boys to the same reason.

Physicians' attitudes toward the HPV vaccine vary according to their specializations. In our study, the practice fields of the physicians who were most apt to vaccinate their sons were radiology (97.3%), orthopedics (80%), and gynecology (78.8%). In a study conducted in Turkey, it was reported that the idea of starting the HPV immunization program for the pediatric and adolescent population by family medicine, pediatrics, gynecology, and obstetrics doctors was significantly higher than in other fields [24]. Previous studies reported that 60% of family physicians, more than 90% of pediatricians, and 79% of obstetricians and gynecologists recommend the HPV vaccine to their patients [25,26]. Topcu et al. [27] reported that 85% of obstetricians and 78% of pediatric and family physicians recommended vaccinations. The reason our study obtained different results from previous studies is the questioning of attitudes about administering the HPV vaccine to boys. In previous studies, recommendation status was questioned without gender determination. We think that the fact that the number of male physicians is generally higher in radiology and orthopedics is reflected in this result.

The most important contribution of this study is that many physicians participated. It is also the first study to examine physicians' approach to their sons regarding vaccinations. Our study determined that the physicians who stated they would not give HPV vaccine to their sons were most frequently specialists in anesthesia and animation, infectious diseases, and clinical microbiology. We attribute the most important reason for this situation to the high number of female physicians, especially in these specialties. We believe that gender-related empathy influences the attitude toward vaccinating boys.

**Limitations**

A limitation of this study is that the attitudes of male and female physicians for each specialty were not evaluated separately. For this, it would be necessary to design multicenter studies over an extended period.

**Conclusion and recommendations**

This study determined that physicians in some specialties had hesitations about giving the HPV vaccine to boys. We believe these results are significant, because they may indicate the situation in developing nations. Furthermore, societies and medical specialists should make recommendations for the HPV vaccine. This would positively contribute to increasing vaccine awareness among physicians. Considering the results of this study and looking at the accuracy rates of the answers, studies addressing education on HPV vaccines are also needed.

**Acknowledgements**

We would like to thank all of the doctors who participated in this study.

## References

1. Einstein MH, Goldberg GL. Human papillomavirus and cervical neoplasia. Cancer Invest. 2002;20(7-8):1080-5.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Du J, Nordfors C, Ahrlund-Richter A, Sobkowiak M, Romanitan M, Näsman A, et al. Prevalence of oral human papillomavirus infection among youth, Sweden. Emerg Infect Dis. 2012;18(9):1468-71.
4. Hanley SJ, Yoshioka E, Ito Y, Kishi R. HPV vaccination crisis in Japan. Lancet. 2015;385(9987):61152-7.
5. Schuler CL, Hanley CJ, Coyne-Beasley T. Misconception: Human papillomavirus vaccine and infertility. Clin Pediatr (Phila). 2014;53(2):158-65.
6. Suppli CH, Hansen ND, Rasmussen M, Valentiner-Branth P, Krause TG, Mølbak K. Decline in HPV-vaccination uptake in Denmark - The association between HPV-related media coverage and HPV-vaccination. BMC Public Health. 2018;18(1):1360-8.
7. Bruni L, Saura-Lázaro A, Montoliu A, Brotons M, Alemany L, Diallo MS, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010–2019. Prev Med (Baltim). 2021;144:1-12.
8. Näsman A, Du J, Dalianis T. A global epidemic increase of an HPV-induced tonsil and tongue base cancer - potential benefit from a pan-gender use of HPV vaccine. J Intern Med. 2020;287(2):134-52.
9. Drolet M, Bénard É, Pérez N, Brisson M; HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019;394(10197):497-509.
10. Gilca V, Boulianne N, Dubé E, Sauvageau C, Ouakki M. Attitudes of nurses toward current and proposed vaccines for public programs: a questionnaire survey. Int J Nurs Stud. 2009;46(9):1219-35.
11. Zimet GD, Mays RM, Fortenberry JD. Vaccines against sexually transmitted infections: promise and problems of the magic bullets for prevention and control. Sex Transm Dis. 2000;27(1):49-52.
12. Shabbir M, Barod R, Hegarty PK, Minhas S. Primary prevention and vaccination for penile cancer. Ther Adv Urol. 2013;5(3):161-9.
13. Mete B, Utuk FA, Demirhindi H, Inaltekin A, Tanır F, Kara E, Nazlıcan E. Human papillomavirus vaccine administration among women in the Eastern Mediterranean region of Turkey: prevalence and barriers. Eur Rev Med Pharmacol Sci. 2023;27(8):3526–33.
14. Beyazgül B, Cindoğlu Ç, Koruk İ. The relationship of stress, self-efficacy and sociodemographic factors among physicians during the COVID-19 pandemic. J Surg Med. 2023;7(6):369–74.
15. Davis K, Dickman ED, Ferris D, Dias JK. Human papillomavirus vaccine acceptability among parents of 10- to 15-year-old adolescents. J Low Genit Tract Dis. 2004;8(3):188-94.
16. Stokley S, Curtis CR, Jeyarajah J, Harrington T, Gee J, Markowitz L. Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States. Morb Mortal Wkly Rep. 2013;62(29):591–5.
17. Kahn JA, Zimet GD, Bernstein DI, Riedesel JM, Lan D, Huang B, et al. Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes. J Adolesc Health. 2005;37(6):502-10.
18. Daley MF, Liddon N, Crane LA, Beaty BL, Barrow J, Babbel C, et al. A national survey of pediatrician knowledge and attitudes regarding human papillomavirus vaccination. Pediatrics. 2006;118(6):2280-9.
19. Esposito S, Bosis S, Pelucchi C, Begliatti E, Rognoni A, Bellasio M, et al. Pediatrician knowledge and attitudes regarding human papillomavirus disease and its prevention. Vaccine. 2007;25(35):6437-46.
20. Taşar S, Bal Yüksel E, Sağcan D, Karadağ Öncel E, Kara Aksay A, Yılmaz Çiftdoğan D. Knowledge and Attitudes of Pediatricians to The Human Papilloma Virus Vaccines. Forbes J Med. 2021;2(1):19-24.
21. Duval B, Gilca V, McNeil S, Dobson S, Money D, Gemmill IM, et al. Vaccination against human papillomavirus: a baseline survey of Canadian clinicians' knowledge, attitudes and beliefs. Vaccine. 2007;25(45):7841-7.
22. Riedesel JM, Rosenthal SL, Zimet GD, Bernstein DI, Huang B, Lan D, et al. Attitudes about human papillomavirus vaccine among family physicians. J Pediatr Adolesc Gynecol. 2005;18(6):391-8.
23. Kartal M. What do primary care physicians know about cervical cancer and HPV vaccine? Turkiye Aile Hekim Derg. 2011;15(1):1-6.
24. Güner PD, Gözükara KH. Factors influencing decision - Making for HPV vaccination of female doctors for their children. Ankara Med J. 2019;18(3):539-49.
25. Revanlı RA, Yüceer C, Şenol E, Azap A, Erbay A, Alp-Çavuş S, et al. Aile hekimlerinin İnsan papilloma virusu ve zona aşıları hakkındaki bilgi düzeyleri ve tutumlarının araştırılması. Klimik Derg. 2016;29(1):15-20.
26. Tan J, Farrell L, Allen DG. The attitudes of Australian gynaecologists to HPV vaccination: an ASCCP survey. Aust N Z J Obstet Gynaecol. 2010;50(5):472-7.
27. Topcu S, Ulukol B, Emuler DS, Topcu HO, Peker GC, Dokmeci F, et al. Physicians' awareness and approaches to human papillomavirus infection and vaccination. Cukurova Med J. 2018;43(2):326-31.

J Surg Med. 2023;7(8):446-449.
DOI: 10.28982/josam.7842

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Removal of foreign objects seen in the upper gastrointestinal tract with the help of endoscopy: A retrospective cohort study

**Alpaslan Fedayi Çalta**

Department of General Surgery, Bandırma Onyedi Eylül University Faculty of Medicine, Balıkesir, Turkey

**ORCID ID of the author(s)**

AFÇ: 0000-0001-8372-0991

**Corresponding Author**
Alpaslan Fedayi Çalta
Department of General Surgery, Bandirma State Hospital, Ayyıldıztepe Mah. Çanakkale yolu asfaltı 6. Km 10200, Balikesir, Turkey
E-mail: acalta@bandirma.edu.tr

**Ethics Committee Approval**
The study was approved by Bandırma Onyedi Eylül University Ethics Committee with the decision numbered 2023-71 on April 13, 2023. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 14

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Delay in diagnosing and treating gastrointestinal (GI) tract foreign bodies may lead to serious complications. In this study, we aimed to retrospectively evaluate the patients who underwent emergency upper GI endoscopy for foreign body ingestion in our clinic.
**Methods:** Between 2015 and 2022, we evaluated 68 patients who underwent emergency upper GI endoscopy with a prediagnosis of foreign body ingestion. The evaluation included factors such as age, gender, presenting complaints, foreign body type, localization, and treatment parameters.
**Results:** Out of the 68 patients included in the study, 21 (30.89%) were female, and the mean age was 54.00 years. Among them, 43 (63.23%) presented with no active complaints, 23 (33.82%) with dysphagia and odynophagia, and two (2.94%) with vomiting. The swallowed objects were classified as follows: coin (n=2), pin (n=5), battery (n=11), drug plaque (n=6), esophageal foreign body (n=7), piece of meat (n=5), chicken bone (n=4), fish bone (n=5), razor (n=7), lighter (n=3), and toothpick (n=1). The foreign bodies were located in the esophagus in 23 cases (33.82%), in the stomach in 32 cases (47.05%), and in the duodenum in one case (1.47%). For 12 patients (17.64%), the foreign body could not be detected endoscopically but was detected using radiologic methods. Among the foreign bodies, 54 (79.41%) were successfully removed. In one patient (1.47%) who could not be removed endoscopically and another patient (1.47%) who developed gastrointestinal perforation due to a foreign body (toothpick), a surgical procedure was performed.
**Conclusion:** Early diagnosis and treatment of foreign body ingestion are crucial in preventing serious complications. Endoscopy, a minimally invasive procedure, can be a safe alternative to surgical procedures, which may carry higher morbidity and mortality risks.

**Keywords:** gastrointestinal tract, endoscopy, foreign body, minimally invasive approach

## Introduction

Gastrointestinal tract (GI) foreign bodies can result in significant morbidity and mortality, particularly in vulnerable populations such as children, the elderly, and psychiatric patients. Notably, around 85% of foreign bodies are asymptomatic and naturally expelled from the body through peristalsis. However, certain foreign bodies may necessitate endoscopic or surgical intervention [1].

Ingestion of foreign bodies can occur in adult patients, particularly in cases of accidental ingestion of needles, inadequately chewed pieces of meat, and animal bones that fail to progress through esophageal peristalsis and end up invading the mucosa. Additionally, it may also be observed in psychiatric populations and among prisoners attempting voluntary suicide while in prison. While some swallowed foreign bodies may pass through the digestive system without causing harm, sharp-edged objects, impaired gastrointestinal motility, and large objects that cannot progress may lead to significant morbidity and mortality [2].

The initial step in the diagnosis involves a detailed history and physical examination. While some patients may exhibit gastrointestinal symptoms, others may remain asymptomatic. The shape and localization of the ingested foreign body and the patient's age and body structure play a crucial role in developing complications and gastrointestinal symptoms [3]. The most frequently reported symptoms include dysphagia, odynophagia, a choking sensation, and vomiting [4]. Prompt diagnosis and treatment are essential for foreign bodies in the gastrointestinal system. In this regard, physical examination is complemented by radiologic imaging for accurate diagnosis [5].

Delay in diagnosing and treating gastrointestinal foreign bodies may result in life-threatening complications, including perforation and obstruction. The size, location, shape, and duration of time elapsed after ingestion are crucial factors influencing the development of complications [6].

Endoscopy presents a minimally invasive alternative when compared to surgery. In this study, we have highlighted the significance of upper GI endoscopy for patients admitted to our clinic with foreign body ingestion.

## Materials and methods

Between January 2015 and January 2022, we conducted a retrospective evaluation of 74 patients who presented to the emergency department of our hospital with foreign body ingestion.

Six of the admitted patients refused treatment and left the hospital. For all patients admitted to the emergency department with a history of foreign body ingestion, the primary evaluation involved a physical examination followed by direct radiography. In cases where opacity was observed on the direct radiography, the patients underwent upper GI endoscopy. Those who did not show opacity on direct radiography but had a reliable history of foreign body ingestion were included in the endoscopy procedure. On the other hand, patients with low reliability in their anamnesis underwent computed tomography.

The endoscopy procedures were carried out using single-channel endoscopes (EPX-3500 HD, Fujifilm, Singapore; EPK- i5000, Pentax, Japan) by endoscopists with 5 years of experience.

The inclusion criteria for this study were being over 18 years of age and providing consent for endoscopic procedures. Patients who could not be anesthetized, those who refused to undergo endoscopic procedures, and individuals below 18 years of age were excluded from the study.

We evaluated 68 patients who underwent emergency upper GI endoscopy for foreign body ingestion. The assessment focused on various aspects, including age, gender, symptoms, physical examination results, radiological findings, type and localization of the foreign body, and the treatment method used.

This study received approval from the Bandırma Onyedi Eylül University Ethics Committee on April 13, 2023, under decision number 2023-71.

**Statistical analysis**

All data analyses were conducted using SPSS statistical software program, version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Chi-square test or Fisher's exact test was utilized for the statistical analysis of categorical data. Ratios were calculated with a 95% confidence level. A *P*-value <0.05 was deemed statistically significant.

## Results

Of the 68 patients included in the study, 21 (30.89%) were female, and 47 (69.11%) were male. The mean age of the patients was 54.00 (14.33) years, with an age range of 22–90 years. Among the patient population, 16 patients (21.2%) had a psychiatric diagnosis (1 with schizophrenia and 15 with psychosis), while 33 patients (48.50%) were prisoners.

When analyzing the patients' complaints, 43 (63.23%) had no active complaints, 23 (33.82%) presented with dysphagia and odynophagia, and two (2.94%) presented with vomiting. The ingested objects were classified as follows: coin (n=2) (Figure 1), pin (n=5), battery (n=11) (Figure 2), drug plaque (n=6), esophageal foreign body (n=7), meat piece (n=5), chicken bone (n=4), fish bone (n=5), razor blade (n=7), lighter (n=3), and toothpick (n=1).

Figure 1: Multiple coins arranged in a row (endoscopic image).

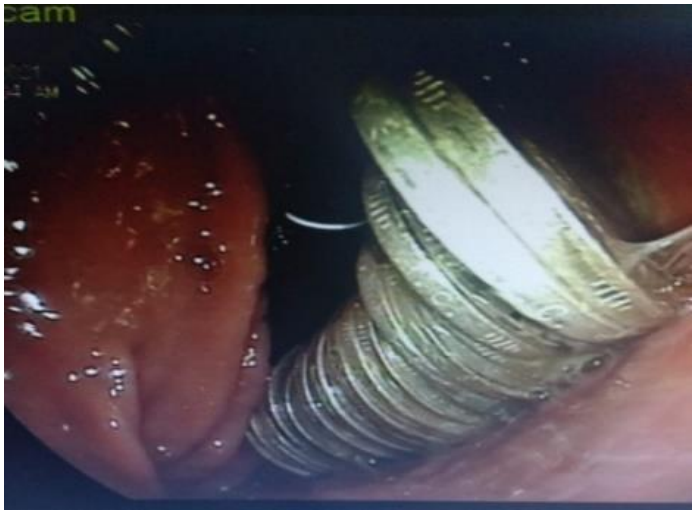
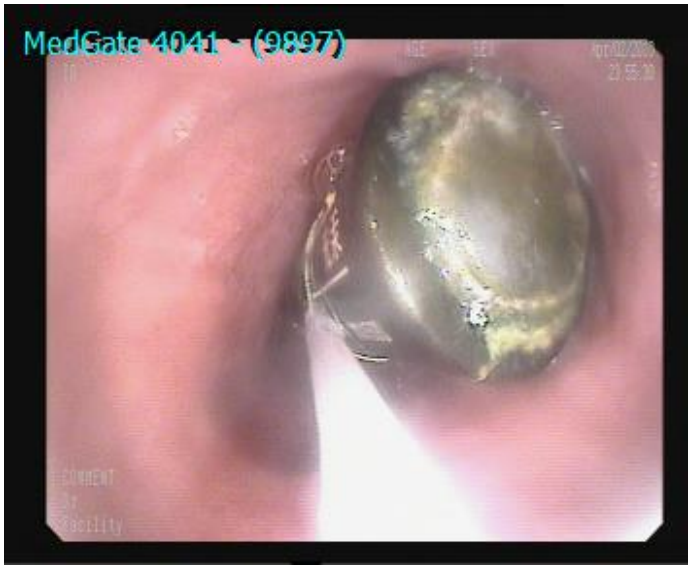


Figure 2: Endoscopic image of swallowed AA battery in the stomach.




All the patients who ingested batteries (AA type and AAA type alkaline batteries) as foreign objects were prisoners. Patients who ingested unchewed meat and chicken bones were mostly elderly (median age 68.00 years, n=32). Esophageally implanted foreign objects, pins, drug plates, batteries, razor blades, lighters, and toothpicks were found in young and middle-aged patients (median age 34.00 years, n=36).

When evaluating the localizations of the foreign bodies, 33.82% were located in the esophagus (n=23), 47.05% in the stomach (n=32), and 1.47% in the duodenum (n=1) (Table 1).

Table 1: Demographic characteristics, foreign body symptoms, types and localizations of the patients.

| **Parameter** | |
|---|---|
| **Age mean (SD), year** | 54.00 (14.33) |
| **Sex** | n (%) |
| Female | 21 (30.89%) |
| Male | 47 (69.11%) |
| **Application complaint** | n (%) |
| Asymptomatic | 43 (63.23%) |
| Dysphagiaandodynophagia | 23 (33.82%) |
| Vomiting | 2 (2.94%) |
| **Foreign body** | n |
| Coin | 2 |
| Pin | 5 |
| Battery | 11 |
| Drugplaque | 6 |
| Implanted in the esophagus | 7 |
| Meatpiece | 5 |
| Chicken bone | 4 |
| Fishbone | 5 |
| Razorblade | 7 |
| Lighter | 3 |
| Toothpick | 1 |
| **Foreign body location** | n (%) |
| Esophagus | 23 (33.82%) |
| Gastric | 32 (47.05%) |
| Duodenum | 1 (1.47%) |

n: number, SD: Standard deviation.

Among the patients with foreign bodies in the esophagus, 22 (95.6%) presented with odynophagia within the first 24 h, while only one (4.4%) patient experienced odynophagia after 24 h. Following anamnesis, direct radiography was performed on all patients. Upper GI endoscopy was conducted in 51 (75.00%) patients who showed opacity on direct radiography. Additionally, endoscopy was performed in 11 (16.17%) patients based on high reliability of anamnesis, even when no opacity was observed on direct radiography, but there was a history of foreign body ingestion. Computed tomography was used as an advanced imaging procedure in six (8.82%) patients with low reliability in anamnesis. In these six cases, endoscopy confirmed the presence of foreign bodies.

Based on the anamnesis, the patients were admitted to the emergency department within a median of 12 h (min–max, 2–74 h). In 54 (79.41%) patients, the foreign body was successfully removed through emergency endoscopy. However, in 12 (17.64%) patients, the foreign body could not be detected even with the advancement of the endoscopy to the second part of the duodenum. These patients were subsequently followed up as outpatients and allowed to pass the foreign body spontaneously. In the followed-up patient group, spontaneous expulsion occurred within a median time of 24 h (min–max, 8–72 h).

In one (1.47%) patient, the foreign body could not be removed using a gastroduodenoscope, and as a result, the foreign body embedded in the gastric mucosa had to be surgically removed. Fortunately, no complications were reported during the surgical procedure.

Gastrointestinal perforation occurred as a complication related to the foreign body (toothpick) in one (1.47%) patient, leading to the need for emergency surgery. During surgical exploration, it was discovered that the patient had gastric perforation, and the stomach was repaired primarily.

Regarding the battery group, endoscopic removal of the foreign body was successful in seven patients (10.29%), while in four patients (5.88%), endoscopy could not detect the foreign body, and it was allowed to pass spontaneously. Additionally, mucosal erosion was found in five (7.35%) battery ingestion cases.

## Discussion

Detailed anamnesis and physical examination are essential for diagnosing ingested foreign bodies. Patients may either be symptomatic or asymptomatic. The shape, localization, structure of the object, age of the patient, and the development of complications all play a role in the emergence of symptoms and signs. The most common symptoms and complaints include pain or discomfort while swallowing, a choking sensation, and vomiting with or without blood [7]. In our study, 43 patients (63.23%) had no active complaints, 23 patients (33.82%) presented with dysphagia and odynophagia, and two patients (2.94%) presented with vomiting.

Foreign bodies in the gastrointestinal system are among the conditions that require urgent diagnosis and treatment. Radiologic imaging methods should be effectively used for diagnosis. The diagnosis can be made through anamnesis and direct radiography. However, objects like glass, plastic, fabric, and wooden items may not be visible on direct radiography. Approximately 88% of ingested foreign bodies are radiopaque, allowing them to be visualized on direct radiographs, including those of the neck and thorax. Computed tomography (CT) may aid in identifying and locating foreign bodies, or gastroscopy may be performed for both diagnosis and treatment [8]. In our study, CT was used as an advanced imaging procedure in six patients (8.82%) with low reliability in anamnesis, and endoscopy was performed upon detecting a foreign body.

Once the diagnosis is made using imaging methods, treatment can be provided through endoscopy as the first option, surgical intervention when necessary, or spontaneous passage in appropriate cases. Approximately 80–90% of swallowed foreign

bodies can pass spontaneously, while endoscopic removal is required in 10–20% of cases, and surgical removal is necessary in less than 1% of cases [9]. Small foreign bodies that are radiopaque and have no sharp edges can be monitored without intervention using direct radiographs [10]. However, objects wider than 2 cm and longer than 10 cm require endoscopic removal as they cannot pass the pylorus [11]. In our study, only one patient (1.47%) underwent a surgical procedure, and the foreign body was successfully removed.

Foreign bodies may disrupt the digestive tract spontaneously or cause impaction, obstruction, perforation, and fistulization [12]. Wang et al. [13] reported an overall complication rate of 4.5%. In our study, one patient (1.47%) experienced gastrointestinal perforation due to a foreign body (toothpick)-related complication, leading to emergency surgery.

Velitchkov et al. [14] reported psychosis in 22.9% of 542 adult patients. A study by Misdrahi et al. [15] found that water intake decisions were influenced by the negative effect of antipsychotic drug non-compliance on treatment efficacy, with rates ranging between 11-80%. Bayindir et al. [16] supported suicidal behavior.

When alkaline batteries come into contact with salty human tissue, they release sodium hydroxide and chlorine gases, causing denaturation and necrosis [17]. One of the most important questions in battery ingestion cases is determining when to perform endoscopic intervention. Anderson et al. [18] reported that in 85% of cases, batteries easily passed through the gastrointestinal tract. Akay [19] emphasized in their study that in cases of battery ingestion in those with stomach ulcers, urgent endoscopic intervention should be performed to remove the batteries instead of allowing them to pass spontaneously.

In our study, among the patients in the battery group, endoscopic removal of the foreign body was performed in seven patients (10.29%), while in four patients (5.88%), endoscopy did not detect the battery, and it was left to pass spontaneously. Notably, the battery group consisted entirely of inmate patients, as the incidence of foreign body ingestion is higher in prisoners or due to psychiatric disorders [20]. The psychiatric examination of the 33 patients evaluated in the prisoner group found that the entire group swallowed foreign bodies as a reaction, with no patients exhibiting suicidal intent.

**Limitations and strengths**

Our study has both limitations and strengths. The main limitation is that it was retrospective. Additionally, the study's sample size was relatively small, which is another limitation. However, it is worth noting that foreign body ingestion patients are not a common population, and we believe that sharing this study with the literature will be valuable for future research endeavors.

**Conclusion**

In conclusion, foreign bodies in the gastrointestinal tract generally do not require surgical intervention and can often be removed endoscopically. However, it is essential to keep in mind that surgery may become necessary in certain cases due to complications. The flexible endoscope is an effective and safe method for removing gastrointestinal foreign bodies.

## References


1. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, et al. Complications of upper GI endoscopy. Gastrointest Endosc. 2002;55(7):784-93. PMID: 12024128 doi: 10.1016/s0016-5107(02)70404-5.
2. Coşkun S. Endoscopic removal of multiple esophagogastric foreign bodies without complication. J Contemp Med 2022;12(2):377-383. doi:10.16899/jcm.985835.
3. Obinwa O, Cooper D, O'Riordan JM, Neary P. Gastrointestinal Foreign Bodies. Actual Problems of Emergency Abdominal Surgery. 2016;75-94. doi: 10.5772/63464.
4. Diaconescu S, Gimiga N, Sarbu I, Stefanescu G, Olaru C, Ioniuc I, et al. Foreign Bodies Ingestion in Children: Experience of 61 Cases in a Pediatric Gastroenterology Unit from Romania. Gastroenterol Res Pract. 2016;2016:1982567. PMID: 26949384 doi: 10.1155/2016/1982567.
5. Kafadar S, Kafadar H. Gastrointestinal Yabancı Cisim Olgularının incelenmesi. ADYÜ Sağlık Bilimleri Derg. 2019;5(2):1620-7. doi: 10.30569/adiyamansaglik.593467.
6. Hong KH, Kim YJ, Kim JH, Chun SW, Kim HM, Cho JH. Risk factors for complications associated with upper gastrointestinal foreign bodies. World J Gastroenterol 2015;21:8125-31. doi: 10.3748/wjg.v21.i26.8125.
7. Smith MT, Wong RK. Esophageal foreign bodies: types and techniques for removal. CurrTreat Options Gastroenterol. 2006;9(1):75-84. PMID: 16423316 doi: 10.1007/s11938-006-0026-3.
8. Weiland ST, Schurr MJ. Conservative management of ingested foreign bodies. J GastrointestSurg. 2002;6(3):496-500. PMID: 12023005 doi: 10.1016/s1091-255x(01)00027-0.
9. Webb WA. Management of foreign bodies of the upper gastrointestinal tract: update. Gastrointest Endosc. 1995;41(1):39-51. PMID: 7698623 doi: 10.1016/s0016-5107(95)70274-1.
10. Litovitz T, Schmitz BF. Ingestion of cylindrical and button batteries: an analysis of 2382 cases. Pediatrics.1992;89:747-57. PMID: 1557273.
11. Guelfguat M, Kaplinskiy V, Reddy SH, DiPoce J. Clinical guidelines for imaging and reporting ingested foreign bodies. Am J Roentgenol. 2014;203(3):694. PMID: 24951194 doi: 10.2214/AJR.13.12185.
12. Litovitz T, Whitaker N, Clark L, White NC, Marsolek M. Emerging battery-ingestion hazard: clinical implications. Pediatrics. 2010;125(6):1168-77. PMID: 20498173 doi: 10.1542/peds.2009-3037.
13. Wang X, Zhao J, Jiao Y, Wang X, Jiang D. Upper gastrointestinal foreign bodies in adults: A systematic review. Am J EmergMed. 2021;50:136-41. PMID: 34365062 doi: 10.1016/j.ajem.2021.07.048.
14. Velitchkov NG, Grigorov GI, Losanoff JE, Kjossev KT. Ingested foreign bodies of the gastrointestinal tract: retrospective analysis of 542 cases. World journal of surgery, 1996;20(8):1001–5. PMID: 8798356 doi: 10.1007/s002689900152.
15. Misdrahi D, Llorca PM, Lancon C, Bayle FJ. Compliance in schizophrenia: predictive factors, therapeutical considerations and research implications. Encephale, 2002;28(3):266-72. PMID: 12091789.
16. Bayındır S, Koçyiğit F, Kahraman M. Interesting Suicidal Attempt of Schizophrenia Patient: Nine Cylindrical Batteries in Abdomen. J ClinPsy. 2016;19(1):52-5. doi: 10.5505/kpd.2016.43531.
17. Hammami MB, Alkaade S, Piraka C, Taylor JR. Endoscopic Retrieval vs Observation in Cylindrical Battery Ingestion. Ochsner J. 2019;19(2):157-65. PMID: 31258428 doi: 10.31486/toj.18.0020.
18. Anderson KL, Dean AJ. Foreign bodies in the gastrointestinal tract and anorectal emergencies. EmergMedClin North Am. 2011;29(2):369-ix. PMID: 21515184 doi: 10.1016/j.emc.2011.01.009.
19. Akay T. Should we remove the alkaline batteries, which are got caught in upper gastrointestinal segment, immediately? Clinical and Experimental Health Sciences. 2020;10(3):275-8. doi: 10.33808/clinexphealthsci.687517.
20. O'Sullivan ST, Reardon CM, McGreal GT, Hehir DJ, Kirwan WO, Brady MP. Deliberate ingestion of foreign bodies by institutionalised psychiatric hospital patients and prison in mates. Irishjournal of medicalscience, 1996;165(4):294–6. PMID: 8990660 doi: 10.1007/BF02943095.

J Surg Med. 2023;7(8):450-457.
DOI: 10.28982/josam.7857

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Colchicine is an effective therapeutic agent in erosive hand osteoarthritis

**Adem Ertürk [1], Alper Sarı [2]**

[1] Division of Rheumatology, Department of Internal Medicine, Afyonkarahisar Health Sciences University Faculty of Medicine, Afyonkarahisar, Turkey
[2] Department of Internal Medicine, Afyonkarahisar Health Sciences University Faculty of Medicine, Afyonkarahisar, Turkey

**ORCID ID of the author(s)**

AE: 0000-0001-8882-0692
AS: 0000-0002-4327-8032

**Corresponding Author**
Adem Erturk
Division of Rheumatology, Department of Internal Medicine, Afyonkarahisar Health Sciences University Faculty of Medicine, Afyonkarahisar, Turkey
E-mail: drademerturk@hotmail.com

**Ethics Committee Approval**
The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (decision date: April 7, 2023; decision number: 2023/193).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 14

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** The efficacy of colchicine has been assessed in hand osteoarthritis; however, no studies have investigated its use in the more severe subtype of hand osteoarthritis, known as erosive hand osteoarthritis (EHOA). This retrospective cohort study investigated whether colchicine therapy could provide symptomatic relief and improve inflammation markers in patients with EHOA.
**Methods:** The study included a total of 43 EHOA patients using colchicine (2×0.5 mg) + paracetamol (3×500 mg) daily (colchicine group) and 43 EHOA patients using only paracetamol (3×500 mg) (standard therapy group). Both groups were evaluated for various parameters.
**Results:** The groups were similar in terms of age, sex distribution, and other sociodemographic variables. The decreases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels from baseline were significantly greater in the colchicine group ($P$<0.001). Additionally, the visual analog scale (VAS) and Australian Canadian Osteoarthritis Hand Index (AUSCAN) scores, which include pain, stiffness, function, and total score, were significantly better in the colchicine group at 3 months compared to the standard therapy group ($P$<0.001). Furthermore, although both groups showed significant improvements in these parameters, the amount of improvement was significantly greater in the colchicine group ($P$<0.001).
**Conclusion:** The combined use of colchicine and paracetamol improved CRP and ESR levels, VAS score, and all AUSCAN scores in patients with EHOA. Moreover, these benefits were significantly greater than standard therapy with paracetamol alone. Colchicine appears to be an effective therapeutic agent in the treatment of EHOA.

**Keywords:** erosive hand osteoarthritis, colchicine, Australian Canadian Osteoarthritis Hand Index, visual analog scale, erythrocyte sedimentation rate, C-reactive protein

How to cite: Ertürk A, Sarı A. Colchicine is an effective therapeutic agent in erosive hand osteoarthritis. J Surg Med. 2023;7(8):450-457.

## Introduction

Osteoarthritis is the most prevalent type of arthritis worldwide, affecting nearly 10% of males and 18% of females aged 60 and above [1,2]. The knee joints are the most commonly affected, followed by the joints of the hands and hips [3]. Hand osteoarthritis (HOA) is particularly common among older populations, with a prevalence of up to 80%, and typically presents with mild symptoms [4].

Three types of HOA have been described: erosive HOA (EHOA), nodal or non-erosive HOA (non-EHOA), and first carpometacarpal joint osteoarthritis [3]. EHOA is the most aggressive form and is estimated to occur in 2.8% of individuals older than 55 years [4]. It presents with an acute onset of pain, joint swelling, and redness (Figure 1). Radiological findings include central joint erosion, gull-wing lesions (saw-tooth appearance), collapse of the subchondral bone, marginal osteophytes, and, rarely, ankylosis (Figure 2) [3,5]. The debate remains on whether EHOA should be considered a completely different type of HOA or a more serious clinical form of non-EHOA [5]. However, it is established that individuals with EHOA experience more severe hand pain and have a higher risk of disability and joint deformity, resulting in worse health-related quality of life compared to subjects with non-EHOA [6,7]. Only a few effective treatments for EHOA address symptoms but have no known benefit in preventing the disease or limiting its progression [4,5]. Although the pathophysiology of EHOA is not fully understood, these data suggest that EHOA differs from non-EHOA in its pathophysiology, which could warrant differences in management [4].

Figure 1: Clinical features of erosive hand osteoarthritis: Demonstrating soft swelling (marked by asterisks) of the proximal and distal interphalangeal joints. Demonstrating deformity and bony enlargement (nodes) of proximal and distal interphalangeal joints (marked by arrows). Subluxation at the interphalangeal joint levels (highlighted by the red lines)

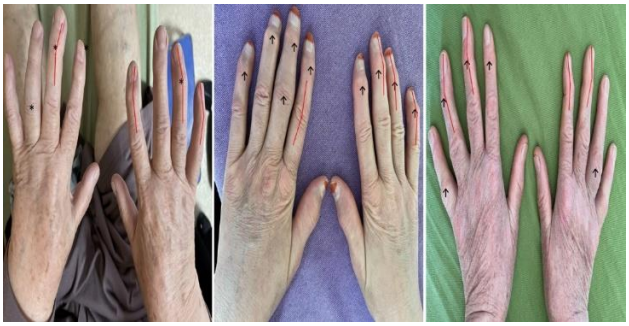
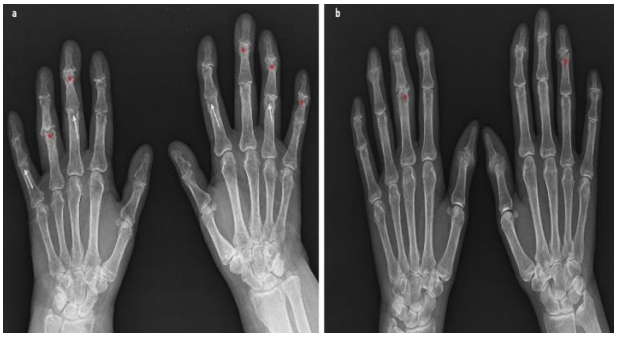


Figure 2: Radiological features of erosive hand osteoarthritis (EHOA): a. Radiograph EHOA, demonstrating 'gull-wing' appearance (red asterisks) and joint-space narrowing (white arrows). b. Radiograph of EHOA, demonstrating 'saw-tooth' appearance (red asterisks)



The possible pathological link between uric acid and osteoarthritis has been a long-standing topic of research [8,9]. Monosodium urate crystals have shown a strong association with cartilage degeneration and lesions [10]. Colchicine, an anti-inflammatory agent primarily known for its mechanism of action involving tubulin disruption and anti-mitotic effects, leading to the downregulation of multiple inflammatory pathways and modulation of innate immunity, has been well-established in gout and familial Mediterranean fever treatment [11]. Furthermore, ongoing investigations are exploring the potential therapeutic roles of colchicine in rheumatic diseases like osteoarthritis and Behçet's disease, as well as non-rheumatic conditions such as pericarditis, atherosclerosis and liver cirrhosis [11].

Studies on the use of colchicine in knee osteoarthritis have presented inconsistent results [12–15]. On the other hand, to the best of our knowledge, only two studies have been conducted so far on the use of colchicine in HOA, which did not report positive results [2,16]. One potential limitation of these studies is that they enrolled both EHOA and non-EHOA patients, which could have obscured the potential beneficial effects, specifically in patients with EHOA [2,16].

We hypothesized that colchicine, an anti-inflammatory agent with potent effects in various inflammatory diseases, might be more effective in EHOA due to the higher prominence of inflammation in this HOA subtype. As the primary goal of this study, we aimed to investigate whether colchicine could offer symptomatic relief to patients with EHOA. Additionally, as a secondary objective, we sought to determine whether colchicine therapy could significantly improve the levels of inflammation markers in these patients.

## Materials and methods

### Ethical statement

The ethical protocol for this study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (decision date: April 7, 2023; decision number: 2023/193). All procedures were conducted in compliance with the ethical standards set forth by the institutional research committee and the Helsinki Declaration and its subsequent amendments. Written informed consent was obtained from all participants.

### Study design and setting

This retrospective cohort study was conducted in the Department of Rheumatology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey, from January 2019 to December 2022.

### Diagnosis of erosive hand osteoarthritis

The diagnosis of EHOA was made according to the following criteria of the American College of Rheumatology (ACR) [17]: Presence of radiological signs of EHOA, categorized as either J phase (complete disappearance of joint space in a relatively short period) or E phase (erosion of the subchondral plate concurrently or shortly after the loss of articular cartilage), observed in one or more finger joints on recently taken hand radiographs (Figure 2). Additionally, clinical findings of inflammatory osteoarthritis (i.e., pain on pressure and/or active joint swelling and/or redness and/or warmth) were identified in more than three finger joints, despite using analgesics and/or nonsteroidal anti-inflammatory drugs for over 3 months (Figure 1) [18].

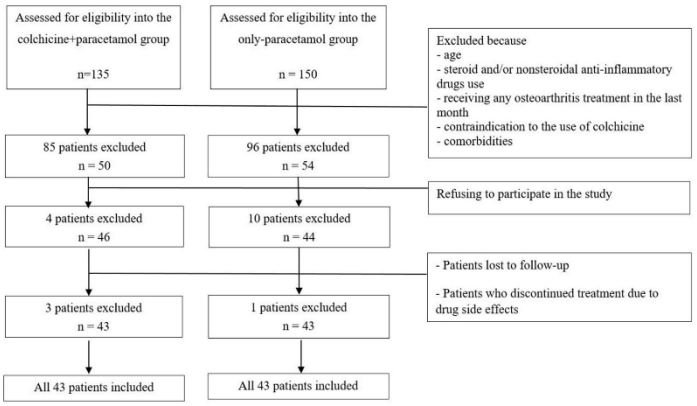
**Administration of colchicine and standard treatment approach**

At our center, patients with EHOA receive comprehensive information about the disease, established management approaches, and potential treatment side effects. Despite the lack of compelling evidence for the efficacy of colchicine, based on our clinical observations, we offer colchicine therapy to patients with EHOA. Before commencing treatment, we explicitly inform the patients that colchicine treatment for EHOA is a management approach not yet fully supported by scientific data, but we have observed significant improvements among recipients. Those who agreed to colchicine treatment and had no contraindications received standardized colchicine therapy and other standard treatments. The colchicine group was administered the following treatment: colchicine 2 × 0.5 mg (1 mg) and paracetamol 3 × 500 mg (1.5 gr) daily. Patients receiving colchicine were designated as the colchicine group, while those receiving paracetamol alone were labeled as the standard therapy group. After receiving the intended interventions for three months (12 weeks), both groups were examined for this study.

**Study population**

The patients' follow-up files were examined to identify the study groups when conducting the present study. A total of 43 EHOA patients undergoing colchicine + paracetamol treatment, who met the inclusion criteria, were included. For the control group, we randomly selected 43 EHOA patients matched for age and sex, receiving only paracetamol treatment. The inclusion criteria for the study were as follows: age between 40–80 years, diagnosed with EHOA based on the ACR criteria, a history of hand pain for at least 6 months, experiencing pain for more than half of the prior 90 days, and having a VAS pain score greater than 40 mm for hand pain within the last 48 hours [2]. Exclusion criteria included: being diagnosed with any chronic comorbidity (diabetes, hypertension, and disorders of cardiovascular, nervous, pulmonary, renal, hepatic, endocrine, or gastrointestinal systems), having any other concomitant inflammatory rheumatic disease (including gout and calcium pyrophosphate arthritis), pregnancy or breastfeeding, body mass index <20 kg/m$^2$ or >35 kg/m$^2$, use of steroid and/or immunosuppressive therapy within the prior month, receiving any osteoarthritis treatment, including physiotherapy and new hand splint(s) in the prior month, documented or suspected allergy to colchicine, failure to provide informed consent, and any drug or device use in the past 30 days related to any other research. Additionally, we excluded patients with the following laboratory values: eGFR <50 mL/min/1.73m$^2$, hemoglobin ≤10 g/dL, leukocyte count ≤3.5 × 10$^9$/L, neutrophil count ≤1.5 × 10$^9$/L, platelet count ≤100 × 10$^9$/L, and detection of >2 times the upper reference limit for alanine aminotransferase or aspartate aminotransferase [2]. Finally, any patients who refused participation or withdrew from the study, those who discontinued treatment due to side effects (paracetamol and/or colchicine), and those who had not attended control visits for at least 3 months were also excluded from the analyses. The flow diagram of the study is presented in Figure 3. We evaluated both groups 3 months after the intervention, as has been done in most previous studies [2,12,16].

Figure 3: Flowchart of the study




**Data collection and instruments**

Sociodemographic data, including age, sex, smoking, and alcohol use status of the participants, were recorded. From the laboratory results routinely studied in the management of patients with osteoarthritis (assessed at baseline and 3 months after treatment), we documented the following from the digital records: hemogram parameters, including hemoglobin, hematocrit, mean corpuscular volume (MCV), absolute leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, as well as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Additionally, inflammation-related indices, such as neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIIV), were calculated using hemogram parameters at baseline and 3 months after treatment.

SII was calculated using the following formula: SII (× 10$^3$) = Absolute neutrophil count (× 10$^3$) × Absolute platelet count (× 10$^3$) / Absolute lymphocyte count (× 10$^3$) [19]. PIIV was calculated with the following formula: PIIV (× 10$^6$) = Absolute neutrophil count (× 10$^3$) × Absolute monocyte count (× 10$^3$) × Absolute platelet count (× 10$^3$) / Absolute lymphocyte count (× 10$^3$) [20].

The changes in laboratory parameters and results (amount of change) from baseline to 3 months after treatment were also included in the study as separate variables.

At baseline, the patients were asked about the duration of their osteoarthritis symptoms. Clinical measures, such as the visual analog scale (VAS) scores for pain (ranging from 0 to 100 mm) and Australian Canadian Osteoarthritis Hand Index (AUSCAN) questionnaire scores, were applied and recorded at baseline and at 3 months after treatment. The AUSCAN questionnaire was used to assess pain, stiffness, and hand function, as previously described [21]. Briefly, the AUSCAN pain score consists of five questions, each scored between 0–4, resulting in a final score between 0–20, with higher scores indicating more severe pain. The AUSCAN stiffness score consists of one question, scored between 0–4, resulting in a score between 0-4, with higher scores indicating more severe stiffness. The AUSCAN function score consists of nine questions, and each question is scored between 0–4, yielding a total function score between 0–36, with higher scores indicating worse function. The overall AUSCAN total score was obtained by summing all AUSCAN domain scores (ranging from 0 to 60). The study also examined the changes from baseline to 3 months for all scores (VAS and all AUSCAN subscores).

### Laboratory analysis

The blood test-related quantitative results mentioned above were obtained from laboratory parameters routinely studied in osteoarthritis patients. No additional blood samples were drawn from the patients, and no extra laboratory work was conducted for this study. Blood samples were collected from the antecubital vein. All measurements were performed in the Clinical Biochemistry Laboratory of Afyonkarahisar Health Sciences University Hospital using routine calibrated devices and following the manufacturer's recommendations and international standards.

### Efforts to address potential sources of bias

To enhance the validity and reliability of our study, we implemented several measures to address potential sources of bias. Standardized treatment protocols were employed to minimize treatment-related bias, with both paracetamol and colchicine administered to their respective groups at standardized dosages. This approach aimed to reduce variability in treatment responses and increase the study's internal validity. Additionally, we assessed demographic and clinical data, including age, sex, disease duration, and osteoarthritis severity, to control for potential confounding variables. During the statistical analysis, these baseline characteristics were considered to adjust for their potential effects on the study outcomes.

### Statistical analysis

All analyses were conducted using IBM SPSS v25.0 (IBM, NY, USA), with a significance threshold set at $P<0.05$. The normality of distribution was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean (standard deviation) or median (1st quartile - 3rd quartile) based on the normality of distribution. Categorical variables were reported as absolute and relative frequencies. For normally distributed variables, the Student's t-test was employed. Non-normally distributed variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using chi-square tests (Fisher's exact and Fisher-Freeman-Halton tests when appropriate). Repeated measurements of normally distributed variables were analyzed with two-way repeated measures analysis of variance (ANOVA). On the other hand, repeated measurements of non-normally distributed variables were analyzed using the Wilcoxon Signed Ranks test. To compare between groups, the Mann-Whitney U test was used to compare the amount of difference between measurements.

Based on the effect size (0.666) reported in the study by Richette et al. [22], a sample size of 37 participants for each group (74 in total) was determined to achieve 80% power with a two-tailed 0.05 threshold for significance. The sample size calculation was performed using PASS's two-sample t-test power analysis function (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

## Results

The mean age of the standard therapy group was 64.79 (7.20) years, while the mean age in the colchicine group was 65.72 (7.25) years ($P=0.552$). Most patients in both groups were female, and the sex distribution was similar (76.74% vs. 79.07%; $P=1.000$). The baseline sociodemographic characteristics of the groups were similar, as summarized in Table 1.

Table 1: Summary of sociodemographic features with regard to treatment groups.

| | Treatment | | |
|---|---|---|---|
| | **Paracetamol (n=43)** | **Colchicine + Paracetamol (n=43)** | ***P*-value** |
| **Age, years** | 64.79 (7.20) | 65.72 (7.25) | 0.552 |
| **Sex** | | | |
| **Female** | 33 (76.74%) | 34 (79.07%) | 1.000 |
| **Male** | 10 (23.26%) | 9 (20.93%) | |
| **Smoking** | | | |
| **Yes** | 7 (16.28%) | 3 (6.98%) | 0.313 |
| **No** | 36 (83.72%) | 40 (93.02%) | |
| **Alcohol use** | | | |
| **Yes** | 3 (6.98%) | 2 (4.65%) | 1.000 |
| **No** | 40 (93.02%) | 41 (95.35%) | |

Data are given as mean (standard deviation and frequency (percentage) for categorical variables.

Table 2: Summary of laboratory measurements with regard to treatment groups.

| | Treatment | | |
|---|---|---|---|
| | **Paracetamol (n=43)** | **Colchicine + Paracetamol (n=43)** | ***P*-value** |
| **Hemoglobin, g/dL** | 13.20 (1.70) | 13.76 (1.70) | 0.127 |
| **Hematocrit, %** | 40.67 (4.73) | 42.42 (4.74) | 0.091 |
| **MCV, fl** | 85.0 (83.4 - 89.1) | 88.9 (85.4 - 92.0) | **0.005** |
| **Leukocyte (x10$^3$)** | | | |
| **Baseline** | 7.56 (6.23 - 8.90) | 7.27 (5.83 - 8.91) | 0.479 |
| **3rd month** | 7.20 (6.10 - 8.46) | 6.82 (5.50 - 8.39) | 0.310 |
| ***P* (within groups)** | 0.717 | 0.187 | |
| **Change (1)** | -0.04 (-0.95 - 0.66) | -0.56 (-1.77 - 1.38) | 0.424 |
| **Neutrophil (x10$^3$)** | | | |
| **Baseline** | 4.56 (3.80 - 5.60) | 4.07 (3.20 - 5.30) | 0.115 |
| **3rd month** | 4.43 (3.60 - 5.40) | 3.61 (3.10 - 4.98) | 0.179 |
| ***P* (within groups)** | 0.174 | 0.163 | |
| **Change (1)** | -0.20 (-1.34 - 0.55) | -0.66 (-1.88 - 1.00) | 0.843 |
| **Lymphocyte (x10$^3$)** | | | |
| **Baseline** | 2.15 (1.85 - 2.53) | 2.27 (1.89 - 2.56) | 0.487 |
| **3rd month** | 2.10 (1.83 - 2.50) | 2.13 (1.64 - 2.58) | 0.829 |
| ***P* (within groups)** | 0.735 | 0.668 | |
| **Change (1)** | 0.05 (-0.50 - 0.21) | -0.12 (-0.69 - 0.30) | 0.843 |
| **Monocyte (x10$^3$)** | | | |
| **Baseline** | 0.57 (0.33 - 0.68) | 0.53 (0.42 - 0.64) | 0.921 |
| **3rd month** | 0.55 (0.40 - 0.70) | 0.46 (0.37 - 0.69) | 0.442 |
| ***P* (within groups)** | 0.305 | 0.582 | |
| **Change (1)** | 0.05 (-0.10 - 0.21) | -0.04 (-0.18 - 0.23) | 0.204 |
| **Platelet (x10$^3$)** | | | |
| **Baseline** | 247 (201 - 335) | 264 (215 - 315) | 0.644 |
| **3rd month** | 250 (174 - 307) | 239 (204 - 281) | 0.962 |
| ***P* (within groups)** | 0.447 | **0.046** | |
| **Change (1)** | -2 (-38 - 21) | -31 (-63 - 18) | 0.106 |
| **NLR** | | | |
| **Baseline** | 2.12 (1.80 - 2.47) | 1.69 (1.25 - 2.49) | 0.053 |
| **3rd month** | 1.95 (1.61 - 2.45) | 1.66 (1.28 - 2.90) | 0.179 |
| ***P* (within groups)** | 0.305 | 0.469 | |
| **Change (1)** | -0.14 (-0.71 - 0.36) | -0.25 (-0.81 - 0.65) | 0.819 |
| **MLR** | | | |
| **Baseline** | 0.26 (0.17 - 0.32) | 0.23 (0.18 - 0.32) | 0.945 |
| **3rd month** | 0.25 (0.17 - 0.37) | 0.22 (0.17 - 0.39) | 0.680 |
| ***P* (within groups)** | 0.274 | 0.875 | |
| **Change (1)** | 0.03 (-0.06 - 0.10) | 0.00 (-0.12 - 0.10) | 0.370 |
| **PLR** | | | |
| **Baseline** | 102.08 (87.57 - 144.39) | 119.17 (96.51 - 141.53) | 0.506 |
| **3rd month** | 112.31 (80.56 - 140.00) | 117.15 (95.54 - 158.54) | 0.554 |
| ***P* (within groups)** | 0.754 | 0.952 | |
| **Change (1)** | -3.53 (-20.13 - 24.97) | -1.79 (-34.20 - 33.49) | 0.826 |
| **SII (x10$^3$)** | | | |
| **Baseline** | 502.02 (341.74 - 819.06) | 487.35 (289.76 - 693.28) | 0.427 |
| **3rd month** | 467.33 (331.29 - 706.48) | 426.52 (277.72 - 709.30) | 0.409 |
| ***P* (within groups)** | 0.218 | 0.218 | |
| **Change (1)** | -36.28 (-243.43 - 92.58) | -96.19 (-379.52 - 142.22) | 0.566 |
| **PIIV (x10$^6$)** | | | |
| **Baseline** | 302.95 (110.55 - 557.84) | 243.91 (135.44 - 414.88) | 0.660 |
| **3rd month** | 287.41 (132.51 - 419.23) | 187.74 (123.73 - 441.95) | 0.409 |
| ***P* (within groups)** | 0.413 | 0.316 | |
| **Change (1)** | -19.45 (-175.35 - 88.49) | -29.80 (-263.90 - 152.04) | 0.758 |
| **ESR, mm/h** | | | |
| **Baseline** | 30.74 (11.10 | 31.02 (12.74 | 0.914 |
| **3rd month** | 32.67 (11.00 | 19.88 (8.52 | **<0.001** |
| ***P* (within groups)** | 0.113 | **<0.001** | |
| **Change (1)** | 1.93 (5.83 | -11.14 (9.54 | **<0.001** |
| **CRP, mg/L** | | | |
| **Baseline** | 5.1 (2.7 - 6.35) | 5.8 (3.0 - 9.3) | 0.183 |
| **3rd month** | 5.4 (3.7 - 7.7) | 2.1 (1.2 - 4.4) | **<0.001** |
| ***P* (within groups)** | **0.022** | **<0.001** | |
| **Change (1)** | 0.2 (-0.3 - 1.03) | -2.93 (-5.0 - -0.9) | **<0.001** |

Data are given as mean (standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. (1) Difference between 3rd month and baseline, negative values represent a decrease, and positive values represent an increase. CRP: C-reactive protein, ESR: Eritrosit sedimentation rate, MCV: Mean corpuscular volume, MLR: Monocyte-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PIIV: Pan-immune-inflammation value, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

Standard therapy recipients' baseline MCV was significantly lower than that of colchicine recipients ($P$=0.005). In the third month, ESR and CRP levels in the colchicine group were significantly lower compared to the standard therapy group (Figure 4). Moreover, the reductions in ESR and CRP levels from baseline were significantly greater in the colchicine group than in the standard therapy group ($P$<0.001 for all). The colchicine group showed significant decreases in platelet count ($P$=0.046), ESR level ($P$<0.001), and CRP level ($P$<0.001) from baseline to 3 months. Interestingly, the standard therapy group demonstrated a significant increase in CRP values at 3 months compared to baseline ($P$=0.022) (Table 2).

At 3 months, the VAS and Australian/Canadian Osteoarthritis Hand Index (AUSCAN) scores (pain, stiffness, function, and total score) of the colchicine group were significantly lower compared to the standard therapy group ($P$<0.001 for all) (Figure 5). The baseline-to-3rd-month decreases in VAS and AUSCAN scores were significant for both treatment groups ($P$<0.001 for all). However, the amount of decrease in these scores (from baseline to 3 months) was significantly greater in colchicine recipients compared to standard therapy recipients ($P$<0.001 for all) (Table 3).

Figure 4: Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) with regard to treatment groups *$P$<0.05, ** $P$<0.001, # $P$>0.05

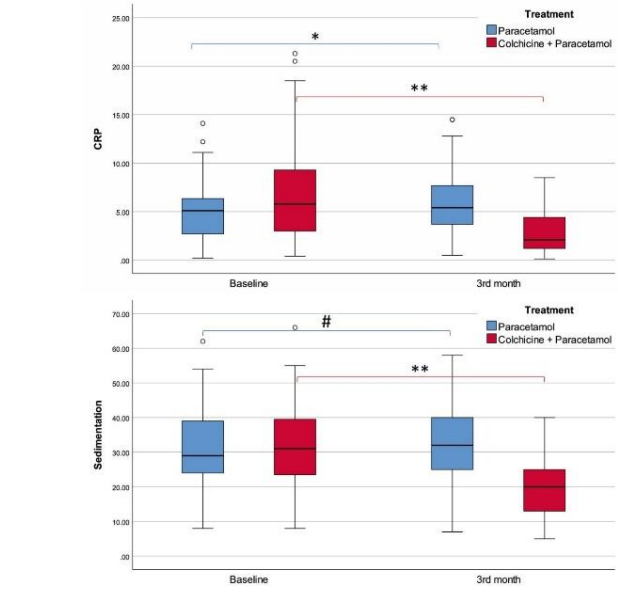



Figure 5: Visual analog scale (VAS) pain score and Australian Canadian Osteoarthritis Hand Index (AUSCAN) total score with regard to treatment groups ** $P$<0.001, *** $P$<0.0001

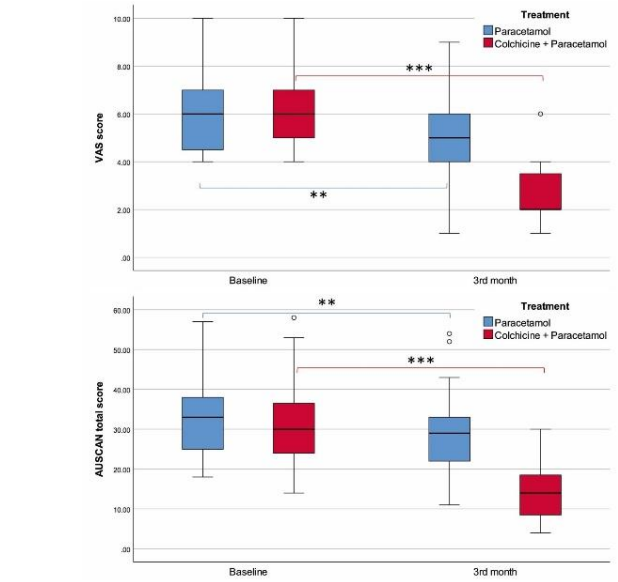



Table 3: Summary of symptomatic features and scale scores with regard to treatment groups

| | Treatment | | |
|---|---|---|---|
| | **Paracetamol (n=43)** | **Colchicine + Paracetamol (n=43)** | ***P*-value** |
| **Duration of symptoms, months** | 30 (15 - 60) | 36 (20 - 62) | 0.320 |
| **Visual analog scale score** | | | |
| **Baseline** | 6 (4.5 - 7) | 6 (5 - 7) | 0.338 |
| **3rd month** | 5 (4 - 6) | 2 (2 - 3.5) | **<0.001** |
| ***P* (within groups)** | **<0.001** | **<0.001** | |
| **Change [(1)]** | -1 (-1 - 0) | -4 (-5 - -2) | **<0.001** |
| **AUSCAN pain score** | | | |
| **Baseline** | 12 (10 - 14) | 12 (9 - 14) | 0.855 |
| **3rd month** | 11 (8 - 12) | 4 (3 - 6) | **<0.001** |
| ***P* (within groups)** | **<0.001** | **<0.001** | |
| **Change [(1)]** | -1 (-2 - -1) | -8 (-9 - -6) | **<0.001** |
| **AUSCAN stiffness score** | | | |
| **Baseline** | 2 (2 - 3) | 2 (1 - 3) | 0.245 |
| **3rd month** | 2 (1 - 3) | 1 (0 - 1) | **<0.001** |
| ***P* (within groups)** | **0.047** | **<0.001** | |
| **Change [(1)]** | 0 (-1 - 0) | -1 (-2 - -1) | **<0.001** |
| **AUSCAN function score** | | | |
| **Baseline** | 19 (13 - 22) | 16 (12 - 20) | 0.196 |
| **3rd month** | 17 (11 - 20) | 8 (5 - 11) | **<0.001** |
| ***P* (within groups)** | **<0.001** | **<0.001** | |
| **Change [(1)]** | -2 (-3 - -1) | -7 (-10 - -5) | **<0.001** |
| **AUSCAN total score** | | | |
| **Baseline** | 33 (25 - 38) | 30 (24 - 36.5) | 0.294 |
| **3rd month** | 29 (22 - 33) | 14 (8.5 - 18.5) | **<0.001** |
| ***P* (within groups)** | **<0.001** | **<0.001** | |
| **Change [(1)]** | -4 (-5 - -2) | -17 (-20 - -13) | **<0.001** |

Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. (1) Difference between 3rd month and baseline, negative values represent a decrease, and positive values represent an increase. AUSCAN: The Australian Canadian Osteoarthritis Hand Index.

## Discussion

This retrospective cohort study utilized a prospective collection of follow-up data from patients with EHOA. The study shows that both treatments, paracetamol + colchicine and paracetamol alone, led to significant improvements in VAS and AUSCAN scores (including pain, stiffness, function, and total score) among patients with EHOA. However, the colchicine group showed greater improvements in VAS and AUSCAN scores, as evidenced by direct comparisons at 3 months and the change in scores. Additionally, recipients of colchicine also demonstrated significant decreases in CRP and ESR levels, with significantly lower ESR and CRP levels at 3 months compared to the standard therapy group.

The main challenge in developing treatments that can effectively control the initiation and progression of EHOA is the lack of understanding of the underlying pathological processes [5]. While analgesics provide temporary and partial relief for EHOA symptoms, no pharmacotherapeutics currently can truly treat EHOA [2]. Given that osteoarthritis is common in old age and the proportion of elderly individuals in the population is increasing, there is an evident need for effective treatments [3,5]. Colchicine is well-established as an effective drug for reducing joint pain and swelling in gouty arthritis and other diseases, but positive results regarding its efficacy in osteoarthritis have not been reported [2]. Although there is a considerable number of studies on the use of colchicine in knee osteoarthritis, research on its efficacy in treating HOA is quite limited. In the present study, a 12-week treatment with 1.5 grams of paracetamol plus 1 mg of colchicine daily resulted in greater reductions in VAS scores and AUSCAN outcomes (pain, stiffness, function, and total score) compared to just 1.5 grams of paracetamol daily. Furthermore, while the scores of the two groups were similar at baseline, the colchicine group demonstrated significantly lower scores after 12 weeks of treatment.

Davis et al. [2] conducted a randomized, double-blind, placebo-controlled clinical trial with the hypothesis that

colchicine might be effective in HOA based on the idea that inflammatory osteoarthritis was more common in HOA than knee osteoarthritis. To our knowledge, this was the first study to investigate the efficacy of colchicine in HOA. The researchers reported that colchicine (1 mg daily for 12 weeks) was ineffective in reducing pain, the number of tender and swollen joints, ultrasound synovitis grade, and scores from the Michigan Hand Questionnaire, or increasing grip strength in symptomatic HOA. Therefore, the results did not support the use of colchicine in HOA. However, it should be noted that approximately 60% of the subjects in this study [2] had EHOA, while almost half of the patients did not have EHOA, which might have confounded findings and masked potential benefits exclusive to patients with EHOA. Plotz et al. [23], in their response to the study mentioned above, emphasized that Davis et al. did not require the presence of erosive, tender, swollen, or painful joints when including patients, which could have limited the number of subjects with active disease since these are well-established indicators of active inflammation.

Additionally, they did not assess Doppler signals when selecting subjects. Therefore, the study population did not consist of a sufficient number of patients with active inflammation, significantly limiting the accuracy of the evaluation of treatment. Large studies testing anti-inflammatory therapy must strive to include patients with inflammation, perhaps exclusively those with active inflammation, as the exposure (treatment) would be expected to demonstrate its effects mainly in these patient subsets. Secondly, the researchers did not consider pre-existing analgesic medications or provide any relevant data in this context. Thirdly, while colchicine is expected to decrease CRP as it suppresses inflammation, the authors did not discuss the possible reasons for the alarming increase in CRP levels after treatment [23]. We agree with the objections put forth by Plotz et al. [23] because it is evident that EHOA differs from non-EHOA in terms of both clinical severity and response to treatment. In a recent study, a group receiving 0.5 mg of colchicine twice daily for 12 weeks was compared to a placebo group for changes in target finger pain from baseline to week 12. The study reported that treatment with colchicine did not effectively reduce pain or improve AUSCAN scores in people with painful hand osteoarthritis and caused more side effects. However, the study population did not solely include EHOA cases [16]. We think it would be a better choice to investigate the efficacy of colchicine in a study population including only patients with EHOA, as was the case with the current study.

Studies on the use of colchicine in the treatment of knee osteoarthritis offer conflicting results. In one study of patients with knee osteoarthritis, treatment with colchicine (in addition to the standard therapy) resulted in greater improvement in patient- and physician-assessed outcomes at 3 months after treatment initiation [12]. A systematic review on colchicine in knee osteoarthritis stated that colchicine appears to be an effective and safe alternative for treating knee osteoarthritis, as evidenced by lower pain and improved functionality [13]. Similarly, some other studies have claimed that colchicine improves symptoms in treating knee osteoarthritis [24–26].

However, in contrast, Leung et al. [14] reported that colchicine (0.5 mg oral, twice daily) did not reduce symptoms of knee osteoarthritis, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index score during a 16-week study period. Another study compared the efficacy of physiotherapy and colchicine in patients with knee osteoarthritis and found that physical therapy was more effective than colchicine in reducing symptoms. Additionally, there were no significant differences in ultrasound-determined parameters at the end of the 16 weeks [15].

ESR and CRP values can detect inflammation, but these tests are not specific to osteoarthritis [26]. CRP is an inflammatory marker produced in the liver and released into the blood as a result of the stimulation of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α [28–30]. Colchicine can inhibit CRP production, but corticosteroids and other anti-inflammatory or immunosuppressive drugs cannot [28]. ESR is a common hematology test that can increase in the presence of inflammatory activity due to various disorders, including autoimmune diseases, acute inflammatory pathologies, infections, tumors, rheumatological diseases, and conditions causing increased physiological stress (such as pregnancy) [27–31]. While ESR and CRP levels are expected to increase in osteoarthritis, the effect of colchicine on the ESR and CRP levels of patients with EHOA is unclear [27].

In the present study, the combined use of colchicine and paracetamol resulted in a significant reduction in both ESR and CRP after 3 months, but no significant reduction was observed in the paracetamol-only group. Furthermore, while the baseline CRP and ESR levels were similar in both groups, the 3rd-month results showed that colchicine recipients' ESR and CRP levels were significantly lower compared to the standard therapy group. This result was further reinforced by the significantly greater decrease in ESR and CRP values in the colchicine group. Intriguingly, there was a significant increase in the CRP levels of the standard therapy group after 3 months of treatment, lending further credibility to the utility of colchicine and demonstrating that paracetamol alone was insufficient to prevent hyperinflammation.

In one study, it was reported that colchicine (0.5 mg orally twice a day) decreased inflammation markers, including CRP and bone turnover biomarkers, known to be associated with osteoarthritis severity and the risk of progression, but these differences were not significant [14]. Conversely, the study by Davis et al. [2] showed that 12 weeks of colchicine treatment did not significantly affect CRP levels in patients with HOA compared to placebo.

The fact that HOA tends to be predominantly symmetrical has an erosive subtype, and occurs in non-weight-bearing joints suggests that it may be affected to a greater degree by the systemic effects of osteoarthritis relative to hip and knee osteoarthritis [32,33]. Despite these data, most studies examining the response of HOA to therapeutic agents targeting specific inflammatory mediators have failed to reach their primary endpoints [23]. These 'unsuccessful' anti-inflammatory agents include hydroxychloroquine [34], lebrikizumab [35], adalimumab [36], etanercept [37], and tocilizumab [22].

On the other hand, the HOPE study stated that 10 mg of prednisolone for 6 weeks was effective and safe in treating patients with painful HOA and signs of inflammation [38].

Although these results suggest a feasible short-term treatment option for patients with HOA exacerbation, it is clear that there is a need for alternative treatment options due to the adverse effects of steroids [39]. Moreover, the possible differences in the pathological processes and inflammatory burdens of HOA subtypes necessitate the differentiation of management strategies. However, no studies have investigated the efficacy of colchicine in patients with EHOA. A recently published review reported that current evidence did not suggest a benefit for colchicine in reducing pain and improving physical function in patients with hand/knee osteoarthritis, but the authors also suggested that future studies investigating colchicine should focus on different osteoarthritis subtypes [40].

In our clinical experience, we have observed that colchicine significantly improves EHOA patients. Furthermore, the significant decrease in ESR and CRP levels supported the anti-inflammatory effect of colchicine. We hope our results will sufficiently trigger further comprehensive studies investigating the efficacy of daily treatment with colchicine (2 × 0.5 mg) + paracetamol (3 × 500 mg) in patients with EHOA.

**Limitations**

To the best of our knowledge, this is the first study investigating the efficacy of colchicine in patients with EHOA. Our results illustrate the utility of colchicine in patients with EHOA, as demonstrated by improvements in pain and AUSCAN scores. However, it should be noted that the study has some limitations. Primarily, it is a retrospective cohort study conducted at a center that offers colchicine therapy to patients. Although including only those with EHOA was necessary to enable reliable comparisons between treatments, the fact that it is a single-centered study with a relatively small sample size of EHOA patients limits the generalizability of its results. The efficacy of colchicine was evaluated using pain and AUSCAN scores, but further objective tools such as ultrasonographic examination, grip strength, and magnetic resonance imaging were not employed, which should be the focus of future prospectively-planned studies.

The treatments were administered for 12 weeks; only patients who attended follow-up studies during therapy were included. Therefore, those who did not benefit would have had a greater likelihood of being lost to follow-up, potentially skewing the results towards patients who benefitted from colchicine therapy. To prevent such confounding, future studies should employ ‘intention-to-treat’ analyses. The short follow-up period also limits the evaluation of long-term effects and potential side effects. Thus, more extended follow-up periods are necessary to assess the treatment’s lasting impact and safety profile.

**Conclusions**

In conclusion, the concomitant use of colchicine and paracetamol for 12 weeks appears to lead to greater improvements in CRP and ESR levels, VAS score, and AUSCAN scores compared to paracetamol alone in patients with EHOA. Despite the need for further studies considering the limitations of the present study, colchicine shows promise as an effective therapeutic agent in the treatment of EHOA.

## References


1. Vilá S. Inflammation in Osteoarthritis. P R Health Sci J. 2017;36:123–9.
2. Davis CR, Ruediger CD, Dyer KA, Lester S, Graf SW, Kroon FPB, et al. Colchicine is not effective for reducing osteoarthritic hand pain compared to placebo: a randomised, placebo-controlled trial (COLAH). Osteoarthritis Cartilage. 2021;29:208–14.
3. Favero M, Belluzzi E, Ortolan A, Lorenzin M, Oliviero F, Doria A, et al. Erosive hand osteoarthritis: latest findings and outlook. Nat Rev Rheumatol. 2022;18:171–83.
4. McAlindon TE, Driban JB, Roberts MB, Duryea J, Haugen IK, Schaefer LF, et al. Erosive Hand Osteoarthritis: Incidence and Predictive Characteristics Among Participants in the Osteoarthritis Initiative. Arthritis & Rheumatology. 2021;73:2015–24.
5. Kazmers NH, Meeks HD, Novak KA, Yu Z, Fulde GL, Thomas JL, et al. Familial Clustering of Erosive Hand Osteoarthritis in a Large Statewide Cohort. Arthritis & Rheumatology. 2021;73:440–7.
6. Kwok WY, Kloppenburg M, Rosendaal FR, van Meurs JB, Hofman A, Bierma-Zeinstra SMA. Erosive hand osteoarthritis: its prevalence and clinical impact in the general population and symptomatic hand osteoarthritis. Ann Rheum Dis. 2011;70:1238–42.
7. Tenti S, Ferretti F, Gusinu R, Gallo I, Giannotti S, Pozza A, et al. Impact of thumb osteoarthritis on pain, function, and quality of life: a comparative study between erosive and non-erosive hand osteoarthritis. Clin Rheumatol. 2020;39:2195–206.
8. Acheson RM, Collart AB. New Haven survey of joint diseases. XVII. Relationship between some systemic characteristics and osteoarthrosis in a general population. Ann Rheum Dis. 1975;34:379–87.
9. Y. Sun HBSSK. Serum uric acid and patterns of radiographic osteoarthritis - the Ulm Osteoarthritis Study. Scand J Rheumatol. 2000;29:380–6.
10. Muehleman C, Li J, Aigner T, Rappoport L, Mattson E, Hirschmugl C, et al. Association between crystals and cartilage degeneration in the ankle. J Rheumatol. 2008;35:1108–17.
11. Leung YY, Yao Hui LL, Kraus VB. Colchicine—Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45:341–50.
12. Aran S, Malekzadeh S, Seifirad S. A double-blind randomized controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee. Clin Exp Rheumatol. 2011;29:513–8.
13. Restrepo-Escobar M, Carmona-Franceschi M de J, Donado Gómez JH. Revisión sistemática de la literatura sobre el tratamiento con colchicina en pacientes adultos con osteoartritis de rodilla. Revista Colombiana de Reumatología. 2017;24:102–11.
14. Leung YY, Haaland B, Huebner JL, Wong SBS, Tjai M, Wang C, et al. Colchicine lack of effectiveness in symptom and inflammation modification in knee osteoarthritis (COLKOA): a randomized controlled trial. Osteoarthritis Cartilage. 2018;26:631–40.
15. Cioroianu GO, Florescu A, Mușetescu AE, Sas TN, Rogoveanu OC. Colchicine versus Physical Therapy in Knee Osteoarthritis. Life. 2022;12:1297.
16. Døssing A, Henriksen M, Ellegaard K, Nielsen SM, Stamp LK, Müller FC, et al. Colchicine twice a day for hand osteoarthritis (COLOR): a double-blind, randomised, placebo-controlled trial. Lancet Rheumatol. 2023;5:e254–62.
17. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum. 1990;33:1601–10.
18. Kedor C, Detert J, Rau R, Wassenberg S, Listing J, Klaus P, et al. Hydroxychloroquine in patients with inflammatory and erosive osteoarthritis of the hands: results of the OA-TREAT study—a randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. RMD Open. 2021;7:e001660.
19. Liu B, Wang J, Li Y, Li K, Zhang Q. The association between systemic immune-inflammation index and rheumatoid arthritis: evidence from NHANES 1999–2018. Arthritis Res Ther. 2023;25:34.
20. Lee LE, Ahn SS, Pyo JY, Song JJ, Park Y-B, Lee S-W. Pan-immune-inflammation value at diagnosis independently predicts all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis. Clin Exp Rheumatol. 2021;39:88–93.
21. Bellamy N, Campbell J, Haraoui B, Buchbinder R, Hobby K, Roth JH, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthritis Cartilage. 2002;10:855–62.
22. Richette P, Latourte A, Sellam J, Wendling D, Piperno M, Goupille P, et al. Efficacy of tocilizumab in patients with hand osteoarthritis: double blind, randomised, placebo-controlled, multicentre trial. Ann Rheum Dis. 2021;80:349–55.
23. Plotz B, Pillinger M, Samuels J. Colchicine and clinical trials for hand osteoarthritis. Osteoarthritis Cartilage. 2022;30:172–3.
24. Das SK, Ramakrishnan S, Mishra K, Srivastava R, Agarwal GG, Singh R, et al. A randomized controlled trial to evaluate the slow-acting symptom-modifying effects of colchicine in osteoarthritis of the knee: A preliminary report. Arthritis Rheum. 2002;47:280–4.
25. Das SK, Mishra K, Ramakrishnan S, Srivastava R, Agarwal GG, Singh R, et al. A randomized controlled trial to evaluate the slow-acting symptom modifying effects of a regimen containing colchicine in a subset of patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2002;10:247–52.
26. Amirpour A. The effect of colchicine in improving the symptoms of patients with knee osteoarthritis. J Babol Univ Med Sci. 2016;18(11):7-13.
27. Marpaung B, Siregar J. Effect of Sidaguri ( Sidarhombifolia L ) on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in osteoarthritis patients. IOP Conf Ser Earth Environ Sci. 2018;125:012188.
28. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. Journal of Clinical Investigation. 2003;111:1805–12.
29. Yalcinkaya R, Öz FN, Durmuş SY, Fettah A, Kaman A, Teke TA, et al. Is There a Role for Laboratory Parameters in Predicting Coronary Artery Involvement in Kawasaki Disease? Klin Padiatr. 2022;234:382–7.
30. Oztas Y, Yalcinkaya A. Oxidative alterations in sickle cell disease: Possible involvement in disease pathogenesis. World Journal of Hematology. 2017;6:55.
31. Tishkowski K, Gupta V. Erythrocyte Sedimentation Rate. 2023.
32. Marshall M, Watt FE, Vincent TL, Dziedzic K. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. Nat Rev Rheumatol. 2018;14:641–56.
33. Meltem CM, Bayram U, Engin C. Methodological quality of randomized controlled trials of home-based rehabilitation in knee osteoarthritis: A cross-sectional survey. J Surg Med. 2023;7(4):280-7.
34. Kingsbury SR, Tharmanathan P, Keding A, Ronaldson SJ, Grainger A, Wakefield RJ, et al. Hydroxychloroquine Effectiveness in Reducing Symptoms of Hand Osteoarthritis. Ann Intern Med. 2018;168:385.
35. Kloppenburg M, Peterfy C, Haugen IK, Kroon F, Chen S, Wang L, et al. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. Ann Rheum Dis. 2019;78:413–20.
36. Aitken D, Laslett LL, Pan F, Haugen IK, Otahal P, Bellamy N, et al. A randomised double-blind placebo-controlled crossover trial of Humira (adalimumab) for erosive hand Osteoarthritis – the HUMOR trial. Osteoarthritis Cartilage. 2018;26:880–7.

37.Kloppenburg M, Ramonda R, Bobacz K, Kwok W-Y, Elewaut D, Huizinga TWJ, et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2018;77:1757–64.
38.Kroon FPB, Kortekaas MC, Boonen A, Böhringer S, Reijnierse M, Rosendaal FR, et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. The Lancet. 2019;394:1993–2001.
39.Grennan D, Wang S. Steroid Side Effects. JAMA. 2019;322:282.
40.Singh A, Molina-Garcia P, Hussain S, Paul A, Das SK, Leung Y-Y, et al. Efficacy and safety of colchicine for the treatment of osteoarthritis: a systematic review and meta-analysis of intervention trials. Clin Rheumatol. 2023;42:889–902.

J Surg Med. 2023;7(8):458-462.
DOI: 10.28982/josam.7855

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Evaluation of high-resolution computed tomography findings and associated factors in hypersensitivity pneumonitis

**Adem Koyuncu [1], Hakan Ertürk[2]**

[1] Department of Occupational Diseases, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey
[2] Department of Radiology, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey

**ORCID ID of the author(s)**

AK: 0000-0003-4834-1317
HE: 0000-0002-5730-9215

**Corresponding Author**
Adem Koyuncu
Department of Occupational Diseases, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey
E-mail: drkadem@gmail.com

**Ethics Committee Approval**
The study was approved by Ankara Atatürk Sanatoryum Training and Research Hospital Ethics Committee, 21/06/2023, 2012-KAEK-15/2727.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 14

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Hypersensitivity pneumonitis (HP) is a lung disease from inhaling diverse environmental and occupational organic substances, such as fungi, bacteria, birds, and occasionally nonorganic materials. An immune response triggers this condition. A high-resolution chest computed tomography (HRCT) scan is typically performed as part of the initial diagnostic assessment. This study assesses HRCT findings in HP patients and examines associated factors between fibrotic and non-fibrotic patient groups.

**Methods:** This retrospective cross-sectional study encompassed all HP patients monitored between 2010 and 2022. The analysis included data from 117 patients. HRCT findings from the patients were categorized based on fibrosis presence, leading to the division of patients into fibrotic and non-fibrotic groups. Comparative analyses were conducted between these groups.

**Results:** Among the 117 subjects analyzed, 59 (50.4%) were male, and 58 (49.6%) were female. The mean age at diagnosis was 52.1 (13.6) years, ranging from 20 to 81. The non-fibrotic HP group comprised 70 (59.8%) patients, while the fibrotic HP group comprised 47 (40.2%). The most prevalent HRCT findings were ground-glass opacity (90.6%), mosaic attenuation (87.2%), and traction bronchiectasis (50.4%). Statistically significant disparities were observed between non-fibrotic and fibrotic HP groups in terms of HRCT findings: ground-glass opacity, irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis ($P$=0.024, $P$<0.001). In contrast, the lymphocyte ratio in bronchoalveolar lavage fluid was 28.78 (16.2) in the non-fibrotic HP group and 14.66 (10.3) in the fibrotic HP group. The fibrotic HP group exhibited a statistically significant lower lymphocyte ratio in bronchoalveolar lavage fluid ($P$<0.001).

**Conclusion:** HRCT findings are pivotal in HP diagnosis and classification. Computed tomography also assists in delineating the HP classification. This study identified ground-glass opacity and mosaic attenuation as the most prevalent HRCT findings in HP patients. Investigating the connection between fibrosis and prognosis is vital for determining patient outcomes, as fibrosis appears to be the principal determinant.

**Keywords:** hypersensitivity pneumonitis, non-fibrotic hypersensitivity pneumonitis, fibrotic hypersensitivity pneumonitis, high-resolution computed tomography

How to cite: Koyuncu A, Ertürk H. Evaluation of high-resolution computed tomography findings and associated factors in hypersensitivity pneumonitis. J Surg Med. 2023;7(8):458-462.

## Introduction

Hypersensitivity pneumonitis (HP) is an immune-mediated lung disorder triggered by inhaling various environmental and occupational organic substances, primarily encompassing fungi, bacteria, avian sources, and, less commonly, nonorganic irritants [1]. This condition's historical identification dates back to 1700 and has been associated with many inciting agents. More than 300 etiological agents have been pinpointed as contributors to the ailment. Understanding the historical evolution of HP is crucial not only for discerning its antigenic triggers but also for comprehending how changes in risk factors over time have impacted its development [2]. In the United Kingdom, the reported incidence stands at 0.9 cases per 100,000 person-years, while the overall age-adjusted mortality rate in the United States is 0.19 per million individuals [3].

HP is conventionally classified as acute, subacute, or chronic, delineated by its clinical attributes and the duration of the ailment [4]. Nevertheless, these categories often prove difficult to confine due to their variable and arbitrary definitions across numerous studies. The ATS/JRS/ALAT guideline committee has opted for an alternative classification, sorting HP into fibrotic (including mixed inflammatory and fibrotic patterns or exclusively fibrotic presentations) and non-fibrotic (purely inflammatory) categories. This classification hinges on the pivotal role of radiographic fibrosis in prognostic determination, offering enhanced clinical applicability [5]. In HP cases, histological identification or detection via chest computed tomography of fibrosis is correlated with reduced survival rates [6].

A chest high-resolution computed tomography (HRCT) scan is often conducted as an integral component of the initial diagnostic assessment. Specific HRCT patterns may indicate the likelihood of HP in a relevant clinical context. Patients diagnosed with HP are categorized into fibrotic or non-fibrotic classifications based on the presence or absence of fibrosis in their HRCT results. HRCT indications of pulmonary fibrosis encompass irregular linear opacities, reticulation, traction bronchiectasis, and honeycomb formations [1]. This study assesses the HRCT findings in HP patients and scrutinizes the factors associated with the division between fibrotic and non-fibrotic patient groups.

## Materials and methods

The population of this retrospective cross-sectional study comprises all patients diagnosed with hypersensitivity pneumonia at the outpatient clinic and service of Ankara Atatürk Sanatorium Training and Research Hospital between January 1, 2010, and December 31, 2022. HP is a rare disease. Due to its rarity, the study aims to encompass the entire patient population rather than opting for a sample selection. The hospital management information system identified patients diagnosed with J67 HP. Over the designated research period, 132 patients with HP were identified in the hospital's management information system. However, fifteen patients were excluded from the study due to the unavailability of their HRCT images and information.

For the study, the hospital employed data from their records on cases of HP. This encompassed laboratory test results, evaluations of pulmonary function, and radiological images stored within their information management system. The HRCT findings were subjected to analysis for a range of observations, including centrilobular nodules, ground-glass opacity, mosaic attenuation, irregular linear opacities, reticulation, traction bronchiectasis, honeycomb formations, fibrosis, and prevalence of distribution of fibrotic opacities. A Radiology Specialist within the research team meticulously reviewed the HRCT scans of the enrolled patients to ascertain the presence of either fibrotic or non-fibrotic findings, aligning with the guidelines stipulated by ATS/JRS/ALAT. The identification of fibrosis hinged on the concurrent presence of a reticular pattern alongside traction bronchiectasis and/or honeycomb formations.

The study's primary dependent variable categorizes HP cases based on their fibrosis status in HRCT scans, distinguishing between fibrotic and non-fibrotic instances. Meanwhile, the independent variables encompass a spectrum of socio-demographic factors such as age, gender, smoking status, and attributes linked to occupational history. Additionally, the independent variables include functional assessment outcomes (FEV1, FVC, FEV1/FVC, DLCO), laboratory findings (hemogram, biochemistry), and exposure-related characteristics. The accumulation of data was facilitated by using a dedicated patient follow-up form.

The study received ethical clearance via decision number 2012-KAEK-15/2727, granted by the Ankara Atatürk Sanatorium Education and Research Hospital Ethics Committee. After obtaining the committee's ethical endorsement, the study was initiated.

**Statistical analysis**

The statistical analysis was performed utilizing the SPSS Windows version 22.0, a commonly employed software package. Descriptive statistics, specifically mean (standard deviation) (SD), were employed to depict numerical data. The independent groups t-test assessed the distinctions between continuous variables within two groups. In contrast, the chi-square test was employed to compare categorical variables. Outcomes with a *P*-value of $<0.05$ were considered statistically significant.

## Results

Between January 1, 2010, and December 31, 2022, a total of 117 cases of HP were diagnosed at the Ankara Atatürk Sanatorium Training and Research Hospital, constituting the research cohort. Among the 117 subjects encompassed in this study, 59 (50.4%) were male, while 58 (49.6%) were female. The mean age of patients at the time of diagnosis was 52.1 (13.6) years, ranging from 20 to 81 years. The cases were stratified into two groups based on their fibrosis status observed in HRCT scans. The non-fibrotic HP group accounted for 70 (59.8%) patients, while the fibrotic HP group comprised 47 (40.2%). Among patients subjected to HRCT evaluation, the most prevalent findings included ground-glass opacity (90.6%), mosaic attenuation (87.2%), traction bronchiectasis (50.4%), centrilobular nodules (45.3%), reticulation (44.4%), and irregular linear opacities (41.0%). Comparatively less common

observations were fibrosis (40.2%), three-density findings (28.2%), and honeycomb formations (13.7%) (Table 1).

No statistically significant differences were observed in centrilobular nodules, mosaic attenuation, and three-density patterns between non-fibrotic HP and fibrotic HP HRCT findings. However, a statistically significant distinction emerged between the two groups concerning ground-glass opacity, irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis (Table 1).

Table 1: HRCT findings of the 117 patients with non-fibrotic HP and fibrotic HP cases.

| Characteristics | Total | HP phenotypes | | *P*-value* |
|---|---|---|---|---|
| | | Non-Fibrotic HP | Fibrotic HP | |
| | n (%) | n (%) | n (%) | |
| **Centrilobular nodules** | 53 (45.3) | 35 (50) | 18 (38.3) | 0.257 |
| **Ground-glass opacity** | 106 (90.6) | 60 (85.7) | 46 (97.7) | 0.024 |
| **Mosaic attenuation** | 102 (87.2) | 58 (82.7) | 44 (93.6) | 0.074 |
| **Three-density pattern** | 33 (28.2) | 20 (28.2) | 13 (27.7) | 0.543 |
| **Irregular linear opacities** | 48 (41.0) | 18 (25.7) | 30 (63.8) | <0.001 |
| **Reticulation** | 52 (44.4) | 5 (7.1) | 47 (100) | <0.001 |
| **Traction bronchiectasis** | 59 (50.4) | 12 (17.1) | 47 (100) | <0.001 |
| **Honeycombing** | 16 (13.7) | 0 (0.0) | 16 (34.0) | <0.001 |
| **Fibrosis** | 47 (40.2) | 0 (0.0) | 47 (100) | <0.001 |

* Chi-square test, HRCT: High-Resolution Computed Tomography, HP: Hypersensitivity pneumonitis

No statistically significant differences were identified in terms of gender, recognized environmental risk factors, presence of cough, shortness of breath, and smoking status, whether considering fibrotic HP or non-fibrotic HP. However, notable statistical significance emerged regarding fibrotic HP and non-fibrotic HP cases concerning the presence of a known occupational risk factor and the detection of crackles during physical examination ($P$=0.022, $P$<0.001) (Table 2).

Table 2: The relationship between non-fibrotic HP and fibrotic HP cases with some demographic characteristics.

| | | Non-Fibrotic HP | | Fibrotic HP | | *P*-value* |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| **Gender (n=117)** | Female | 36 | 51.4 | 22 | 46.8 | 0.382 |
| | Male | 34 | 48.6 | 25 | 53.2 | |
| **Occupational risk (n=117)** | Yes | 25 | 35.7 | 8 | 17 | 0.022 |
| | None | 45 | 64.3 | 39 | 83 | |
| **Environmental risk (n=117)** | Yes | 30 | 42.9 | 17 | 36.2 | 0.298 |
| | None | 40 | 57.1 | 30 | 63.8 | |
| **Cough (n=117)** | Yes | 54 | 77.1 | 42 | 89.4 | 0.072 |
| | None | 16 | 22.9 | 5 | 10.6 | |
| **Breathlessness (n=117)** | Yes | 66 | 94.3 | 42 | 91.5 | 0.408 |
| | None | 4 | 5.7 | 5 | 8.5 | |
| **Crackles on physical examination (n=117)** | Yes | 13 | 18.6 | 23 | 48.9 | <0.001 |
| | None | 57 | 81.4 | 24 | 51.1 | |
| **Cigarette (n=117)** | Non-smoker | 35 | 50 | 20 | 42.6 | 0.160 |
| | Ex-smoker | 17 | 24,3 | 19 | 40.4 | |
| | Smoker | 18 | 25,7 | 8 | 17.0 | |

* Chi-square test

The average age at diagnosis in the non-fibrotic HP group was 47.79 (13.1) years, while in the fibrotic HP group, it was 58.68 (11.6) years. The non-fibrotic HP group received a statistically significant diagnosis at a younger age than the fibrotic HP group ($P$<0.001). Furthermore, the mean duration of smoking was notably higher in the fibrotic HP group than in the non-fibrotic HP group, displaying statistical significance ($P$=0.010). Laboratory tests revealed that lactate dehydrogenase and white blood cell values were significantly elevated in the fibrotic HP group ($P$=0.003, $P$=0.024). Additionally, the lymphocyte ratio in bronchoalveolar lavage fluid was recorded as 28.78 (16.2) in the non-fibrotic HP group and 14.66 (10.3) in the fibrotic HP group, exhibiting a statistically significant reduction in the fibrotic HP group ($P$<0.001). No statistically significant differences were observed between the two groups regarding time from symptom onset to diagnosis, C-reactive protein levels, or pulmonary function values (FVC, FEV1, FEV1/FVC, DLCO) (Table 3).

Table 3: Evaluation of the relationship between non-fibrotic HP and fibrotic HP cases with laboratory and pulmonary function tests.

| | Non-Fibrotic HP mean (SD) | Fibrotic HP mean (SD) | *P*-value* |
|---|---|---|---|
| **Age, years (n=117)** | 47.79 (13.1) | 58.68 (11.6) | <0.001 |
| **Cigarettes (pack/year) (n=24)** | 17.8 (12.2) | 30.0 (8.6) | <0.010 |
| **Time from symptom onset to diagnosis, months (n=117)** | 14.4 (26.2) | 19.5 (25.0) | 0.299 |
| **CRP, (n=117)** | 12.04 (25.1) | 22.28 (45.3) | 0.164 |
| **LDH,) (n=117)** | 230.47 (82.4) | 286.12 (106) | 0.003 |
| **WBC, (n=117)** | 8727 (2644) | 9810 (2295) | 0.024 |
| **FVC, (n=105)** | 79.98 (16.5) | 76.7 (20.4) | 0.384 |
| **FEV1, (n=105)** | 75.4 (16.9) | 70.43 (19.2) | 0.166 |
| **FEV/FVC, (n=105)** | 81.9 (10.9) | 85.61 (7.7) | 0.580 |
| **DLCO, (n=83)** | 88.87 (22.3) | 77.47 (20.7) | 0.200 |
| **The ratio of lymphocytes (n=75)** | 28.78 (16.2) | 14.66 (10.3) | <0.001 |

* Independent groups t-test, SD: standard deviation, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase, WBC: White Blood Cell, FVC: Forced vital capacity, FEV1: Forced expiratory volume in the first second, DLCO: Diffusing Capacity of the lung for carbon monoxide.

## Discussion

A characteristic HRCT pattern can suggest the diagnosis. A compatible HRCT pattern becomes indicative of HP when supported by multidisciplinary discussions. The HRCT pattern may point toward an alternative diagnosis in cases where it is indeterminate. A higher confidence level in diagnosing HP is generally achieved when a more distinct HRCT confidence level is attainable [7].

It is crucial to thoroughly evaluate the computed tomography features of HP to determine the extent of radiological certainty. According to the ATS/JRS/ALAT algorithm, a non-fibrotic HP with a typical HRCT pattern indicates diffuse parenchymal infiltration and signs of small airway disease. Parenchymal infiltration might manifest as ground-glass opacity or mosaicism, while small airway disease could exhibit signs of air trapping and vaguely defined centrilobular nodules up to 5 mm in size. In cases where fibrotic patterns are observed on HRCT scans, compatible with HP, it suggests a combination of fibrosis and small airway disease in specific areas [5].

The study encompassed the assessment of HRCT findings from 117 cases that had been diagnosed with HP. The HRCT outcomes revealed that ground-glass opacities (90.6%) and mosaic attenuation (87.2%) were the most frequently observed features. Similar evaluations were carried out in a separate study conducted by Shobeiri et al. [8] involving 45 HP patients. Additionally, in a study focused on 92 patients with fibrotic HP, Walsh et al. [9] identified ground-glass opacification (93.3%) and reticulation (93.3%) as the predominant HRCT findings.

Mosaic attenuation and three-density findings are radiological terms associated with heterogeneous lung attenuation. “mosaic attenuation” pertains specifically to computed tomography during the inspiratory phase. It is defined as distinctly demarcated areas of both low and high attenuation. This phenomenon can be observed in vascular, airway, or infiltrative diseases [5]. Recognizing that the “headcheese” sign might not resonate with most individuals, the term “three-density pattern” has become the preferred nomenclature [10]. This term is utilized to depict a scenario where obstructions and infiltrations coexist with regions of healthy lung tissue, resulting in well-defined zones exhibiting three distinct levels of

attenuation [11]. Within the domain of fibrotic HP, three-density findings have been identified [10].

Our study revealed no significant distinction between fibrotic and non-fibrotic HP patients concerning mosaic attenuation and three-density findings. However, our research exhibited statistically notable elevations in irregular linear opacities, reticulation, Traction Bronchiectasis, honeycombing, and fibrosis within the fibrotic patient group. This aligns with the findings of Nishida et al. [12], who, in their investigation involving 121 HP patients, identified higher statistical significance in honeycombing, traction bronchiectasis, and lung distortion findings within the fibrotic patient group, akin to our study.

When dealing with individuals suspected of having HP, it is recommended to amalgamate HP-specific HRCT findings with clinical information to bolster the diagnosis of HP. However, relying solely on CT findings for a definitive diagnosis is cautioned against [11].

Numerous studies have underscored the pivotal role of lung fibrosis in prognostic determination [13-17]. In their examination of 69 HP patients, Hanak et al. [16] categorized 37.6% as having fibrotic HP. Similarly, Nishida et al. [12] reported a fibrotic patient rate of 38.8% among 121 patients. In concurrence with this literature, our study found 40.2% of patients fall into the fibrotic HP category.

While the mean age of all diagnosed patients was 52.1 (13.6) years, the non-fibrotic HP group exhibited a mean age at diagnosis of 47.79 (13.1) years, while the fibrotic HP group skewed older, with a mean age of 58.68 (11.6) years. In the study conducted by Nishida et al. [12], the mean age of HP patients was 63.0, with the non-fibrotic patient group averaging 59 years and the fibrotic patient group averaging 67 years. In a separate investigation, Wang et al. [18] identified the mean age across all patients as 53.6, with the acute hypersensitivity group averaging 51.9 and the chronic hypersensitivity group averaging 57.8. Corresponding with our findings, the literature also indicates that fibrotic HP patients tend to receive their diagnosis at an older age.

Despite thoroughly evaluating exposure histories, laboratory results, and radiological findings in HP cases, the causative agent may remain undetectable in 49-60% of instances [1,19]. The responsible agent can be identified in approximately half of HP cases by meticulously exploring environmental and occupational backgrounds. A notable observation emerged in our study: while there was a statistically significant increase in non-fibrotic HP cases within the group exposed to occupational risk factors, no statistically significant distinction was noted for either group in patients with environmental risk factors.

A parallel discovery was made in the study conducted by Walters et al., where, akin to our results, no disparity surfaced within the group harboring environmental risk factors. However, they did find a statistically significant reduction in fibrosis among individuals with occupational risk factors. By delving into a comprehensive occupational history, detecting non-fibrotic HP cases early becomes feasible, facilitating their treatment by removing the causative agent [19].

Frequently observed symptoms and indications in non-fibrotic and fibrotic HP encompass breathlessness, cough, and mid-inspiratory squat. Our investigation unveiled no noteworthy contrast between patient groups with fibrotic and non-fibrotic HP concerning symptoms like cough and shortness of breath. However, a significant elevation was identified in the occurrence of crackles during physical examinations within the fibrotic patient group.

Consistent with our findings, Walters et al. reported no discernible differences in cough, fever, weight loss, or dyspnea. Nevertheless, they did establish a statistically significant increase in crackles detected through physical examination within the fibrotic patient cohort [19].

Recently published reports have ignited a discourse regarding the influence of smoking on individuals with HP. Warren [20] and Terho et al. [21] proposed a notable association between HP and non-smoking, asserting that acute hypersensitivity pneumonitis is less prevalent among current smokers than non-smokers with similar exposure risks. A study by Furuiye et al. [22] demonstrated that cigarette smoke could dampen inflammation and lymphocyte proliferation in cases of acute hypersensitivity pneumonitis. However, an intriguing counterpoint emerges: if an individual who smokes develops HP, the condition may progress into a chronic state, accompanied by poorer survival rates than their non-smoking counterparts. This divergence stems from prolonged exposure to cigarette smoke can exacerbate both lung inflammation and fibrosis [23].

In line with the existing literature, our research found a parallel pattern; specifically, the duration of smoking within the fibrotic group significantly exceeded that of the non-fibrotic group.

Pulmonary function tests are a valuable tool for assessing the pattern and extent of respiratory impairment, although neither model stands alone as diagnostic. Distinguishing between non-fibrotic HP and fibrotic HP is beyond the capabilities of pulmonary function tests. Within our study, despite lacking a statistically significant differentiation in the pulmonary function tests (FEV1, FVC, FEV1/FVC, DLCO) of the fibrotic and non-fibrotic patient groups, it was observed that the FEV1, FVC, and DLCO values were notably lower within the fibrotic patient cohort. Consistent with our findings, Nishida et al.'s study reported similar results: while no discernible disparity existed in diffusion between the fibrotic and non-fibrotic patient groups, the FVC value was reduced in the fibrotic patient group [12].

Bronchoscopy plays a pivotal role in diagnosing HP, with bronchoalveolar lavage (BAL) fluid collection and analysis and lung biopsy serving as the principal procedures conducted through this method. BAL testing emerges as a highly effective means of identifying alveolitis in individuals suspected of having HP. Typically, patients afflicted with HP exhibit alveolitis characterized by a notable abundance of lymphocytes. However, it's noteworthy that individuals with fibrotic HP tend to display lower levels of lymphocytes in their BAL fluids when contrasted with those suffering from non-fibrotic HP [5].

Within our investigation, the lymphocyte ratio in the BAL samples of fibrotic HP cases was measured at 14.66 (10.3), while non-fibrotic HP cases exhibited a lymphocyte ratio of 28.78 (16.2), resulting in a statistically significant discrepancy. In alignment with our study, Nishida et al. [12] also identified a

significantly lower lymphocyte ratio in the BAL samples of the fibrotic HP patient group compared to the non-fibrotic HP patient group. Notably, a diminished lymphocyte ratio in BAL has been linked to an unfavorable prognosis in patients diagnosed with HP [5].

**Limitations**

Our study possesses certain limitations. The primary limitations of our research stem from the small sample size and retrospective design employed in the study. Due to the retrospective design of the study, we were unable to access the prognosis of the patients. Consequently, there is a need for future studies to examine the correlation between fibrosis and prognosis.

**Conclusion**

The outcomes of an HRCT scan hold substantial significance in identifying HP. Computed tomography aids in categorizing HP. Following this study, ground-glass opacity and mosaic attenuation were frequently noted in HRCT scans of individuals with HP. Irregular linear opacities, reticulation, traction bronchiectasis, honeycombing, and fibrosis exhibit a statistically higher prevalence in fibrotic HP cases than in non-fibrotic HP cases. Our investigation revealed that the non-fibrotic patient group skewed younger, and the lymphocyte ratio was elevated in BAL fluid. HP patients who are cigarette smokers face an increased likelihood of developing fibrosis. Since fibrosis is the principal determinant of prognosis, investigations exploring the relationship between fibrosis and prognosis are imperative.

## References


1. Fernández Pérez ER, Travis WD, Lynch DA, Brown KK, Johannson KA, Selman M, et al. Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report. Chest. 2021 Aug;160(2):e97-e156. doi: 10.1016/j.chest.2021.03.066. Epub 2021 April 20. PMID: 33861992.
2. Barnes H, Jones K, Blanc P. The hidden history of hypersensitivity pneumonitis. Eur Respir J. 2022 Jan 20;59(1):2100252. doi: 10.1183/13993003.00252-2021. PMID: 34083405.
3. Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia. Where We Stand and Where We Need to Go. Am J Respir Crit Care Med. 2017 Sep 15;196(6):690-9. doi: 10.1164/rccm.201608-1675PP. PMID: 28002680; PMCID: PMC5620675.
4. Richerson HB, Bernstein IL, Fink JN, Hunninghake GW, Novey HS, Reed CE, et al. Guidelines for the clinical evaluation of hypersensitivity pneumonitis. Report of the Subcommittee on Hypersensitivity Pneumonitis. J Allergy Clin Immunol. 1989 Nov;84(5 Pt 2):839-44. doi: 10.1016/0091-6749(89)90349-7. PMID: 2809034.
5. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2020 Aug 1;202(3):e36-e69. doi: 10.1164/rccm.202005-2032ST. Erratum in: Am J Respir Crit Care Med. 2021 Jan 1;203(1):150-1. Erratum in: Am J Respir Crit Care Med. 2022 Aug 15;206(4):518. PMID: 32706311; PMCID: PMC7397797.
6. Kouranos V, Jacob J, Nicholson A, Renzoni E. Fibrotic Hypersensitivity Pneumonitis: Key Issues in Diagnosis and Management. J Clin Med. 2017 June 15;6(6):62. doi: 10.3390/jcm6060062. PMID: 28617305; PMCID: PMC5483872.
7. Chelala L, Adegunsoye A, Cody BA, Husain AN, Chung JH. Updated Imaging Classification of Hypersensitivity Pneumonitis. Radiol Clin North Am. 2022 Nov;60(6):901-13. doi: 10.1016/j.rcl.2022.06.013. Epub 2022 September 7. PMID: 36202477.
8. Shobeirian F, Mehrian P, Doroudinia A. Hypersensitivity Pneumonitis High-resolution Computed Tomography Findings, and Their Correlation with the Etiology and the Disease Duration. Prague medical report. 2020;121(3):133-41. doi: 10.14712/23362936.2020.12. PMID: 33030142.
9. Walsh SL, Sverzellati N, Devaraj A, Wells AU, Hansell DM. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. Eur Radiol. 2012 Aug;22(8):1672-9. doi: 10.1007/s00330-012-2427-0. Epub 2012 April 1. PMID: 22466512.
10. Dabiri M, Jehangir M, Khoshpouri P, Chalian H. Hypersensitivity Pneumonitis: A Pictorial Review Based on the New ATS/JRS/ALAT Clinical Practice Guideline for Radiologists and Pulmonologists. Diagnostics (Basel). 2022 Nov 20;12(11):2874. doi: 10.3390/diagnostics12112874. PMID: 36428934; PMCID: PMC9689332.
11. Barnett J, Molyneaux PL, Rawal B, Abdullah R, Hare SS, Vancheeswaran R, Desai SR, et al. Variable utility of mosaic attenuation to distinguish fibrotic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis. Eur Respir J. 2019;54:1900531. doi: 10.1183/13993003.00531-2019. PMID: 31164428.
12. Nishida T, Kawate E, Ishiguro T, Kanauchi T, Shimizu Y, Takayanagi N. Antigen avoidance and outcome of non-fibrotic and fibrotic hypersensitivity pneumonitis. ERJ Open Res. 2021 Feb 7;8(1):00474-2021. doi: 10.1183/23120541.00474-2021. PMID: 35141326; PMCID: PMC8819255.
13. Fernández Pérez ER, Swigris JJ, Forssén AV, Tourin O, Solomon JJ, Huie TJ, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. Chest. 2013 Nov;144(5):1644-51. doi: 10.1378/chest.12-2685. PMID: 23828161; PMCID: PMC4694094.
14. Salisbury ML, Gu T, Murray S, Gross BH, Chughtai A, Sayyouh M, et al. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest. 2019 Apr;155(4):699-711. doi: 10.1016/j.chest.2018.08.1076. Epub 2018 September 19. PMID: 30243979; PMCID: PMC6514431.
15. De Sadeleer LJ, Hermans F, De Dycker E, Yserbyt J, Verschakelen JA, Verbeken EK, et al. Effects of Corticosteroid Treatment and Antigen Avoidance in a Large Hypersensitivity Pneumonitis Cohort: A Single-Centre Cohort Study. J Clin Med. 2018 December 21;8(1):14. doi: 10.3390/jcm8010014. PMID: 30577667; PMCID: PMC6352061.
16. Hanak V, Golbin JM, Hartman TE, Ryu JH. High-resolution CT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis. Chest. 2008 Jul;134(1):133-8. doi: 10.1378/chest.07-3005. Epub 2008 April 10. PMID: 18403660.
17. Mooney JJ, Elicker BM, Urbania TH, Agarwal MR, Ryerson CJ, Nguyen MLT, et al. Radiographic fibrosis score predicts survival in hypersensitivity pneumonitis. Chest. 2013 Aug;144(2):586-92. doi: 10.1378/chest.12-2623. PMID: 23392130.
18. Wang LJ, Cai HR, Xiao YL, Wang Y, Cao MS. Clinical characteristics and outcomes of hypersensitivity pneumonitis: a population-based study in China. Chin Med J (Engl). 2019 June 5;132(11):1283-92. doi: 10.1097/CM9.0000000000000256. Erratum in: Chin Med J (Engl). 2021 Jan 11;134(3):378. PMID: 31021982; PMCID: PMC6629344.
19. Walters GI, Mokhlis JM, Moore VC, Robertson AS, Burge GA, Bhomra PS, et al. Characteristics of hypersensitivity pneumonitis diagnosed by interstitial and occupational lung disease multidisciplinary team consensus. Respir Med. 2019 Aug;155:19-25. doi: 10.1016/j.rmed.2019.06.026. Epub 2019 June 29. PMID: 31295673.
20. Warren CP. Extrinsic allergic alveolitis: a disease commoner in non-smokers. Thorax. 1977 Oct;32(5):567-9. doi: 10.1136/thx.32.5.567. PMID: 594937; PMCID: PMC470791.
21. Terho EO, Husman K, Vohlonen I. Prevalence and incidence of chronic bronchitis and farmer's lung with respect to age, sex, atopy, and smoking. Eur J Respir Dis Suppl. 1987;152:19-28. PMID: 3499342.
22. Furuiye M, Miyake S, Miyazaki Y, Ohtani Y, Inase N, Umino T, et al. Effect of cigarette smoking on the development of murine chronic pigeon breeder's lung. The difference between a short-term and a long-term exposure. J Med Dent Sci. 2007 Mar;54(1):87-95. PMID: 19845140.
23. Churg A, Sin DD, Everett D, Brown K, Cool C. Pathologic patterns and survival in chronic hypersensitivity pneumonitis. Am J Surg Pathol. 2009 Dec;33(12):1765-70. doi: 10.1097/PAS.0b013e3181bb2538. PMID: 19809277.
24. Kumar R, Spalgais S, Ranga V. Hypersensitivity pneumonitis: clinical, radiological and pathological profile of 103 patients from North India. Monaldi Arch Chest Dis. 2020 Aug 3;90(3). doi: 10.4081/monaldi.2020.1307. PMID: 32885932.

J Surg Med. 2023;7(8):463-467.
DOI: 10.28982/josam.7878

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Heavy metals in human bones from the Roman Imperial Period

**Hatice Güler, Hilal Kübra Güçlü Ekinci**

Department of Anatomy, Erciyes University, Faculty of Medicine, Kayseri, Turkey

**ORCID ID of the author(s)**

HG: 0000-0001-9364-5948
HKGE: 0000-0001-7849-1768

## Abstract

**Background/Aim:** Heavy metals are elements known for their toxic effects even at low concentrations, and human exposure to these elements spans history. This study aimed to investigate trace element levels in the bones of individuals from the Roman Imperial Period. The objectives were to determine the values of specific metals, including heavy metals, make a rough comparison with present-day values, and gain insights into the environmental conditions of that era.

**Methods:** Due to the use of dry bone samples, ethical committee approval was not required for this research. The study analyzed element levels in human bones dated back to the Roman Imperial Period (218-244 AD), unearthed in 2018 during excavations in Turkey-Kayseri. Only bones that archaeologists verified to belong to the specified period were included, while those with uncertain origins were excluded. The samples were taken from os coxae of 15 individuals (eight males and seven females) to analyze Ca, P, Zn, Cu, Pb, and Hg levels. Instrumental techniques such as Wavelength Dispersive X-ray Fluorescence (WDXRF) (X-ray fluorescence) and ICP-MS (Inductive Coupling Plasma-Mass Spectrometer) were used to determine element concentrations. The Ca/P ratio was assessed for diagenesis evaluation, and statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 22.0, with a significance threshold set at *P*-value <0.05.

**Results:** The Ca/P ratio for the general population was calculated as 2.34 (0.10). The mean concentrations of heavy metals in the bones were as follows: Cu 18.27 (11.04) ppm, Pb 13.30 (5.66) ppm, Zn 27.22 (13.84) ppm, and Hg 2.45 (2.86) ppm. The corresponding *P*-values for Ca, P, Ca/P, Cu, Zn, Pb, and Hg were 0.109, 0.120, 0.104, 0.063, 0.113, 0.089, and 0.070. No statistically significant difference emerged when comparing elemental accumulations between males and females. Notably, copper and mercury levels were higher in Roman Imperial Period bones than contemporary ones, whereas zinc levels were lower, and lead concentrations aligned with reference values.

**Conclusion:** The study results underscore the historical exposure of Roman Imperial Period individuals to heavy metals. These findings suggest that environmental health concerns related to heavy metal exposure date back millennia, emphasizing the long-standing nature of this issue.

**Keywords:** bone, anatomy, heavy metals

**Corresponding Author**
Hatice Güler
Department of Anatomy, Erciyes University
Faculty of Medicine, Kayseri, Turkey
E-mail: hsusar@erciyes.edu.tr

**Ethics Committee Approval**
An ethics committee decision was not required since dry bones were used.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 19

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

How to cite: Güler H, Güçlü Ekinci HK. Heavy metals in human bones from the Roman Imperial Period: The example of Turkey. J Surg Med. 2023;7(8):463-467.

## Introduction

Archaeological investigations illuminate the obscure facets of history [1,2]. These studies strive to recreate the existence of ancient societies while establishing connections between bygone eras and the contemporary world [2]. In essence, deciphering the chemical composition of ancient bones furnishes insights into bone characteristics and permits observations on the era when they were living tissue. Bones represent metabolically active organs, wherein trace elements such as Zn, Cu, Ca, and P orchestrate bone metabolism and growth. These trace elements' imbalances, be they deficiency or excess, are postulated to carry inherent risks [3]. The acquisition of elements can occur through dietary intake or contamination of food storage receptacles and water conduits. Toxicity is associated with all elements when present above certain thresholds, yet Pb and Hg exhibit toxicity even at minute levels [4].

Kayseri, formerly recognized as Caesarea or Mazaca in antiquity, is a prominent city in the Cappadocia region. In the contemporary context, a substantial portion of what was once Kaisarea, a vital stronghold during the Roman Empire, lies beneath the veneer of the modern cityscape [5]. The inception of human habitation in Kayseri finds its roots in Kültepe (Kaniş/Karum), an establishment that emerged during the Early Bronze Age. Kültepe endured as a steadfast settlement from 4000 BC through the culmination of the Roman epoch. Situated along the historical silk road pathway, Kayseri's significance has endured from ancient epochs to the present [6].

The historical opulence of Kayseri province has perennially magnetized the attention of illicit traders, occasionally leading to a detrimental impact on valuable artifacts. To counteract these occurrences, the Kayseri Museum Directorate diligently undertakes systematic excavations and conscientiously safeguards and documents the cultural heirlooms. The unearthing of the Kayseri/Köşkdağı burial site transpired as a consequence of a salvage excavation orchestrated by experts from the Kayseri Museum Directorate on 09.03.2018, prompted by reports of unauthorized excavations. The skeletal remains unearthed during these efforts were subsequently entrusted to the Anatomy Department of Erciyes University Medical Faculty. The precious artifacts retrieved from this burial site are curated and protected by the Directorate.

The primary objective of this research is to ascertain the levels of specific hazardous metals (notably lead and mercury) as well as trace elements (such as zinc and copper) within bones procured from the Köşkdağı excavation site. This site's historical context is linked to the Roman Imperial Period in Anatolia. The overarching goal is to unveil the intricate interplay between societies and their surrounding environment during this historical epoch. Furthermore, this study endeavors to enrich the "Late Roman/Byzantine period dataset." Comprehensive permissions were secured from the Department of Anatomy to facilitate the scrutiny of elemental concentrations within the skeletal remains.

## Materials and methods

### Obtaining the samples

The human skeletal remains from the Roman Imperial Period included in our study were excavated from a stone sarcophagus and an adjacent burial site. These remains were uncovered during excavations in the Kayseri/Köşkdağı District in 2018 (Figure 1). Alongside the human skeletons, artifacts such as gold coins, gold jewelry, and pottery from the same period were unearthed during the excavation (Figure 2).

Figure 1: A. Burial site B. Stone sarcophagus


Figure 2: A. Skeletal remains B, C. Coin D. Jewelry E. Pot

Among the recovered artifacts, two of the coins were identified as belonging to the reign of Emperor Elagabalus (218-222 AD), while another coin bears the inscription 'Emperor III,' which archaeologists have attributed to the period of Gordian III (238-244). The grave goods found in the vicinity can be dated to the period spanning from the 1st century AD to the middle of the 3rd century AD.

Notably, the absence of evidence indicating that the tombs had been previously disturbed and the presence of gold coins within the same burial site as the skeletons served as valuable clues for dating the skeletal remains.

**Selection of bone materials**

Given the commingling of bones within the graves, we focused on selecting those bones that could be accurately identified by sex and attributed to specific skeletons. To determine the sex of the bones, we followed the method proposed by Buikstra and Ubelaker [7]. Our bone selection process aimed to encompass diverse skeletal regions. Accordingly, we opted for two bones: the os frontale from the neurocranium and the mandible from the viscerocranium, both representing the cranium; the humerus for the upper extremity; the femur for the lower extremity; and the os sacrum for the columna vertebralis.

Following the sex determination process, it was established that seven of the bones (46.67%) could be attributed to females, while the remaining eight belonged to males (53.33%).

In order to delve into the lives of individuals from the Roman Imperial Period (218-244 AD), we scrutinized elemental concentrations within bones from a sample group of 15 individuals. These concentrations were assessed using samples extracted from the os coxae (Figure 3). The analysis focused on Ca, P, Zn, Cu, Pb, and Hg elemental levels. These measurements were obtained using WDXRF Spectroscopy) and ICP-MS (Inductively Coupled Plasma-Mass Spectrometry) instruments. The Ca/P ratio was also determined to glean insights into potential diagenetic processes impacting the bones.

Figure 3: Coxa bones (Photos by Kayseri Museum Directorate Team)

**WDXRF analysis (used for the determination of Ca and P percentages)**

Each sample underwent a meticulous process to ensure the accuracy of our analysis. Initially, the samples were mechanically cleansed of soil or debris and subsequently rinsed with distilled water for 10 min. To mitigate potential external influences, the samples were air-dried for 2 days, followed by repeated washing with distilled water on at least two occasions.

Upon 15 days of air-drying, the samples were further subjected to 24 h of oven drying at an approximate temperature of 80°C. These dried bones were methodically numbered and then securely placed within ziplock bags. The collection of bagged bones was then transported to the Erciyes University Technology Research and Application Center.

Subsequently, bones that had completed the requisite washing and grinding procedures were positioned within platinum crucibles. The hydroxyapatite segment of the bone was utilized for the subsequent trace element analysis. A high-temperature procedure was employed to isolate the inorganic constituents from the hydroxyapatite portion. Samples were incinerated in a PROTHERM Furnaces brand oven at 1000°C for an hour to eliminate organic matter.

Following this, 1.3 g of the samples were meticulously combined with a mixture of 5% gold and 95% platinum within crucibles. This blend introduced 13 g of lithium tetraborate and lithium metaborate. The prepared amalgams were then subjected to fusion within a Leneo FLUXER brand apparatus at a temperature of 1065°C for 23 min. The molten samples were subsequently analyzed using the PANalytical AXIOS ADVANCED device, and the results were seamlessly transferred to the computer environment for further interpretation.

**Sample thawing process for ICP-MS device**

Roughly 0.200–0.300 g of meticulously washed, dried, and finely ground samples were measured for further analysis. 8 ml of $HNO_3$ and 2 ml of HCl were added to these samples. Employing the wet burning method, a controlled temperature and pressure regimen was executed within a closed system, utilizing a microwave solubilizer of the Speed Wave brand.

Upon completion of this process, the resulting clear solutions were carefully collected. Subsequently, distilled water brought these solutions to a final volume of 25 ml.

Before the analysis, standard solutions were meticulously prepared at predetermined concentrations (ranging from 0 to 50 ppb) for the elements earmarked for examination. A Tune solution (containing 200 ppb of Li, Yb, and Cs) was introduced into the system, facilitating performance calibration adjustments to ensure the device's measurement parameters were optimal. Following this calibration, the analysis of the appropriately diluted samples commenced.

The dissolved samples were analyzed using an Agilent 7500a model ICP-MS device [8].

**Statistical analysis**

Statistical evaluations of trace element levels within the samples from the Kayseri-Köşkdağı Roman Imperial Period were executed using the IBM SPSS Statistics 22.0 software. Key statistical parameters, including minimum, maximum, mean, median, percentage, and standard deviation, were computed to gauge the concentrations of elements within the bones.

As part of the statistical analyses, an initial normality assessment was conducted using SPSS (IBM SPSS, 2021). While elements like Ca, P, Cu, and Pb exhibited a normal distribution, Zn and Hg displayed deviations from normality. To discern variations in element concentrations based on gender, the Student's T-Test was employed for elements conforming to normal distribution, whereas the Mann-Whitney U test was chosen for those with non-normal distribution.

A significance threshold of *P*-values <0.05 was adopted to delineate between statistically significant and non-significant differences.

## Results

Table 1 displays the concentrations of six elements, analyzed without gender discrimination, alongside the Ca/P ratio, a crucial finding for diagenesis. The variance between the minimum and maximum element concentrations is indicated. However, the minimum and maximum values of Ca/P ratios exhibit proximity.

Table 2 presents the element concentrations and Ca/P ratios categorized by gender. A comparison between males and females reveals non-statistically significant differences (*P*>0.05).

Table 1: Element levels of bones (without gender discrimination)

| Total (n=15) | Ca % | P % | Ca/P | Cu (ppm) | Zn (ppm) | Pb (ppm) | Hg (ppm) |
|---|---|---|---|---|---|---|---|
| **Mean** | 22.71 | 9.76 | 2.34 | 18.27 | 27.22 | 13.30 | 2.45 |
| **Median** | 23.28 | 9.90 | 2.37 | 16.17 | 24.27 | 12.67 | 0.65 |
| **Standard deviation** | 5.79 | 2.75 | 0.10 | 11.04 | 13.84 | 5.66 | 2.86 |
| **Minimum** | 11.88 | 4.76 | 2.12 | 1.33 | 11.49 | 2.85 | 0.04 |
| **Maximum** | 32.83 | 15.45 | 2.50 | 39.52 | 67.80 | 25.54 | 8.31 |

Table 2: Comparison of female and male element levels and Ca/P ratios

| Element | Gender | n | Mean | (SD) | *P*-value |
|---|---|---|---|---|---|
| **Ca %** | female | 7 | 22.67 | (3.10) | 0.109 |
| | male | 8 | 22.75 | (7.67) | |
| **P %** | female | 7 | 9.71 | (1.24) | 0.120 |
| | male | 8 | 9.80 | (3.71) | |
| **Ca/P** | female | 7 | 2.33 | (0.08) | 0.104 |
| | male | 8 | 2.35 | (0.12) | |
| **Cu (ppm)** | female | 7 | 21.00 | (8.10) | 0.063 |
| | male | 8 | 15.87 | (13.17) | |
| **Zn (ppm)** | female | 7 | 27.09 | (7.59) | 0.113 |
| | male | 8 | 27.33 | (18.26) | |
| **Pb (ppm)** | female | 7 | 15.93 | (6.60) | 0.089 |
| | male | 8 | 11.01 | (3.71) | |
| **Hg (ppm)** | female | 7 | 3.70 | (3.35) | 0.070 |
| | Male | 8 | 1.36 | (1.98) | |

## Discussion

Chemical analysis of archaeological bones aids in comprehending the ecological relationships and health status of ancient societies. This data significantly contributes to reconstructing the lifestyles prevalent in those times [9]. Calcified tissues, including bones and teeth, can harbor indicators pertinent to diet and environmental conditions. These tissues are regarded as biological archives of past organisms [10,11]. In chemical investigations, the extent of environmental pollution becomes discernible by scrutinizing heavy metal accumulation in calcified tissues [9,12,13]. Consequently, elemental analysis of archaeological bones is a pivotal tool for assessing the prevailing environmental conditions of the era.

In our research, we conducted analyses of toxic metals and trace elements in the os coxae of 15 individuals presumed to have lived during the Roman Imperial Period in Kayseri, Turkey. The os coxae was selected based on its suitability for examination in cases where skeletal remains were intact across all individuals. Calcium (Ca) and phosphorus (P) percentages (%) were assessed using the WDXRF instrument. Additionally, zinc (Zn), copper (Cu), lead (Pb), and mercury (Hg) levels were measured in parts per million (ppm) using the Inductively Coupled Plasma Mass Spectrometry (ICP-MS) device.

Diagenesis, encompassing chemical and physical alterations occurring post-burial, presents a universal challenge impacting skeletons across archaeological sites. Changes within bones manifest through the calcium-to-phosphorus ratio, a value historically established at 2.16 for all humans [14,15]. Any deviation from this ratio signifies a diagenetic influence on the bone. This phenomenon, encountered in various locales, indicates elemental exchange within the Köşkdağı society's skeletal remains post-interment. The findings imply a greater susceptibility of men to elemental modifications (diagenesis) than women within the Köşkdağı society. This could be attributed to variations in individual lifespans. Archaeological studies have noted fluctuating lifespans for women, with some indicating longer durations [16] and others suggesting shorter spans [17], adding complexity to the understanding of prehistoric epochs. Our study hypothesizes that the observed sex-based disparities in diagenesis outcomes might be linked to differing lifespans between men and women.

While the Ca/P ratios provide insight into the occurrence of diagenesis in the bones, it is noteworthy that the bones were situated within an environment characterized by gravel and stone. Moreover, while a conventional Ca/P ratio is commonly assumed for assessing diagenesis, recent research has proposed an alternative ratio of 5.3. This perspective asserts that the Ca/P ratio might exhibit regional variability, challenging its application as a steadfast constant [4,18].

Based on these findings, it can be inferred that diagenesis exposure remains confined, assuming suitable storage conditions for the bones, and a fixed Ca/P ratio cannot definitively demarcate diagenetic effects. Hence, we posit that the elemental levels detected in the bones surpass those in the soil.

Güner et al. [9] documented copper (Cu) levels at 44.23 ppm in rib samples obtained from 17 individuals dating back to the Early Byzantine Period, uncovered during excavations in the Adramytteion (Örentepe, Balıkesir) region. This outcome was construed as not being attributed to diagenesis; instead, introducing the metal into the area from an external source was proposed as an explanation.

In a Byzantine bone investigation, Grattan et al. [19] documented a copper (Cu) concentration of 52.57 ppm within skeletons originating from the Faynan Valley, a location characterized by extensive copper mining activities. The contrast between the average Cu level observed in the Köşkdağı skeletons and the Cu levels within skeletons from regions known for copper exposure in our study underscores the significance of environmental pollution exposure.

As per Wilson's assessment [20], the copper (Cu) concentration in contemporary dry bone should ideally remain under 30 ppm. On average, the Gültepe community os coxae exhibits a Cu concentration of 18.27 ppm. Upon gender-based scrutiny, this value proves higher in women compared to men. This discrepancy arises because women are more frequently

exposed to copper-containing kitchenware materials. Considering Wilson's specified benchmark, we infer that the copper values identified in our study are devoid of contamination and remain unaffected by diagenetic processes.

While it is evident that environmental pollution significantly elevates the copper (Cu) levels, we deduce that the Cu concentration in our study surpasses that found in contemporary bones. This discrepancy could potentially stem from diagenetic influences. Furthermore, our investigation reveals a higher Cu level among women. This trend could be attributed to women's increased involvement in food preparation activities and interaction with kitchen utensils.

In the investigation conducted by Güner et al. [9] and Zapata et al. [21], elevated zinc (Zn) values were attributed to diagenetic processes. In the tombs of the ancient city of Iasos, the average Zn concentration within rib samples was recorded as 111.24 ppm, whereas the Camihöyük skeletons exhibited a Zn value of 96.40 ppm [2]. Interestingly, our study presents a markedly lower Zn concentration than similar or disparate region-based studies. Moreover, our findings reveal that the Zn levels are inferior to those observed in modern bones.

Zinc, a divalent cation, is not synthesized within the human body and necessitates appropriate levels for its maintenance. Elevated phytate consumption, particularly from legumes, cereals, and their seeds, notably contributes to zinc deficiency [22]. Notably, the continental climate prevalent in the region promotes a predominantly plant-focused diet. Consequently, we hypothesize that impaired Zn absorption and subsequent concentration reduction occur.

In our investigation, lead (Pb) values were higher in women than in men. This divergence might be attributed to increased lead exposure among women, potentially originating from using lead-containing kitchen utensils.

Mercury (Hg) exerts toxic effects even at minimal concentrations. Our study identified a notably elevated Hg content. Limited attention has been directed toward Hg analysis in the realm of heavy element investigations about prehistoric eras. We attribute this scarcity of studies to the prevailing disparity in interest between elemental analyses targeting environmental pollution versus those centered on historical dietary practices.

**Limitations**

Given the restricted temporal scope of this study focusing on bones from a specific era, the limited bone sample size poses a constraint. Despite the modest number of bones, their contribution to illuminating the environmental pollution during the post-Christ period renders the study highly valuable. However, a conclusive elucidation of the extent of diagenetic exposure on the bones remained elusive.

Subsequent research endeavors could enhance understanding by investigating the surrounding soil and water near the bones. Analyzing these elements would allow for a more comprehensive evaluation of environmental pollution levels and the influence of diagenesis, thereby refining our comprehension in this domain.

**Conclusion**

The elevated levels of copper (Cu) and mercury (Hg) detected in bone tissues from Köşkdağı could potentially be linked to environmental factors and culinary practices, such as the use of copper utensils for cooking and food storage. Although the lead (Pb) concentration within the bone tissues aligns with reference values, the absence of leaded materials in excavations at the Köşkdağı archaeological sites suggests that elemental accumulation within the bones likely results from dietary choices and/or the living environment. Furthermore, we conjecture that our study's diminished zinc (Zn) concentrations might be associated with dietary habits.

Collectively, these findings underscore a lasting continuum of environmental pollution driven by heavy metals, with associated public health implications spanning from historical times to the present day.

**Acknowledgments**

Thanks to the Department of Anatomy and Kayseri Museum Directorate faculty members for allowing us to work with bones.

## References

1. Degryse P, Muchez P, Cupere BD, Neer WV, Waelkens M. Statistical Treatment of Trace Element Data from Modern and Ancient Animal Bone: Evaluation of Roman and Byzantine Environmental Pollution. Analytical Letters. 2004;37(13):2819-34.
2. Usta NDY, Başoğlu O, Erdem O, Kural C, İzci Y. Iasos (Erken Bizans) ve Camihöyük (Helenistik-Roma) Kazıları İskelet Toplulukları Üzerinde Karşılaştırmalı Element Analizi. Antropoloji. 2019;37:7-14.
3. Ciosek Ż, Kot K, Kosik-Bogacka D, Łanocha-Arendarczyk N, Rotter I. The Effects of Calcium, Magnesium, Phosphorus, Fluoride, and Lead on Bone Tissue. Biomolecules. 2021;11(4):506.
4. Arıhan SK, Akyol A A, Özer İsmail, Arıhan Okan. Elemental analysıs of Beybağ-Muğla (Turkey) Byzantıne Skeletons. TÜBA-AR 21/2017.
5. Altun Ö. Types of Tombs at Köşkdağı Grave Area and Finds. Anatolian Research. 2023;193-214.
6. Doğan AD. Kayseri Medeniyetlerin Beşiği. Kayseri Büyükşehir Belediyesi Kültür Yayınları. 2018;140:13-57.
7. Buikstra JE, Ubelaker D. Standards for Data Collection from Human Skeletal Remains. Arkansas Archeological Survey Research, 1994;44.
8. Richardson C, Roberts E, Nelms S, Roberts NB. Optimisation of whole blood and plasma manganese assay by ICP-MS without use of a collision cell. Clin Chem Lab Med. 2012;50(2):317-23.
9. Güner C, Türksoy V, Atamtürk D, Duyar İ. Adramytteion (Örentepe, Balıkesir) Erken Bizans dönemi insan iskeletlerinin kimyasal analizi. İnsanbil Derg. 2012;1(2):81-93.
10. Abdel-Salam A, Galmed AH, Tognoni E, Harith MA. Estimation of calcified tissues hardness via calcium and magnesium ionic to atomic line intensity ratio in laser induced breakdown spectra. Spectrochimica Acta Part B: Atomic Spectroscopy. 2007;62(12):1343-7.
11. Al-Khafif GD, El-Banna R. Reconstructing Ancient Egyptian Diet through Bone Elemental Analysis Using LIBS (Qubbet el Hawa Cemetery). Biomed Res Int. 2015;2015:281056.
12. Jurkiewicz A, Wiechula D, Nowak R, Gazdzik T, Loska K. Metal content in femoral head spongious bone of people living in regions of different degrees of environmental pollution in Southern and Middle Poland. Ecotoxicology and Environmental Safety. 2004;59:95-101.
13. Martínez-García MJ, Moreno JM, Moreno-Clavel J, Vergara N, García-Sánchez A et al. Heavy metals in human bones in different historical epoch. Science of the Total Environment. 2005;348:51-72.
14. Posner AS. Crystal Chemistry Of Bone Mineral. Physical Review. 1969;49:760-92.
15. Çırak MT. Kelenderis Toplumu'nda Element Analiziyle Paleodiyet'in Ortaya Çıkarılması ve Diagenesis. Suna & Inan Kıraç Research Instıtute on Medıterranean Cıvılızatıon. Festschrift Series: 2013;3:161-74.
16. Ozer I, Sağır M, Satar Z, Güleç E. Gümüşlük (Milas) İskeletleri ve Anadolu Klasik-Helenistik Dönem Toplumlarının Sağlık Profili. Ankara Üniversitesi Dil ve Tarih-Coğrafya Dergisi. 2012;52(1):29-42.
17. Şahin S, Ozbulut Z, Ozer I, Sağır M, Güleç E. Pınarkent Roma Dönemi Iskeletlerinin Paleoantropolojik Analizi. Ankara Üniversitesi Sosyal Bilimler Dergisi. 2015;6(1):57-70.
18. Klepınger LK, Kurn LJ, Wıllıams WS. An Elementary Analysis of Archaeological Bone from Sieily as Test of Predictability of Diagenetic Change. American Journal Of Physical Anthropology. 1986;70:325-31.
19. Grattan J, Huxley S, Karaki LA, Toland H, Gilbertson D, Pyatt B, Saad Z. 'Death..more desirable than life'? The human skeletal record and toxicological implications of ancient copper mining and smelting in Wadi Faynan, southwestern Jordan. Toxicology and Industrial Health. 2002;18:297-307.
20. Wilson J. Sorption of Metals from Adequeos Solution by Bone Charcoal, Phill D Thesis. UK: University of Glasgow 2002.
21. Zapata J, Perz-Sirvent C, Martinez-Sanchez MJ, Tovar P. Diagenesis, not biogenesis: Two late Roman skeletal examples. Science of the Total Environment. 2006;369:357-68.
22. Doğan M. Zinc Deficiency and Excess. Klinik Tıp Pediatri Dergisi. 2020;12(1):13-9.

J Surg Med. 2023;7(8):468-472.
DOI: 10.28982/josam.7888

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Comparison of two anastomosis techniques in terms of postoperative pancreatic fistula development: A retrospective cohort study

**Gülten Çiçek Okuyan, Mehmet Talu**

Department of General Surgery, Haydarpaşa Numune Education and Training Hospital, İstanbul, Turkey

**ORCID ID of the author(s)**

GÇO: 0000-0002-9909-1840
MT: 0000-0003-2600-6315

**Corresponding Author**
Gülten Çiçek Okuyan
Haydarpaşa Numune Education and Training Hospital, Tıbbiye Cad. No: 23 34668, Üsküdar / Istanbul, Turkey
E-mail: dr.cicekgulten@gmail.com

**Ethics Committee Approval**
The study was approved by Haydarpasa Numune Training and Research Hospital Ethics Committee approved the study protocol (Date: 05.03.2021, Number: HNEAH KAEK 2021/KK/49). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 22

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Postoperative pancreatic fistula (POPF) development is a common complication after pancreaticoduodenectomy. Various surgical anastomosis techniques have been proposed to mitigate this risk. This study compares two techniques: the two-layer duct-to-mucosa pancreaticojejunostomy (TLPJ) and the modified layer-to-layer end-to-side duct-to-mucosa pancreaticojejunostomy with jejunal serosa resection (MLLPJ).

**Methods**: A retrospective cohort study was conducted on patients who underwent pancreaticoduodenectomy between January 2012 and December 2020. The primary outcome was the rate of biochemical leak and clinically relevant POPF (grades B and C POPFs).

**Results**: The rate of biochemical leak was significantly higher in the TLPJ group than in the MLLPJ group (54.5% vs. 4.0%, $P<0.001$). Clinically relevant POPFs developed in 5.2% of all patients, with rates of 6.1% in the TLPJ group and 4.0% in the MLLPJ group. Patients with longer surgery durations, increased bleeding, and a soft pancreas texture had significantly higher risk of developing clinically relevant POPFs ($P=0.009$, $P=0.039$, and $P=0.022$, respectively).

**Conclusion**: The MLLPJ anastomosis technique demonstrated a significant reduction in biochemical leak rates. However, the choice between TLPJ and MLLPJ did not significantly impact the rates of clinically relevant POPFs. Other factors, such as surgery duration, bleeding volume, and pancreas texture, were identified as significant risk factors for the development of these fistulas.

**Keywords:** pancreaticoduodenectomy, pancreaticojejunostomy, pancreatic fistula, postoperative complications, jejunum, serosa

How to cite: Okuyan GÇ, Talu M. Comparison of two anastomosis techniques in terms of postoperative pancreatic fistula development: A retrospective cohort study. J Surg Med. 2023;7(8):468-472.

## Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in developed countries [1]. Surgical resection is the primary treatment method in operable pancreatic cancer patients. The operative mortality related to pancreaticoduodenectomy (PD) has been reduced to below 3% as a result of improved surgical techniques, new technologies, and increased surgical experience [2]. Nevertheless, the rate of patients who develop a postoperative pancreatic fistula (POPF) after PD is still above 10%. Up to 40% mortality rates have been reported, depending on the severity of POPF [2,3].

According to the International Study Group of Pancreatic Fistula (ISGPF), three times more drain amylase levels than serum amylase levels on the third postoperative day [4] indicate POPF. POPF, graded as A in the older version of the ISGPF guidelines, has been redefined as a biochemical leak in the updated guidelines. Thus, POPFs are currently categorized as either Grade B or C. The incidence of POPF reported in the literature varies considerably based on the different definitions of POPF [3,4]. Therefore, the incidence rate of clinically relevant POPFs needs to be revised.

Narrow pancreatic duct (<3 mm) and soft pancreatic tissue, which are among the risk factors for the development of POPF, have been studied extensively [5,6]. It has been speculated that technical modifications, including external stenting of the pancreatic duct, pancreatico-jejunal or pancreatico-gastric anastomosis, and reinforcement of the anastomosis via several materials, might reduce POPF rates compared to the use of only two-layer end-to-side duct-to-mucosal pancreaticojejunostomy (TLPJ) [7,8]. Nevertheless, the use of techniques or modifications, such as the Blumgart method with one to six transpancreatic jejunal seromuscular U-sutures, modified Kakita anastomosis with two to eight nonabsorbable interrupted penetrating sutures between the pancreatic stump and jejunal seromuscular layer, two-layer duct-to-mucosa anastomosis with resection of jejunal serosa (layer-to-layer PJ), and modified layer-to-layer PJ (MLLPJ), resulted in controversial outcomes [7,9–14]. Several studies have proposed that MLLPJ might be an effective way to reduce the rates of POPF [10,12].

In light of the preceding evidence, this study aimed to compare the efficacies of TLPJ and MLLPJ in terms of the rate of POPF after PD and determine the risk factors associated with the development of clinically relevant POPFs.

## Materials and methods

### Population and sample

The population of this retrospective cohort study consisted of 186 patients who underwent PD with the diagnosis of a benign or malignant pancreatic tumor at Haydarpaşa Numune Training and Research Hospital between January 2012 and December 2020. Patients with neoadjuvant chemoradiotherapy (n=20) and incomplete medical data (n=108) were excluded from the study. In the end, 58 patients were included in the study sample. The patients were divided into two groups based on the type of PF anastomosis technique, i.e., TLPJ or MLLPJ, performed by two different surgical teams. Accordingly, 33 (56.9%) and 25 (43.1%) patients who were operated on using the TLPJ and MLLPJ techniques constituted TLPJ and MLLPJ groups, respectively.

The Haydarpasa Numune Training and Research Hospital Ethics Committee approved the study protocol (date: 05.03.2021; number: HNEAH KAEK 2021/KK/49). The study was performed in accordance with the principles set forth in the Declaration of Helsinki. Written informed consent could not be acquired from the patients due to the study's retrospective design and the data's anonymity.

### Data collection

Patients' demographic characteristics, intraoperative findings, pathological diagnoses, postoperative morbidities, including biochemical leak, Grades B and C POPFs, intra-abdominal abscess, intra-abdominal bleeding, and delayed gastric emptying, and 90-day mortality rates were obtained from the medical files of the patients and the hospital information system.

We diagnosed biochemical leak, Grades B and C POPFs, based on the 2016 ISGPF criteria [4].

The pancreatic duct size was measured using images from preoperative radiological examinations. The hardness of the pancreatic tissue, which is categorized as either hard or soft, was determined intraoperatively.

Patients with high total bilirubin values received preoperative drainage with endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), as well as biliary stenting, where necessary.

### Surgical procedure

In Group TLPJ, the jejunal serosa and pancreatic capsule were sutured intermittently with 4/0 polydioxanone (PDS) without resection of the serosa, and duct-to-mucosa anastomosis was performed with 4/0 PDS [8]. Conversely, in Group MLLPJ, a segment of the jejunal serosa smaller than the surface of the pancreas was excised using a scalpel, allowing the pancreas to invaginate into the small intestine, with surgeons taking care not to open the mucosa. After the posterior wall was sutured with 4/0 PDS, the jejunal mucosa was opened from the section corresponding to the level of the duct. A duct-to-mucosa anastomosis was performed with four to six individual sutures with 4/0 PDS. The anastomosis was completed by ensuring that the jejunum serosa and pancreatic capsule were more inverted, employing intermittent sutures with 4/0 PDS on the anterior side [10].

In both anastomosis groups, a silicone internal stent was placed in the pancreatic duct. Choledochojejunostomy and gastrojejunostomy were performed to conduct Roux-Y anastomosis as described previously [8,10].

### Postoperative follow-up

A standard follow-up procedure was applied to all patients. Feeding was started early in patients who did not have gastric emptying problems. Somatostatin was started in patients with a narrow pancreatic duct (<3 mm), soft pancreatic tissue, or high drain amylase levels. A lasting need for nasogastric decompression by the tenth postoperative day or the inability to tolerate oral intake was considered a delay in gastric emptying [15].

Postoperative complications were classified according to the Clavien-Dindo staging system [16]. In order to follow the development of POPF, serum amylase levels on the first and third postoperative days and drain amylase levels on the third postoperative day were checked.

**Statistical analysis**

The study's primary outcome was the incidence of the biochemical leak and Grade B and Grade C POPFs, whereas the study's secondary outcome was the risk factors with an impact on the development of clinically relevant POPFs (Grades B and C).

For descriptive statistics, mean (standard deviation) was used to present continuous data with normal distribution. Median with minimum-maximum values was applied for continuous variables without normal distribution. Numbers and percentages were used for categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests analyzed the normal distribution of the numerical variables.

The Independent Samples t-test compared two independent groups in which numerical variables had a normal distribution. For the variables without normal distribution, the Mann-Whitney U test was used to compare two independent groups. The Pearson Chi-Square and Fisher's Exact tests were used to compare the differences between categorical variables in 2x2 tables. The Fisher-Freeman-Halton test was used in RxC tables.

For statistical analysis, Jamovi (Version 2.2.5.0) and JASP (Version 0.16.1) were used. The significance level (*P*-value) was determined at 0.05 in all statistical analyses.

## Results

The age and gender distribution of the patients in Groups TLPJ and MLLPW were similar (*P*=0.986 and *P*=0.279, respectively). The comparison of preoperative and postoperative clinical findings revealed no significant difference between the groups (*P*>0.05 for all comparisons) (Table 1). The median duration of surgery was 315 and 300 min in Groups TLPJ and MLLPJ, respectively (*P*=0.641). The pancreatic duct width and the proportion of patients with soft pancreas were similar between the groups (*P*=0.879 and *P*=0.287, respectively). Adenocarcinoma was the most common diagnosis in both groups (75.8% in Group TLPJ and 76.0% in Group MLLPJ). There was no significant difference between the groups in the frequencies of the pathological diagnoses (*P*=0.287). Other characteristics of the patients are summarized in Table 1.

There was a significant difference between the groups in the rates of patients with a biochemical leak and different POPF grades (*P*<0.001). The rate of patients with biochemical leak was 54.5% in Group TLPJ and 4.0% in Group MLLPJ. There was one (3.0%) patient with Grade B POPF in Group TLPJ and one with Grade C POPF in each group (3.0% in Group TLPF and 4.0% in Group MLLPJ). The rate of patients who developed clinically relevant POPFs, either Grade B or C, was 6.1% and 4.0% in Groups TLPJ and MLLPJ, respectively (*P*=0.999). The distribution of other postoperative complications, except for gastric paresis, was similar between the groups (*P*>0.05 for all comparisons). The incidence of gastric paresis was significantly higher in Group TLPJ than in Group MLLPJ (*P*=0.022). There was a significant difference between the groups in terms of grades of surgical complications as determined by the Clavien-Dindo classification system (*P*=0.008). The length of hospitalization was significantly shorter in Group MLLPJ than in Group TLPJ (*P*=0.002). The 30-day and 90-day mortality rates were similar between the groups (*P*=0.999 and *P*=0.687, respectively) (Table 2).

Table 1: Distribution of demographic and clinical characteristics by the anastomosis technique.

| | Groups | | |
|---|---|---|---|
| | **TLPJ (n=33)** | **MLLPJ (n=25)** | ***P*-value** |
| **Sex** † | | | |
| Female | 15 (45.5) | 7 (28) | 0.279[c] |
| Male | 18 (54.5) | 18 (72) | |
| **Age (year)** ‡ | 62.8 (14.2) | 62.9 (12.0) | 0.986[a] |
| **BMI (kg/m$^2$)** ‡ | 28.9 (6.2) | 30.7 (5.1) | 0.228[a] |
| **Comorbidities** † | 24 (72.7) | 18 (72.0) | 0.999[c] |
| **ASA stages** † | | | |
| 1 | 2 (6.1) | 3 (12) | 0.698[c] |
| 2 | 23 (69.7) | 14 (56) | |
| 3 | 6 (18.2) | 6 (24) | |
| 4 | 2 (6.1) | 2 (8) | |
| **Biliary drainage method** † | | | |
| ERCP | 6 (28.6) | 8 (57.1) | 0.181[c] |
| PTC | 15 (71.4) | 6 (42.9) | |
| Biliary stenting † | 6 (18.2) | 8 (34.8) | 0.272[c] |
| Duration of surgery (min) § | 315 (180–540) | 300 (235–480) | 0.641[b] |
| Amount of bleeding (ml) § | 600 (50–1600) | 450 (200–2000) | 0.819[b] |
| Pancreatic duct width (mm) § | 4 (2–10) | 4 (2–15) | 0.879[b] |
| **Structure of pancreatic tissue** † | | | |
| Soft | 12 (36.4) | 5 (20) | 0.287[c] |
| Hard | 21 (63.6) | 20 (80) | |
| **Pathological diagnosis** † | | | |
| Adenocarcinoma | 25 (75.8) | 19 (76.0) | 0.287[c] |
| Neuroendocrine tumor | 3 (9.1) | 3 (12.0) | |
| Chronic Pancreatitis | 0 (0) | 3 (12.0) | |
| Other | 5 (15.2) | 0 (0) | |
| **TNM Stage** † | | | |
| 1B | 3 (10.7) | 3 (13.6) | 0.752[c] |
| 2A | 4 (14.3) | 5 (22.7) | |
| 2B | 18 (64.3) | 11 (50) | |
| 3 | 3 (10.7) | 3 (13.6) | |

†: n (%), ‡: mean (standard deviation), §: median (min-max), [a] Independent Samples T-Test, [b] Mann-Whitney U test, [c] Pearson Chi-Square/Fisher's Exact test/Fisher Freeman Halton test, TLPJ: two-layered end-to-side duct-to-mucosal pancreaticojejunostomy, MLLPJ: modified layer-to-layer pancreaticojejunostomy, BMI: body mass index, ASA: American Society of Anesthesiologists, ERCP: endoscopic retrograde cholangiopancreatography, PTC: percutaneous cholangiopancreatography.

Table 2: Distribution of postoperative findings in the groups based on the anastomosis technique.

| | Groups | | |
|---|---|---|---|
| | **TLPJ (n=33)** | **MLLPJ (n=25)** | ***P*-value** |
| **Postoperative third day drain amylase level (IU/mL)** § | 558 (5–32865) | 29 (4–15748) | 0.001[b] |
| **POPF Grades** † | | | |
| Biochemical leak | 18 (54.5) | 1 (4.0) | <0.001[c] |
| POPF Grade B | 1 (3.0) | 0 (0) | |
| POPF Grade C | 1 (3.0) | 1 (4.0) | |
| **Patients with clinically relevant POPF** | 2 (6.1) | 1 (4.0) | 0.999[c] |
| **Biliary fistula** † | 3 (9.1) | 0 (0) | 0.251[c] |
| **Gastric paresis** † | 16 (48.5) | 4 (16.0) | 0.022[c] |
| **Intraabdominal abscess** † | 3 (9.1) | 1 (4.0) | 0.627[c] |
| **Bleeding** † | 3 (9.1 | 1 (4.0) | 0.627[c] |
| **Wound infection** † | 11 (33.3) | 8 (32.0) | 0.999[c] |
| **Clavien-Dindo grades** † | | | |
| 1 | 3 (12) | 7 (63.6) | 0.008[c] |
| 2 | 16 (64) | 2 (18.2) | |
| 3 | 4 (16) | 1 (9.1) | |
| 5 | 2 (8) | 1 (9.1) | |
| **Length of hospital stay** § | 16 (8–60) | 11 (7–20) | 0.002[b] |
| **30-day mortality** † | 2 (6.1) | 2 (8.0) | 0.999[c] |
| **90-day mortality** † | 5 (15.2) | 2 (8.0) | 0.687[c] |

†: n (%), §: median (min-max), [b] Mann-Whitney U test, [c] Pearson Chi-Square/Fisher's Exact test/Fisher Freeman Halton test, TLPJ: two-layered end-to-side duct-to-mucosal pancreaticojejunostomy, MLLPJ: modified layer-to-layer pancreaticojejunostomy, POPF: postoperative pancreatic fistula.

There were three (5.2%) patients with clinically relevant POPFs in the entire study group. There was no significant difference between the groups in terms of the demographic and preoperative clinical characteristics of the patients with clinically relevant POPFs (*P*>0.05 for all comparisons) (Table 3). The patients with clinically relevant POPFs had a significantly longer

duration of surgery and a significantly higher amount of bleeding ($P$=0.009 and $P$=0.039, respectively). All three patients with clinically relevant POPFs had soft pancreas ($P$=0.022). There was no significant difference between the groups in other intraoperative and postoperative characteristics ($P$>0.05 for all comparisons) (Table 3).

Table 3: Distribution of demographic and clinical characteristics in patients with and without clinically relevant fistula.

| | Patients | | |
|---|---|---|---|
| | **Without POPF (n=55)** | **With POPF (n=3)** | ***P*-value** |
| **Sex** † | | | |
| Female | 20 (36.4) | 2 (66.7) | 0.551[c] |
| Male | 35 (63.6) | 1 (33.3) | |
| **Age (year)** ‡ | 62 (31–93) | 67 (59–78) | 0.493[b] |
| **BMI (kg/m²)** ‡ | 29.0 (17.5–45.0) | 29.6 (28.2–33.0) | 0.686[b] |
| **Comorbidities** † | 39 (70.9) | 3 (100.0) | 0.554[c] |
| **ASA stages** † | | | |
| 1 | 5 (9.1) | 0 (0.0) | 0.999[c] |
| 2 | 35 (63.6) | 2 (66.7) | |
| 3 | 11 (20.0) | 1 (33.3) | |
| 4 | 4 (7.3) | 0 (0.0) | |
| **Biliary drainage method** † | | | |
| ERCP | 13 (39.4) | 1 (50.0) | 0.999[c] |
| PTC | 20 (60.6) | 1 (50.0) | |
| Biliary stenting † | 13 (24.5) | 1 (33.3) | 0.999[c] |
| **Duration of surgery (min)** § | 300 (180–540) | 480 (420–480) | 0.009[b] |
| **Amount of bleeding (ml)** § | 450 (50–2000) | 1050.0 (800–1700) | 0.039[b] |
| **Pancreatic duct width (mm)** § | 4 (2–150) | 3 (3-3) | 0.333[b] |
| **Structure of pancreatic tissue** † | | | |
| Soft | 14 (25.5) | 3 (100) | 0.022[c] |
| Hard | 41 (74.5) | 0 (0) | |
| **Anastomosis type** | | | |
| TLPJ | 31 (56.4) | 2 (66.7) | 0.999[c] |
| MLLPJ | 24 (43.6) | 1 (33.3) | |
| **Pathological diagnosis** † | | | |
| Adenocarcinoma | 42 (76.4) | 2 (66.7) | 0.571[c] |
| Neuroendocrine tumor | 5 (9.1) | 1 (33.3) | |
| Chronic Pancreatitis | 3 (5.5) | 0 (0) | |
| Other | 5 (15.2) | 0 (0) | |
| **TNM Stage** † | | | |
| 1B | 5 (10.6) | 1 (33.3) | 0.619[c] |
| 2A | 9 (19.1) | 0 (0.0) | |
| 2B | 27 (57.4) | 2 (66.7) | |
| 3 | 6 (12.8) | 0 (0.0) | |

†: n (%), ‡: mean standard deviation, §: median (min-max), b Mann-Whitney U test, c Pearson Chi-Square/Fisher's Exact test/Fisher Freeman Halton test, POPF: postoperative pancreatic fistula, BMI: body mass index, ASA: American Society of Anesthesiologists, ERCP: endoscopic retrograde cholangiopancreatography, PTC: percutaneous cholangiopancreatography, TLPJ: two-layered end-to-side duct-to-mucosal pancreaticojejunostomy, MLLPJ: modified layer-to-layer pancreaticojejunostomy.

In addition, there were significant differences between the groups in the postoperative clinical findings of the patients with clinically relevant POPFs. Accordingly, the rates of gastric paresis, intra-abdominal abscess, and wound infection were significantly higher in patients with POPF than those without POPF ($P$<0.05 for all comparisons) (Table 4). There were significant differences between the patients with and without POPF in the grades of surgical complications graded according to the Clavien-Dindo classification system, the length of hospital stay, and the 90-day mortality (Table 4).

Table 4: Distribution of postoperative clinical characteristics in patients with and without clinically relevant fistula.

| | Patients | | |
|---|---|---|---|
| | **Without POPF (n=55)** | **With POPF (n=3)** | ***P*-value** |
| **Biliary fistula** † | 2 (3.6) | 1 (33.3) | 0.150[c] |
| **Gastric paresis** † | 17 (30.9) | 3 (100.0) | 0.037[c] |
| **Intraabdominal abscess** † | 2 (3.6) | 2 (66.7) | 0.011[c] |
| **Bleeding** † | 3 (5.5) | 1 (33.3) | 0.196[c] |
| **Wound infection** † | 16 (29.1) | 3 (100.0) | 0.031[c] |
| **Clavien-Dindo grades** † | | | |
| 1 | 10 (30.3) | 0 (0.0) | 0.012[c] |
| 2 | 18 (54.5) | 0 (0.0) | |
| 3 | 3 (9.1) | 2 (66.7) | |
| 5 | 2 (6.1) | 1 (33.3) | |
| **Length of hospital stay** § | 14 (7–60) | 35 (18–38) | 0.025[b] |
| **30-day mortality** † | 3 (5.5) | 1 (33.3) | 0.196[c] |
| **90-day mortality** † | 5 (9.1) | 2 (66.7) | 0.036[c] |

†: n (%), §: median (min-max), [b] Mann-Whitney U test, [c] Pearson Chi-Square/Fisher's Exact test/Fisher Freeman Halton test, POPF: postoperative pancreatic fistula

## Discussion

The study findings indicated that the MLLPJ anastomosis technique significantly prevented the development of biochemical leaks. In addition, it was determined that the length of surgery, the amount of bleeding, and the texture of the pancreas were significant risk factors for clinically relevant POPFs. On the other hand, the anastomosis type used—TLPJ or MLLPF—had no impact on the development of clinically relevant POPFs. Therefore, intraoperative findings and pancreatic tissue characteristics seem to have a higher prognostic value in predicting POPF than the technical variances.

Reconstruction in relation to the PD procedure and the effects of reconstruction on the development of POPF are still a matter of debate. Invagination PJ and duct-to-mucosa PJ continue to be the most popular reconstruction procedures. Although each procedure has some advantages and disadvantages, several systematic reviews and meta-analyses failed to show the superiority of either technique [17–19]. In the Pancreatic Anastomosis Audit (PARANOIA) study, the authors reported that invagination PJ, compared to the duct-to-mucosa technique, was associated with reduced rates of all POPF, including biochemical leaks and clinically relevant fistula types [17]. The most recent version of the Cochrane review did not find any significant difference between duct-to-mucosa and invagination PJs in terms of the development of Grade B or C POPFs [18]. Although several studies have reported that the modified Blumgart technique was associated with significantly lower POPF rates [7,9], the Cochrane review reported that the evidence on the superiority of duct-to-mucosa PJ using the modified Blumgart technique was inconclusive [18]. Another study that compared six-stitch PJ and standard PJ determined that six-stitch PJ reduced POPF development by 81.7% and that pancreatic tissue hardness, pancreatic duct size, and anastomosis technique were important risk factors for the development of POPF [20]. Kone et al. [21] compared invagination PJ and duct-to-mucosa PJ techniques and reported that multivariate logistic regression and propensity score analyses did not reveal any significant difference between the two techniques in terms of POPF development rate. Thus, it is still unclear which anastomosis technique has the lowest rate of developing clinically relevant POPFs after PD.

Hayashibe et al. [14], in 2005, were the first researchers to perform the duct-to-mucosa PJ with resection of jejunal serosa (layer-to-layer PJ). This technique did not result in any leakage after PD in any of their consecutive studies [12–14]. They suggested that promoting the vascularization and enhancement of the anastomotic healing process could be possible via the resection of the serosa. This new duct-to-mucosa PJ technique with resection of the jejunal serosa (layer-to-layer PJ) is regarded as a safe, reliable, and favorable anastomosis technique after PD. In 2006, Ibrahim et al. [22] added a new anastomotic layer (triple-layer duct-to-mucosa PJ) to the technique previously described by Hayashibe et al. [14] and found that 1.96% of patients operated on with this modified technique developed POPF. Su et al. [10] abbreviated this modified technique as MLLPJ in an article published in 2014. They performed triple-layer duct-to-mucosa PJ with jejunal serosal resection and found that a significantly higher rate of patients with soft pancreatic

tissue and pancreatic duct diameter <3 mm and patients in whom anastomosis with the TLPJ technique was used developed POPF. Accordingly, they speculated that the partial invagination achieved in the MLLPJ technique reduced the tension over the anastomosis, as there be no dead space around the anastomosis, and that the alignment of the pancreatic stump and the jejunal mucosa might have resulted in better healing. In contrast, the findings of this study did not reveal any significant relationship between the anastomosis type and the development of clinically relevant POPFs. Although the MLLPJ technique resulted in significantly lower rates of biochemical leak compared to the TLPJ technique, this significant difference did not translate into a clinical benefit. Therefore, a definitive conclusion on the superiority of MLLPJ in reducing POPF after PD could not be made.

POPF can lead to severe complications such as delayed gastric emptying, intra-abdominal abscess, and intra-abdominal bleeding [23]. Delayed gastric emptying, which is reported in 19% to 57% of the patients with POPF, is a non-life-threatening morbidity that decreases the quality of life and prolongs hospitalization. It has been reported that delayed gastric emptying can predict complications such as POPF or intra-abdominal abscess [24, 25]. In fact, the incidence of gastric paresis was significantly higher in patients who developed POPF in this study.

**Limitations**

The most important limitations of this study were its retrospective nature and relatively small sample size. Additionally, the fact that the two surgical techniques investigated within the scope of this study were performed by two different teams might have impacted the results, given the differences between the teams in surgical experience. The size and heterogeneity of the sample and lack of control might have prevented significant differences. The performance of each technique by two different teams might be regarded as a strength of the study, considering the standardized surgical experience. Future large-scale studies are needed to obtain more evident outcomes for the optimum anastomotic technique for pancreaticojejunostomy.

**Conclusion**

In conclusion, the findings of this study indicated that the use of the MLLPJ anastomosis technique might have prevented the occurrence of biochemical leaks following PD. The length of surgery, the amount of bleeding, and the texture of the pancreas were significant risk factors for the development of clinically relevant POPFs. However, further studies are needed to shed light on the debate about the optimum PJ technique.

## References


1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492.
2. Chen BP, Bennett S, Bertens KA, Balaa FK, Martel G. Use and acceptance of the International Study Group for Pancreatic Fistula (ISGPF) definition and criteria in the surgical literature. HPB (Oxford). 2018 Jan;20(1):69-75. doi: 10.1016/j.hpb.2017.08.022.
3. Fu SJ, Shen SL, Li SQ, Hu WJ, Hua YP, Kuang M, et al. Risk factors and outcomes of postoperative pancreatic fistula after pancreatico-duodenectomy: an audit of 532 consecutive cases. BMC Surg. 2015 Mar 26;15:34. doi: 10.1186/s12893-015-0011-7.
4. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017 Mar;161(3):584-91. doi: 10.1016/j.surg.2016.11.014.
5. Ke Z, Cui J, Hu N, Yang Z, Chen H, Hu J, et al. Risk factors for postoperative pancreatic fistula: Analysis of 170 consecutive cases of pancreaticoduodenectomy based on the updated ISGPS classification and grading system. Medicine (Baltimore). 2018 Aug;97(35):e12151. doi: 10.1097/MD.0000000000012151.
6. Pedrazzoli S. Pancreatoduodenectomy (PD) and postoperative pancreatic fistula (POPF): A systematic review and analysis of the POPF-related mortality rate in 60,739 patients retrieved from the English literature published between 1990 and 2015. Medicine (Baltimore). 2017 May;96(19):e6858. doi: 10.1097/MD.0000000000006858.
7. Satoi S, Yamamoto T, Yanagimoto H, Yamaki S, Kosaka H, Hirooka S, et al. Does modified Blumgart anastomosis without intra-pancreatic ductal stenting reduce post-operative pancreatic fistula after pancreaticojejunostomy? Asian J Surg. 2019 Jan;42(1):343-9. doi: 10.1016/j.asjsur.2018.06.008.
8. Liang H, Wu JG, Wang F, Chen BX, Zou ST, Wang C, et al. Choice of operative method for pancreaticojejunostomy and a multivariable study of pancreatic leakage in pancreaticoduodenectomy. World J Gastrointest Surg. 2021 Nov 27;13(11):1405-13. doi: 10.4240/wjgs.v13.i11.1405.
9. Fujii T, Sugimoto H, Yamada S, Kanda M, Suenaga M, Takami H, et al. Modified Blumgart anastomosis for pancreaticojejunostomy: technical improvement in matched historical control study. J Gastrointest Surg. 2014 Jun;18(6):1108-15. doi: 10.1007/s11605-014-2523-3.
10. Su AP, Zhang Y, Ke NW, Lu HM, Tian BL, Hu WM, et al. Triple-layer duct-to-mucosa pancreaticojejunostomy with resection of jejunal serosa decreased pancreatic fistula after pancreaticoduodenectomy. J Surg Res. 2014 Jan;186(1):184-91. doi: 10.1016/j.jss.2013.08.029.
11. Hashimoto D, Hirota M, Yagi Y, Baba H. End-to-side pancreaticojejunostomy without stitches in the pancreatic stump. Surg Today. 2013 Jul;43(7):821-4. doi: 10.1007/s00595-012-0371-x.
12. Hayashibe A, Kameyama M. Duct-to-mucosa pancreaticojejunostomies with a hard pancreas and dilated pancreatic duct and duct-to-mucosa pancreaticojejunostomies with a soft pancreas and non-dilated duct. HPB (Oxford). 2008;10(1):54-7. doi: 10.1080/13651820701883130.
13. Hayashibe A, Kameyama M. The clinical results of duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy in consecutive 55 cases. Pancreas. 2007 Oct;35(3):273-5. doi: 10.1097/MPA.0b013e3180676dc2.
14. Hayashibe A, Sakamoto K, Shinbo M, Makimoto S, Nakamoto T. The surgical procedure and clinical results of the duct to mucosa pancreaticojejunostomies with resection of jejunal serosa. Int J Surg. 2005;3(3):188-92. doi: 10.1016/j.ijsu.2005.07.001.
15. Balzano G, Zerbi A, Braga M, Rocchetti S, Beneduce AA, Di Carlo V. Fast-track recovery programme after pancreatico- duodenectomy reduces delayed gastric emptying. Br J Surg. 2008 Nov;95(11):1387-93. doi: 10.1002/bjs.6324.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13. doi: 10.1097/01.sla.0000133083.54934.ae.
17. Halle-Smith JM, Pande R, Hall L, Hodson J, Roberts KJ, Arshad A, et al. Perioperative interventions to reduce pancreatic fistula following pancreatoduodenectomy: meta-analysis. Br J Surg. 2022 Aug 16;109(9):812-21. doi: 10.1093/bjs/znac074.
18. Hai H, Li Z, Zhang Z, Cheng Y, Liu Z, Gong J, et al. Duct-to-mucosa versus other types of pancreaticojejunostomy for the prevention of postoperative pancreatic fistula following pancreaticoduodenectomy. Cochrane Database Syst Rev. 2022 Mar 15;3(3):CD013462. doi: 10.1002/14651858.CD013462.pub2.
19. Fernández-Cruz L, Belli A, Acosta M, Chavarria EJ, Adelsdorfer W, López-Boado MA, et al. Which is the best technique for pancreaticoenteric reconstruction after pancreaticoduodenectomy? A critical analysis. Surg Today. 2011 Jun;41(6):761-6. doi: 10.1007/s00595-011-4515-1.
20. Zeng ZL, Sun Y, Xue D, Liu PL, Chen WM, Zhang L. Effect of six-stitch pancreaticojejunostomy on pancreatic fistula: A propensity score-matched comparative cohort study. Hepatobiliary Pancreat Dis Int. 2020 Jun;19(3):277-83. doi: 10.1016/j.hbpd.2020.04.006.
21. Kone LB, Maker VK, Banulescu M, Maker AV. A propensity score analysis of over 12,000 pancreaticojejunal anastomoses after pancreaticoduodenectomy: does technique impact the clinically relevant fistula rate? HPB (Oxford). 2020 Oct;22(10):1394-401. doi: 10.1016/j.hpb.2020.01.002.
22. Ibrahim S, Tay KH, Launois B, Ta NC. Triple-layer duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy. Dig Surg. 2006;23(5-6):296-302. doi: 10.1159/000096244.
23. Van Buren G 2nd, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. Ann Surg. 2014 Apr;259(4):605-12. doi: 10.1097/SLA.0000000000000460.
24. McMillan MT, Allegrini V, Asbun HJ, Ball CG, Bassi C, Beane JD, et al. Incorporation of Procedure-specific Risk Into the ACS-NSQIP Surgical Risk Calculator Improves the Prediction of Morbidity and Mortality After Pancreatoduodenectomy. Ann Surg. 2017 May;265(5):978-86. doi: 10.1097/SLA.0000000000001796.
25. Caruso F, Alessandri G, Cesana G, Castello G, Uccelli M, Ciccarese F, et al. Laparoscopic pancreaticoduodenectomy for tumors of the head of pancreas; 10 cases for a single center experience. Eur Rev Med Pharmacol Sci. 2017 Oct;21(17):3745-53.

J Surg Med. 2023;7(8):473-476.
DOI: 10.28982/josam.7881

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Comparison of thyroid volumes in patients with and without endometrioma

**Sevtap Seyfettinoglu [1], Burcak Pekoz [2], Gulsum Uysal [1], Gökhan Kablan [1]**

[1] University of Health Sciences, Adana City Training and Research Hospital, Department of Obstetrics and Gynecology, Adana, Turkey
[2] University of Health Sciences, Adana City Training and Research Hospital, Department of Radiology, Adana, Turkey

**ORCID ID of the author(s)**

SS: 0000-0001-8607-6628
BP: 0000-0002-7286-5535
GU: 0000-0002-9381-4892
GK: 0000-0002-9038-759X

**Corresponding Author**
Sevtap Seyfettinoglu
Adana City Training and Research Hospital, Department of Obstetrics and Gynecology, Adana, Turkey
E-mail: sevtaponcul@gmail.com

**Ethics Committee Approval**
The study was approved by the Ethical Committee of Adana City Training and Research Hospital, Adana, Turkey (Decree No: 1557/2021). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 20

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Endometriosis is a condition characterized by endometrial tissue outside the uterus; it can lead to pelvic pain, although most cases remain asymptomatic. Abnormalities in the immune system have been hypothesized to contribute to development of ectopic endometrial tissues. Endometriosis is a chronic local inflammatory disorder associated with autoimmunity and thyroid disorders. This study aims to compare thyroid gland volumes between patients diagnosed with pathological endometrioma and those undergoing the removal of ovarian cysts for other gynecological reasons. Additionally, the study seeks to identify the coexistence of thyroid disease and determine the threshold value for thyroid volume in cases of endometriosis.

**Methods:** This prospective cohort study included 64 patients who met the defined inclusion criteria. Thyroid volumes were measured in women aged 18–45 with ovarian cysts before surgery. Group 1 comprised individuals with surgically planned endometrioma diagnoses later histologically confirmed after surgery. The control group (Group 2) consisted of women with similar anthropometric characteristics undergoing gynecological surgery for non-endometrioma ovarian cysts. Thyroid volume, functional thyroid hormone levels, tumor markers, and demographic data were compared between the groups.

**Results:** The endometrioma group exhibited a significantly higher thyroid volume. The thyroid volume variable demonstrated a diagnostic performance of 0.863 (0.771–0.956) regarding ROC-AUC in the presence of endometrioma, with a determined cutoff of 7.40. Although patients with endometrioma displayed a notably larger thyroid volume, cases of goiter were not observed. While there was no significant difference in thyroid hormones (serum TSH, T3 levels) between the groups, serum T4 was elevated in the endometrioma group, albeit within the normal laboratory range. All thyroid levels were within the normal range (euthyroid). As anticipated, serum CA-125 and CA19-9 levels were notably higher in the endometrioma group. Pathological reports did not indicate the presence of malignant cysts.

**Conclusions:** Patients with endometriosis experience increased thyroid volume, even without clinical signs of thyroid disease. The potential clinical interplay between thyroid diseases, thyroid volume, and endometriosis warrants consideration during patient follow-ups.

**Keywords:** endometriosis, thyroid disease, thyroid volume, ultrasonography

How to cite: Seyfettinoglu S, Pekoz B, Uysal G, Kablan G. Comparison of thyroid volumes in patients with and without endometrioma. J Surg Med. 2023;7(8):473-476.

## Introduction

Endometriosis is a condition characterized by the presence of tissues resembling the endometrium outside the uterine cavity. This estrogen-dependent chronic inflammatory process affects 5–10% of women of reproductive age [1]. Despite extensive research, the definitive etiology of this condition remains elusive. The prevailing hypothesis suggests that recurrent retrograde menstruation, followed by the implantation of ectopic endometrial tissue within the pelvic or abdominal cavities, is the most widely accepted cause [1,2]. Moreover, it is noteworthy that immunological factors can contribute to the persistence of endometriotic tissues beyond the uterus. These factors may also induce alterations in progesterone receptor levels and the production of crucial transcription factors [1-3]. The realm of endometriosis holds much yet to be unveiled.

The clinical manifestations of this condition, which encompass pelvic pain, gastric reflux, inflammatory bowel disease, and infertility, exhibit a spectrum of variation due to its distinct molecular pathogenesis [2-4]. Surgical detection and pathological confirmation yields designations such as endometriomas (ovarian endometriosis), peritoneal endometriotic implants, and rectovaginal nodules, all representing forms of pelvic endometriosis [5].

Recent studies have illuminated the relationship between autoimmune and endocrine disorders in individuals with endometriosis [6,7]. Aghajanova et al. [8] conducted a study elucidating the expression and cellular localization of thyroid receptors and thyroid-stimulating hormone receptors (TSHR) within the endometrium of women devoid of prior medical history. Additionally, they unveiled that thyrotropin could bind to TSHR in endometrial cells independently of the hypothalamic-pituitary system. Thyroid disorders are often intertwined with conditions such as miscarriage, preterm delivery, or infertility, and thyroid hormones have already been linked to the physiology of the endometrium and ovaries [9].

This study aimed to perform a comparative analysis of thyroid gland volume and investigate the coexistence of concurrent thyroid disease in patients diagnosed with endometrioma via pathological examination who had undergone surgery for diverse gynecological indications involving the ovaries. As far as we know, there is a lack of research concerning thyroid volume in individuals with endometriosis. Thyroid volume measurements have been undertaken in patients with diabetes mellitus and pregnant women [10-12]. Should a substantial association between thyroid volume and endometriosis emerge, our study could potentially provide insights into the monitoring and management of patients.

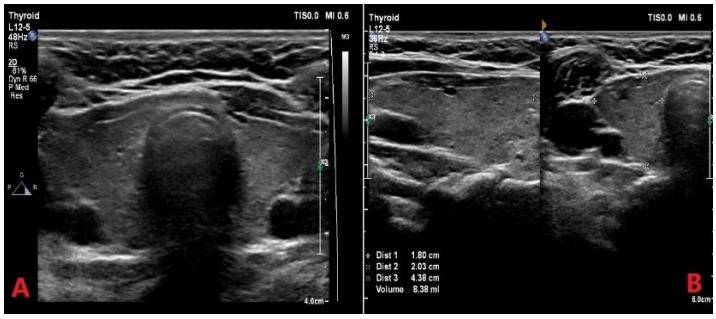
## Materials and methods

This study was conducted at a tertiary Training and Research Hospital from September 2021 to May 2022. Written informed consent was acquired from all participants. The Ethical Committee of Adana City Training and Research Hospital approved the study under Decree No: 1557/2021. The clinical trial number assigned was NCT05323539.

The study included 18–45-year-old women who presented at our clinic with a pre-diagnosis of surgically planned endometrioma (Group 1). The control group (Group 2) consisted of women undergoing gynecological surgery for reasons other than endometriosis, specifically non-endometrioma ovarian cysts. Prior to surgery, gynecological ultrasounds and assessments were conducted for all patients. Following surgery, all cysts underwent pathological examination to confirm the histology of endometriosis.

During preoperative hospitalization, ultrasonography was employed to measure the thyroid volume of all participants. Longitudinal and transverse scans were conducted while participants were supine, encompassing depth, width, and length measurements for each lobe. The ellipsoid formula was applied to estimate thyroid volume, calculated as the sum of both lobes with the exclusion of the isthmus [12]. These measurements were consistently acquired by a single experienced radiologist (BP) using the same equipment – an advanced high-resolution ultrasound system (Philips EPIQ 7) equipped with a high-resolution linear transducer (12-5 MHz) manufactured by Philips Healthcare, Bothell, WA, USA (Figure 1).

Figure 1: Thyroid volume measurement A: Thyroid gland, B: Measurement of thyroid volume.




Confirmation of the patients' pathological diagnoses was undertaken, and those with divergent results (e.g., malignancy or pelvic abscess) were excluded from the study. Patients with diabetes goiter, individuals with historical or current autoimmune thyroid dysfunction, those undergoing thyroid hormone or iodine-containing medication treatments, patients with chronic autoimmune conditions, and pregnant participants were also excluded.

Body mass index (BMI, kg/m²) and demographic characteristics of the patients, including gravidity (G), parity (P), and comprehensive gynecological history, were meticulously documented. Moreover, serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (T3), total thyroxine (T4), and ovarian cyst-related serum tumor markers such as carbohydrate-associated antigen 19-9 (CA19-9) and cancer antigen 125 (CA125) were meticulously analyzed and recorded for all enrolled patients. The reference ranges for normal serum TSH, T4, and T3 levels are 0.34–5.6 mU/L, 0.61–1.38 ng/dL, and 2.6–4.37 ng/dL, respectively.

The sample size was determined based on a power analysis utilizing the study by Gomez et al., which investigated thyroid volume in patients with type 1 diabetes mellitus [13]. The calculated number of participants needed for the study was 60, with 30 allocated to the study group and an additional 30 for the endometrioma-negative group.

**Statistical analysis**

All analyses were executed utilizing the SPSS 22.0 statistical software package. Normally distributed continuous variables in the group data were presented as mean (standard

deviation). Calculations were performed using the G*power 3.1.9.7 software, with an effect size of 1.019, a study power of 95%, and a type I error of 5%. For non-normally distributed variables in the study, descriptive statistics were provided in the form of the median and the range of values (from minimum to maximum). Categorical variables were represented using numerical values along with corresponding percentages. The normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. The continuous variables between the two groups were compared by employing either Student's t-test or the Mann-Whitney U test, based on the fulfillment of statistical assumptions. A receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point for thyroid volume. A significance threshold of 0.05 was applied to all statistical tests.

## Results

The mean age of women in the endometrioma-positive group was 41 (8.2), while 46 (7.5) was in the endometrioma-negative group. Gravida and parity were significantly higher in the endometrioma-negative group ($P$=0.003 and $P$=0.006, respectively). No statistical differences were observed in mean BMI and abortion history. The comparison of variables between the groups with and without endometrioma is presented in Table 1. There was no significant difference in thyroid hormones (serum TSH and T3 levels) between the groups, although serum T4 was found to be higher in the endometrioma group ($P$=0.016). Notably, the T4 levels fell within the normal laboratory range, indicating euthyroid status. Serum CA-125 and CA19-9 levels were significantly higher in the endometrioma group, as anticipated. Pathological reports did not indicate the presence of any malignant cysts.

Table 1: Comparison of variables between groups with and without endometrioma.

| Variables | Endometrioma | | *P*-value |
|---|---|---|---|
| | Negative Mean (SD) | Positive Mean (SD) | |
| **Age (year)** | 48.750 (7.556) | 41.000 (8.219) | <0.001 |
| **BMI (kg/m²)** | 25.090 (3.052) | 24.380 (3280) | 0.368 |
| **Gravidity*** | 2.50 (0.0–6.0) | 2.00 (0.0–7.0) | 0.003 |
| **Parity*** | 2.00 (0.0–5.0) | 1.00 (0.0–6.0) | 0.009 |
| **Abortion*** | 0.00 (0.0–2.0) | 0,.0 (0.0–2.0) | >0.999 |
| **CA125*** | 28.50 (8.0–56.0) | 46.50 (29.0–108.0) | <0.001 |
| **CA19-9*** | 14.00 (6.0–32.0) | 29.00 (21.0–49.0) | <0.001 |
| **Thyroid volume (mL)** | 5.972 (1.981) | 8.859 (1,936) | <0.001 |
| **T3 (mg/dL) (2.6–4.37)*** | 3.700 (2.10–4.60) | 3.555 (2.50–4.60) | 0.984 |
| **T4 (mg/dL) (0.61–1.38)*** | 0.975 (0.60–1.40) | 1.280 (0.76–165) | 0.016 |
| **TSH (MUI/L) (0.34–5.6)** | 2.869 (1.342) | 3.462 (1.184) | 0.065 |

BMI: body mass index, TSH: thyroid-stimulating hormone, * Median (min-max) was used as descriptive statistics.

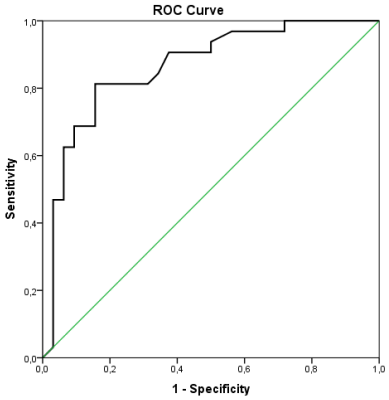
Thyroid volume exhibited a noteworthy increase in the endometrioma group. When considering the presence of endometrioma, the diagnostic performance of the thyroid volume variable yielded a value of 0.863 (0.771–0.956) in terms of ROC-AUC, and an optimal cutoff value of 7.40 was identified. Refer to Table 2 and Figure 2 for the ROC curve representation.

Table 2: ROC curve characteristics of the thyroid volume.

| | ROC-AUC | *P*-value | Cutoff | Sensitivity | Specificity |
|---|---|---|---|---|---|
| **Thyroid volume** | 0.863 (0.771-0.956) | <0.001 | 7.40 | 0.813 | 0.844 |

ROC: receiver operating characteristic, AUC: area under the curve

Figure 2: The thyroid volume and cutoff value in the ROC curve.




## Discussion

This study discovered a greater thyroid volume in women with endometrioma. In the context of endometrioma, the diagnostic accuracy of thyroid volume was calculated to be 7.40 for the optimal cutoff level. Among the patients, there were no thyroid dysfunction, diabetes, or other chronic diseases. As a result, our findings demonstrated no notable elevation in thyroid function hormones.

Petta et al. [14] assessed the risk of autoimmune thyroid disease or dysfunction in women with endometriosis. They collected data through self-administered questionnaires and compared serum values of thyroid function hormones, thyroid peroxidase antibody (TPO-Ab), and thyroglobulin antibody (TG-Ab) between groups with endometriosis (n=148) and control subjects (n=158). According to their findings, women with endometriosis do not face an elevated risk of developing thyroid disease. It is important to note that these results pertain specifically to the Brazilian female population of reproductive age.

On a different note, Sinaii et al. [6] concluded that women with endometriosis exhibited increased rates of hypothyroidism in a comprehensive survey analysis of the female population in the US. However, it is worth mentioning that they did not substantiate these diagnoses with laboratory tests.

A recent study compared the prevalence of thyroid diseases between women with and without endometriosis. The study participants were drawn from Korean health insurance reviews, resulting in two distinct groups (5615 with endometriosis and 22,460 controls). Their findings indicated an association between Graves' disease and endometriosis, whereas hypothyroidism, including autoimmune hypothyroidism, did not display a similar correlation [15]. The potential link between Graves' disease and endometriosis could be explained by autoimmunity. While the cause of endometriosis remains unknown, the disease shares common pathways with autoimmune disorders, encompassing factors like polyclonal B cell activation, imbalanced T and B cell ratios, and inflammation [16].

Furthermore, estrogen is pivotal in the pathogenesis of endometriosis and Graves' disease [15]. This is primarily due to antibodies binding to the TSH receptor, which leads to hyperplasia and hypertrophy within the thyroid gland. However, it is noteworthy that Yuk et al. [15] did not delve into the

assessment of thyroid volume or the histology of endometriosis within their study group.

In contrast, our study undertook a comprehensive approach. We not only compared the thyroid gland volume but also scrutinized the presence of concurrent thyroid diseases among patients diagnosed with endometrioma and those with ovarian cysts who underwent surgical procedures for other gynecological indications. It is crucial to mention that individuals with diabetes, goiter, prior or ongoing autoimmune thyroid dysfunction, and those utilizing thyroid hormones or medications containing iodine were deliberately excluded from our study. Consequently, we did not investigate serum TPO-Ab or TG-Ab levels.

Remarkably, our investigation yielded a noteworthy cutoff value of 7.4 concerning thyroid volume measurement. It is important to acknowledge that thyroid gland volume can exhibit variability across different nations and is influenced by factors such as age, gender, and BMI. In our country, a total thyroid volume exceeding 10.94 ml indicates goiter [17]. Despite observing a significantly larger thyroid volume in patients with endometrioma, no instances of goiter were detected among them. This outcome implies an inflammation-linked condition in patients with endometrioma who exhibit neither thyroid-related complaints nor abnormal hormone levels.

Within our study, patients with endometrioma displayed elevated tumor marker levels, aligning with existing literature. Notably, the average age of patients lacking endometrioma was significantly greater. This disparity can be attributed to endometrioma predominantly precipitating infertility, pelvic discomfort, and mass-related complications during the reproductive years. Consequently, the mean age of patients within the endometrioma-negative group skewed higher. Moreover, this divergence in age also translated into distinct patterns concerning gravidity and parity, with both parameters being notably lower among individuals in the endometrioma-positive group.

Gomez et al. [13] conducted a study involving individuals with type 1 diabetes mellitus (DM1) who lacked thyroid dysfunction. Their findings suggested that DM1 patients exhibited a greater thyroid volume than healthy controls within similar anthropometric populations. It is worth noting that factors like autoimmunity and inflammation could potentially contribute to alterations in thyroid volume among these patients. However, it is important to highlight that a consensus has yet to be reached, as discrepancies in thyroid volume have not been consistently observed in analogous studies conducted in diverse nations [18].

A notable strength of the present study lies in the histological confirmation of endometriosis diagnosis and the absence of any chronic conditions that might impact the thyroid gland.

**Limitations**

The primary limitation of the study was its small sample size. Conducting larger-scale investigations across diverse nations could potentially influence the outcomes.

**Conclusion and recommendations**

In summary, endometriosis presents a challenging scenario with many symptoms and no definitive treatment options. Given its multifaceted pathophysiology, exploring its connections and interactions with other organ systems is imperative. Specifically, diligent monitoring of patients for potential thyroid diseases and assessing potential goiter development should be undertaken. Additionally, prospective longitudinal studies are warranted to unravel the clinical interplay between thyroid health and endometriosis, providing valuable insights for patient follow-up protocols.

## References


1. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, et al. Endometriosis. Endocr Rev. 2019 Aug 1;40(4):1048-79. doi: 10.1210/er.2018-00242. PMID: 30994890; PMCID: PMC6693056.
2. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10(5):261-75.
3. Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 10 years. Hum Reprod Update. 2016;22(2):137-63.
4. Chen LC, Hsu JW, Huang KL, Bai YM, Su TP, Li CT, et al. Risk of developing major depression and anxiety disorders among women with endometriosis: A longitudinal follow-up study. J Affect Disord. 2016;190:282-5.
5. Apostolopoulos NV, Alexandraki KI, Gorry A, Coker A. Association between chronic pelvic pain symptoms and the presence of endometriosis. Arch Gynecol Obstet. 2016;293(2):439-45.
6. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. Hum Reprod. 2002;17(10):2715-24.
7. Shigesi N, Kvaskoff M, Kirtley S, Feng Q, Fang H, Knight JC, Missmer SA, Rahmioglu N, Zondervan KT, Becker CM. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. Hum Reprod Update. 2019;25(4):486-503.
8. Aghajanova L, Stavreus-Evers A, Lindeberg M, Landgren BM, Sparre LS, Hovatta O. Thyroid-stimulating hormone receptor and thyroid hormone receptors are involved in human endometrial physiology. Fertil Steril. 2011;95(1):230-7.
9. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010;31(5):702-55.
10. Junik R, Kozinski M, Debska-Kozinska K. Thyroid ultrasound in diabetic patients without overt thyroid disease. Acta Radiol. 2006;47(7):687-91.
11. Sahin SB, Ogullar S, Ural UM, Ilkkilic K, Metin Y, Ayaz T. Alterations of thyroid volume and nodular size during and after pregnancy in a severe iodine-deficient area. Clin Endocrinol (Oxf). 2014;81(5):762-8.
12. Choi YJ, Baek JH, Hong MJ, Lee JH. Inter-observer variation in ultrasound measurement of the volume and diameter of thyroid nodules. Korean J Radiol. 2015;16(3):560-5.
13. Gómez JM, Maravall FJ, Gumà A, Abós R, Soler J, Fernández-Castañer M. Thyroid volume as measured by ultrasonography in patients With type 1 diabetes mellitus without thyroid dysfunction. Horm Metab Res. 2003;35(8):486-91.
14. Petta CA, Arruda MS, Zantut-Wittmann DE, Benetti-Pinto CL. Thyroid autoimmunity and thyroid dysfunction in women with endometriosis. Hum Reprod. 2007;22(10):2693-7.
15. Yuk JS, Park EJ, Seo YS, Kim HJ, Kwon SY, Park WI. Graves Disease Is Associated With Endometriosis: A 3-Year Population-Based Cross-Sectional Study. Medicine (Baltimore). 2016;95(10):e2975.
16. Pasoto SG, Abrao MS, Viana VS, Bueno C, Leon EP, Bonfa E. Endometriosis and systemic lupus erythematosus: a comparative evaluation of clinical manifestations and serological autoimmune phenomena. Am J Reprod Immunol. 2005;53(2):85-93.
17. Şeker S, Taş İ. Determination of Thyroid Volume and Its Relation with Isthmus Thickness. Eur J Gen Med. 2010;7(2):125-9.
18. Darendeliler FF, Kadioğlu A, Bas F, Bundak R, Günöz H, Saka N, et al. Thyroid ultrasound in IDDM. J Pediatr Endocrinol. 1994;7(1):33-7.

J Surg Med. 2023;7(8):477-480.
DOI: 10.28982/josam.7898

Research article

**Journal of Surgery and Medicine**
e-ISSN: 2602-2079
https://jsurgmed.com/

# Retrospective cohort analysis of pediatric daycare anesthesia in dentistry: An assessment of postoperative complications

**Seher Orbay Yaşlı, Dilek Günay Canpolat, Ebru Baydan**

Department of Oral and Maxillofacial Surgery, Erciyes University, Turkey, Kayseri, Turkey

**ORCID ID of the author(s)**

SOY: 0000-0001-5163-3893
DGC: 0000-0002-8985-6918
EB: 0000-0001-5902-0039

**Corresponding Author**
Seher Orbay Yaşlı
Erciyes University Faculty of Dentistry, Kayseri, Tukey
E-mail: sehersin81@hotmail.com

**Ethics Committee Approval**
The study was approved by Ethics Committee of Erciyes University Faculty of Medicine with approval number 2018/315.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Previous Presentation**
The authors presented their research at the Erciyes University Faculty of Dentistry International Congress, known as ERDİŞ 2020, which took place in Kayseri, Turkey, from February 26th to 29th, 2020.

**Published**
2023 August 23

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** In pediatric populations, the frequent challenges of patient cooperation often necessitate treatments to be performed under general anesthesia. Since these procedures do not fall under the category of major surgery, daycare anesthesia has become a prevalent approach in this field. The advantages of daycare anesthesia, such as reduced hospital stay durations and costs, make it a preferred method. It is well-recognized that daycare anesthesia, when applied across various surgical fields, has unique postoperative complications, which can sometimes be linked to the surgical procedure itself. Dental treatments represent a specific surgical domain, and elucidating potential postoperative complications in this area draws attention to preventive measures and is vital for enhancing postoperative patient comfort. The primary objective of this study was to evaluate and identify the most prevalent postoperative symptoms and complications associated with pediatric dentistry.

**Methods:** This retrospective cohort study was conducted at the Erciyes University Faculty of Dentistry between January 15 and April 15, 2019. We analyzed records of 245 pediatric patients aged 3 to 13 who underwent day-case dental procedures. The inclusion criteria encompassed all patients who underwent dental procedures under general anesthesia and were classified as ASA 1-2. Variables such as demographic data, procedure duration, comorbidities, and postoperative complications were extracted and analyzed for the current study.

**Results:** Out of the 245 pediatric patients, the median age was 6.0 years, ranging from 3.0 to 13.0 years. Females comprised 52.7% of the cohort. Most patients (62.9%) were classified under ASA class one. 27.8% of the patients reported postoperative complications such as sore throat, hoarseness, cough, or nausea/vomiting. The most prevalent postoperative complications were hoarseness (11.4%) and sore throat (9.8%). Demographic and clinical characteristics of patients with and without postoperative complications were compared. Gender significantly influences the occurrence of postoperative complications. Males had a rate of 11.0% (27 out of 245), while females had a rate of 16.7% (41 out of 245), with females experiencing complications at a higher rate than males ($P$=0.01). Age also played a role in complications: the mean age for patients with complications was 6.0 years, compared to 5.0 years for those without complications ($P$=0.02).

**Conclusion:** Pediatric daycare anesthesia, especially for dental procedures, has proven effective and safe. However, each child presents a unique set of challenges, and it's crucial to recognize and mitigate potential risks. By understanding common postoperative symptoms and tailoring anesthesia techniques accordingly, healthcare professionals can optimize outcomes and enhance the quality of pediatric patient care.

**Keywords:** ambulatory surgical procedures, day surgery, pediatric dentistry

How to cite: Orbay Yaşlı S, Günay Canpolat D, Baydan E. Retrospective cohort analysis of pediatric daycare anesthesia in dentistry: an assessment of postoperative complications. J Surg Med. 2023;7(8):477-480.

## Introduction

Day surgery, entailing the discharge of patients on the same day as their surgical procedure, offers numerous advantages, including cost savings, shorter hospital stays, and diminished postoperative complications [1]. The adoption of day surgery and anesthesia, particularly in pediatric care, has been steadily increasing, driven by enhanced patient and family comfort, cost reduction, and a decreased reliance on bed availability. Day surgeries now account for 51% to 65% of all surgical procedures, a percentage that continues to rise incrementally [2].

The inception of day surgery and anesthesia for children can be attributed to Nicoll in 1909. Generally, children are deemed optimal candidates for day surgery anesthesia due to their overall good health and their procedures' predictable, brief nature. Although complications stemming from outpatient anesthesia in children are infrequent, when they do arise, they predominantly manifest as nausea, vomiting, respiratory challenges, or cardiovascular issues [3].

Numerous studies have emphasized pediatric day surgeries' advantages and potential considerations. For example, in a 30-year hospital experience, Postuma et al. [4] illuminated pediatric daycare surgery's changing patterns and safety aspects. In a parallel vein, during a five-year investigation, Letts and coauthors [2] assessed the effectiveness of pediatric day surgery and identified its numerous benefits, including cost-effectiveness, abbreviated hospital stays, and diminished postoperative complications. Lerman [5] also delivered a comprehensive overview of pediatric ambulatory anesthesia, highlighting contemporary optimal practices and field-related challenges.

The objective of this study was to conduct a retrospective assessment of the outcomes and complications linked to day surgery and anesthesia for pediatric dental procedures conducted at our hospital from January to April 2019.

This study aimed to assess the safety and effectiveness of day surgery and anesthesia procedures in pediatric dentistry. Additionally, the study aimed to identify prevalent complications stemming from these procedures and provide recommendations for optimal practices and opportunities for enhancement to elevate patient care standards and mitigate complications.

## Materials and methods

### Study design and patient selection

This retrospective study was undertaken with the endorsement of the Ethics Committee of Erciyes University Faculty of Medicine, under the approval number 2018/315. Throughout this study, the authors strictly adhered to the ethical standards outlined in the principles of the Helsinki Declaration. The analysis encompassed the medical records of pediatric patients, aged between 3 and 13, who underwent day-case dental procedures at the Erciyes University Faculty of Dentistry from January 15 to April 15, 2019. A comprehensive evaluation of 245 patient medical records was conducted. Patients who underwent procedures under sedation and those subjected to general anesthesia with laryngeal mask airway were deliberately excluded from the study.

Postoperative complications were determined based on observation sheets meticulously filled out by nurses in both the recovery room and ward areas. These uniform observation sheets were utilized to maintain a standardized and impartial evaluation across all patients. The criteria and protocols governing nurse observations were established beforehand, ensuring all patients underwent assessment under equivalent conditions.

### Study variables

In pursuit of the study's objectives, we thoroughly reviewed and extracted diverse data elements from the patient records. This encompassed demographic particulars, such as age, gender, and body mass index (BMI). Furthermore, we examined the procedural duration, concurrent comorbidities, the distinct categories and occurrences of postoperative complications noted, and the comprehensive prevalence of postoperative complications. Each of these variables underwent a methodical analysis to glean significant insights concerning the outcomes of the day-case dental procedures.

### Statistical analysis

The collected data were analyzed using SPSS 22.0 (Statistical Package for the Social Sciences). For categorical variables, frequencies and percentages were computed, while for continuous variables, metrics such as mean, standard deviation, minimum, and maximum values were calculated. To ascertain distinctions between groups, the Chi-square test was employed. A *P*-value of <0.05 was deemed as indicating statistical significance.

## Results

The demographic and clinical characteristics of the study group, consisting of 245 patients, are described below. The median age of the participants was 6.0 years, ranging from 3.0 to 13.0 years. The cohort exhibited an almost equal distribution between genders, with females comprising 52.7% and males accounting for the remaining 47.4%.

Regarding the ASA classification, the majority (62.9%) belonged to ASA class 1, while the remaining individuals (37.1%) fell under ASA class 2. The group's average BMI was 15.39 kg/m$^2$, and the typical duration of operations averaged around 71.11 minutes.

Most participants (74.9%) reported no additional health issues when investigating comorbidities. The remaining patients presented with various conditions: asthma (7.3%), epilepsy (3.2%), autism (0.8%), and other miscellaneous health concerns (13.1%). Regarding postoperative complications, the majority (72.2%) reported none. However, some individuals did encounter problems such as hoarseness (11.4%), sore throat (9.8%), cough (3.3%), and nausea or vomiting (3.3%) (Table 1).

Table 2 presents a comparative analysis of demographic and clinical characteristics among patients with and without postoperative complications. In our study involving 245 pediatric patients, 68 experienced postoperative complications, while 177 did not encounter such issues. The median age for patients with complications was 6.0 years (range: 4.0-13.0), in contrast to a median age of 5.0 years (range: 3.0-13.0) for those who remained complication-free. A statistically significant age difference was observed between the two groups ($P$=0.02). Regarding gender distribution, among the 68 patients with

complications, 27 were male (11.0%), and 41 were female (16.7%). Conversely, among the 177 patients without complications, 102 were male (41.6%), and 75 were female (30.6%). Gender was found to exert a statistically significant influence on the occurrence of postoperative complications ($P$=0.01).

Table 1: Demographic and clinical characteristics of the study group.

| | Overall (n=245) |
|---|---|
| **Age (year) §** | 6.0 [3.0-13.0] |
| **Sex ‡** | |
| **Female** | 129 (52.7) |
| **Male** | 116 (47.4) |
| **ASA class ‡** | |
| **1** | 154 (62.9) |
| **2** | 91 (37.1) |
| **BMI (kg/m²) †** | 15.39 (3.1) |
| **Operation time†** | 71.11 (28.5) |
| **Comorbidities ‡** | |
| **No additional problems** | 185 (74.9) |
| **Asthma** | 18 (7.3) |
| **Epilepsy** | 8 (3.2) |
| **Autism** | 2 (0.8) |
| **Others** | 32 (13.1) |
| **Postoperative complication‡** | |
| **No complications** | 177 (72.2) |
| **Hoarseness** | 28 (11.4) |
| **Sore Throat** | 24 (9.8) |
| **Cough** | 8 (3.3) |
| **Nause or vomiting** | 8 (3.3) |

‡: n (%), †: mean (standard deviation), §: median [min-max], ASA: the American Society of Anesthesiologists, BMI: body mass index

Table 2: Comparison of the patients with and without postoperative complications in terms of the demographic and clinical characteristics.

| | Post-op complications | | *P*-value |
|---|---|---|---|
| | Yes (n=68) | No (n=177) | |
| **Age (year) §** | 6.0 [4.0-13.0] | 5.0 [3.0-13.0] | 0.02*** |
| **Sex ‡** | | | 0.01** |
| **Male** | 27 (11.0) | 102 (41.6) | |
| **Female** | 41.0 (16.7) | 75.0 (30.6) | |
| **ASA class ‡** | | | 0.08** |
| **1** | 46 (18.8) | 140 (57.1) | |
| **2** | 22 (8.9) | 37 (15.1) | |
| **BMI (kg/m²) †** | 14.91 (2.6) | 15.58 (3.3) | 0.09 *** |
| **Operation time†** | 71.38 (25.9) | 71.00 (28.6) | 0.92*** |
| **Comorbidities ‡** | | | 0.1 ** |
| **No Additional Problems** | 46 (18.7) | 139 (56.7) | |
| **Asthma** | 9 (3.7) | 9 (3.7) | |
| **Epilepsy** | 3 (1.2) | 5 (2.0) | |
| **Autism** | 1 (0.4) | 1 (0.4) | |
| **Others** | 9 (3.7) | 23 (9.4) | |

‡: n (%), †: mean (standard deviation), §: median [min-max], ASA: the American Society of Anesthesiologists, BMI: body mass index, * Mann-Whitney U test, ** Pearson Chi-Square, or Fisher's exact test, *** Independent samples t-test.

## Discussion

Pediatric daycare anesthesia in dentistry is gaining prominence due to its numerous benefits compared to traditional inpatient procedures. A significant global shift is occurring towards adopting day-case anesthesia, driven by cost-effectiveness, enhanced patient and guardian satisfaction, shorter hospital stays, and reduced risks of hospital-acquired infections. The swift return to a familiar environment often contributes to a faster recovery for pediatric patients, thereby diminishing the psychological distress associated with prolonged hospitalization [6]. The frequency of pediatric ambulatory surgery has recently surged, resulting in 80-90% of pediatric surgeries being performed as ambulatory procedures [5].

The safety and effectiveness of outpatient surgical procedures in pediatric patients remain a significant concern among healthcare professionals. In a 5-year study, Letts and colleagues [2] investigated 4900 pediatric patients who underwent outpatient anesthesia for procedures such as myringotomy, tonsillectomy, adenoidectomy, dental procedures, and inguinal hernia repair. They identified several advantages of this approach, including cost savings, abbreviated hospital stays, and decreased postoperative complications.

In our study, which observed a relatively high rate of postoperative complications, we compared the incidence of these complications with the demographic and clinical data of the patients. Our analysis revealed that age and gender exerted statistically significant influences on the occurrence of postoperative complications. In line with our findings, a study conducted by Chao et al. [7] on pediatric patients undergoing dental treatments under general anesthesia as daycare procedures also noted a significant correlation between postoperative complications, operation time, and age.

Lerman [5] has extensively reviewed pediatric daycare anesthesia procedures, using adenotonsillectomy as a primary example. This review delves deeply into preoperative and postoperative events within this field, providing a comprehensive understanding of pediatric daycare anesthesia on a broader scale. In contrast, our study concentrates on a more specific procedure, an area with limited representation in the current literature. Consequently, our contribution offers a valuable addition to the existing body of knowledge.

Pediatric populations undergoing day-case anesthesia frequently report procedure-specific postoperative symptoms, such as nausea or bleeding [2,8]. However, our pediatric cohort, which specifically focused on dental procedures, exhibited a distinct profile, with complications like hoarseness and sore throat being more prevalent. This disparity highlights children's distinctive postoperative challenges, a viewpoint also shared by Kain et al. [9] in their study, which delved into behavioral outcomes in children following surgery.

According to our findings, 245 patients underwent dental treatments under general anesthesia and underwent retrospective review. The rates of postoperative complications were as follows: hoarseness in 28 patients, sore throat in 24 patients, cough in eight patients, and nausea or vomiting in eight patients, resulting in an overall complication rate of 27.76%. The otolaryngology service has been among the most frequent users of day surgery. Existing literature reports complication rates associated with tonsillectomy procedures ranging from 2.2% to 20% [2].

In a study examining postoperative complications among children undergoing dental treatments with general anesthesia as a day surgery procedure, a postoperative complication rate of 61.9% was identified. The most frequently reported complications were drowsiness, pain, and difficulty eating [10]. In contrast, our study revealed that hoarseness and sore throat were the most common postoperative complications. Our postoperative complication rate stood at around 30%. This lower rate in our study may be attributed to a combination of improved preoperative assessment, the proficiency of our surgical and anesthetic team, and rigorous postoperative care protocols.

In dental practices, procedures conducted under general anesthesia inherently carry a risk for postoperative complications such as sore throats and hoarseness. Considering that these procedures are performed within the oral cavity and involve the utilization of general anesthesia equipment, the occurrence of such complications can be foreseen. Our study highlights the

necessity for supplementary measures to improve postoperative comfort within this context. These measures might involve a more cautious approach to intraoral instrument and device usage, particularly selecting softer throat tampons for use during general anesthesia.

The importance of multidisciplinary collaboration in modern healthcare cannot be emphasized enough. This is especially crucial in the realm of pediatric anesthesia. Incorporating perspectives from pediatricians, anesthetists, and dentists can lead to a more comprehensive care approach [11]. Additionally, existing literature underscores the pivotal role of preoperative counseling and postoperative support systems in improving outcomes [12].

**Limitations**

Despite our meticulous methodology, this study has its limitations. The findings might not be universally applicable due to the region-specific nature of our sample. Furthermore, our postoperative evaluation may not comprehensively capture potential long-term complications.

**Conclusion**

In conclusion, pediatric daycare anesthesia in dentistry demands specialized skills, interdisciplinary teamwork, and a profound comprehension of the distinctive challenges pediatric patients pose. We found that patients undergoing dental treatments under general anesthesia as daycare procedures most frequently encountered postoperative sore throat and hoarseness. Given our findings, it is imperative to implement targeted measures, such as utilizing softer tampon materials within the oral cavity, ensuring cautious manipulation of intraoral instruments to prevent trauma, and the anesthetist's selection of appropriate tube size, to mitigate these complications. Such approaches hold the potential to significantly heighten postoperative patient comfort and satisfaction.

Given the procedure-specific nature of our sample, future studies might contemplate incorporating a more diverse and expansive population to amplify the external validity of the results. Furthermore, extended postoperative follow-ups could prove pivotal in comprehensively understanding potential long-term complications.

## References


1. Kache SA, Sale D, Ajah JL, Makama JG. Paediatric day-case surgery in a new paediatric surgical unit in Northwestern Nigeria. Afr J Paediatr Surg. 2018;15(2):97-9. doi: 10.4103/ajps.AJPS_50_17.
2. Letts M, Davidson D, Splinter W, Conway P. Analysis of the efficacy of pediatric day surgery. Can J Surg. 2001;44(3):193-8. PMID: 11407829.
3. Healy K. A descriptive survey of the information needs of parents of children admitted for same day surgery. J Pediatr Nurs. 2013;28(2):179-85. doi: 10.1016/j.pedn.2012.07.010.
4. Postuma R, Ferguson CC, Stanwick RS, Horne JM. Pediatric day-care surgery: a 30-year hospital experience. J Pediatr Surg. 1987;22(4):304-7. doi: 10.1016/s0022-3468(87)80229-4.
5. Lerman J. Pediatric ambulatory anesthesia: an update. Curr Opin Anaesthesiol. 2019;32(6):708-13. doi: 10.1097/ACO.0000000000000787.
6. Bartier S, Gharzouli I, Kiblut N, Bendimered H, Cloutier L, Salvan D. Tonsillectomy in children and in adults: changes in practice following the opening of a day-surgery unit with dedicated operating room. Eur Ann Otorhinolaryngol Head Neck Dis. 2018;135(5):301-5. doi: 10.1016/j.anorl.2018.05.003.
7. Chao Z, Gui Jin H, Cong Y. The effect of general anesthesia for ambulatory dental treatment on children in Chongqing, Southwest China. Paediatr Anaesth. 2017;27(1):98-105. doi: 10.1111/pan.12983.
8. Tan AK, Rothstein J, Tewfik TL. Ambulatory tonsillectomy and adenoidectomy: complications and associated factors. J Otolaryngol. 1993;22(6):442-6. PMID: 8158742.
9. Kain ZN, Mayes LC, Weisman SJ, Hofstadter MB. Social adaptability, cognitive abilities, and other predictors for children's reactions to surgery. J Clin Anesth. 2000 Nov;12(7):549-54. doi: 10.1016/s0952-8180(00)00214-2. PMID: 11137417.
10. Brailo V, Janković B, Gabrić D, Lozić M, Stambolija V, Vidović Juras D, Verzak Ž. Post-Discharge Complications of Dental Treatment in General Anesthesia Performed in a Day-Care Service. Acta Stomatol Croat. 2021;55(2):168-76. doi: 10.15644/asc55/2/6.
11. Wright KD, Stewart SH, Finley GA, Buffett-Jerrott SE. Prevention and intervention strategies to alleviate preoperative anxiety in children: a critical review. Behav Modif. 2007;31(1):52-79. doi: 10.1177/0145445506295055.
12. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med. 1996;150(12):1238-45. doi: 10.1001/archpedi.1996.02170370016002.

J Surg Med. 2023;7(8):481-485.
DOI: 10.28982/josam.7829

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# The prognostic effect of lymphocyte, monocyte, and platelet counts, mean platelet volume, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio on different stages of pressure ulcers

**Leman Acun Delen [1], Mesut Öterkuş [2]**

[1] Malatya Education and Research Hospital, Department of Anesthesiology and Reanimation, Malatya, Turkey
[2] Malatya Turgut Özal University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Malatya, Turkey

**ORCID ID of the author(s)**

LAD: 0000-0001-9441-6979
MÖ: 0000-0003-1025-7662

**Corresponding Author**
Leman Acun Delen
Malatya Education and Research Hospital, Department of Anesthesiology and Reanimation, Post Code: 44100 Malatya, Turkey
E-mail: lmndelen@hotmail.com

**Ethics Committee Approval**
The study was approved by Malatya Turgut Özal University Clinical Research Ethics Committee (date: November 3, 2022, number: 2022/49). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 23

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Pressure ulcers (PU) pose a significant problem for patients in intensive care. Various factors contribute to the development of pressure sores. The primary focus of treatment is to implement measures that prevent factors such as nutrition and positioning, which can lead to PUs. Therefore, it is crucial to identify parameters that can serve as warning signals for the formation and progression of PU. This study investigates the potential use of hematological parameters as warning signals.
**Methods:** Demographic data, co-morbidities, PU stages, and laboratory parameters of 158 patients hospitalized in the intensive care unit who developed pressure ulcers during their hospital stay were recorded and analyzed.
**Results:** Among the 158 cases included in the study, PUs were more prevalent in patients of advanced age, those with pneumonia, chronic obstructive pulmonary disease (COPD), coronary diseases, and neurodegenerative diseases. Mean platelet volume (MPV) was significantly higher in PU stages 2 and 3 compared to stage 1. However, age, lymphocyte count, monocyte count, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) did not exhibit significant differences among the stages of PU ($P$<0.05).
**Conclusion:** Advanced age, pneumonia, COPD, coronary diseases, and neurodegenerative diseases are identified as risk factors for PU. Although MPV was initially considered a potential, stimulating parameter, the evidence was insufficient. Further research is required to explore this issue. The impact of parameters other than MPV did not show any excitatory signal in this study.

**Keywords:** pressure ulcer, pressure ulcer stage, hematological parameters, intensive care unit

How to cite: Delen LA, Öterkuş M. The prognostic effect of lymphocyte, monocyte, and platelet counts, mean platelet volume, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio on different stages of pressure ulcers. J Surg Med. 2023;7(8):481-485.

## Introduction

Thanks to advancements in technology and medicine and improvements in the standard of care provided in intensive care units (ICUs), patients' life expectancy has been steadily increasing. However, this prolonged life expectancy comes with certain challenges, including a rise in the number of days patients spend in intensive care, increased healthcare costs, and higher occupancy rates in ICUs. Despite implementing measures such as air beds and regular repositioning, pressure ulcers (PUs), commonly known as pressure sores, remain a significant issue during extended hospital stays, particularly among patients connected to mechanical ventilators. The incidence of PUs in ICUs ranges from 10% to 56% [1].

While PU can occur across all age groups, the risk is particularly elevated in geriatric patients. Aging is often accompanied by co-morbidities such as heart failure, coronary artery diseases, and neurodegenerative conditions like Alzheimer's disease and stroke. Furthermore, respiratory ailments stemming from smoking and a decline in respiratory capacity become more prevalent with advancing age. Geriatric patients also face additional factors such as incontinence, reduced subcutaneous adipose tissue, malnutrition, and dehydration, which can contribute to the development of PU, often exacerbated by prostate issues and Alzheimer's disease [2]. Therefore, accurate prediction of PUs, implementation of preventive measures, adequate pain management, and early treatment are vital for significantly enhancing the quality of life, particularly among these patient groups.

Studies have demonstrated that in addition to age and co-morbidities, certain parameters derived from complete blood counts, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), can serve as valuable predictors of PU formation and wound healing. Therefore, this study also examines the potential of these parameters [3]. PUs give rise to significant issues, including infection, pain, and increased healthcare costs. Hence, our study aims to guide for predicting PUs, implementing preventive measures, and determining appropriate treatment strategies.

In this study, we investigated the impact of hematological changes, hospitalization diagnoses, and co-morbidities on the development of PUs and their progression across different stages.

## Materials and methods

This retrospective cohort study was conducted in compliance with the Declaration of Helsinki and STROBE guidelines, following approval from Malatya Turgut Özal University Clinical Research Ethics Committee (date: November 3, 2022, number: 2022/49). The minimum required sample size for the study was determined as 150 patients, based on similar studies, with an alpha error of 0.05 and a beta error of 0.8. The study was carried out from January 1, 2022, to September 30, 2022. All participants were informed about the study, and written consent was obtained from them and/or their legal guardians.

Initially, a total of 180 patients with PUs who were hospitalized in the tertiary ICU were included for analysis. However, 22 patients were excluded due to their refusal to participate or the unavailability of their medical data. Consequently, the study continued with a final sample of 158 patients aged between 18 and 100 years. Exclusion criteria included patients who developed PUs before ICU admission, those with a history of diabetes or sepsis, individuals with peripheral arterial disease, patients requiring inotropic support, those unwilling to participate in the research, individuals with short postoperative hospital stays, and pediatric patients. Furthermore, patients who had PUs during hospitalization or had previously undergone plastic surgery or PU surgery were not included to optimize the study.

In our hospital's intensive care unit, all patient beds are equipped with air mattresses, and patients were regularly repositioned. To address the nutritional factor, each patient received enteral or oral feeding tailored to their specific caloric, protein, and electrolyte requirements. Patient data, including age, gender, hospitalization diagnoses, co-morbidities, laboratory results, and PU stages, were retrieved from the hospital's automation system. The study aimed to analyze the effects of these parameters on PU formation and staging.

PU stages were evaluated as: Stage 1, redness on intact skin that does not fade with pressure; Stage 2, partial thickness skin loss with exposed dermis; Stage 3, full-thickness skin loss; and stage 4, full-thickness skin and tissue loss.

**Statistical analysis**

Data analysis was performed using SPSS 22 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) software. Descriptive statistics were presented as n and % values for categorical variables, while continuous variables were expressed as mean (standard deviation [SD]) or median with interquartile range (IQR) (25th–75th percentiles). The Pearson chi-square test was employed to compare categorical variables between groups. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The Kruskal-Wallis test was utilized for comparisons involving more than two variables. A statistical significance level of $P$-value <0.05 was considered in the analysis of continuous variables.

## Results

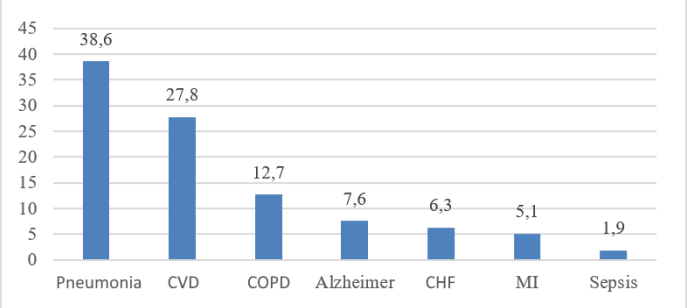
Of the 158 cases included in the search, 84 (53.2%) patients were males. The mean age of the cases was 73.9 (13.5) years, and 100 (63.3%) had co-morbidities. The PU stages of the patients were as follows: Stage 1 in 95 (60.1%) patients, stage 2 in 37 (23.4%) patients, and stage 3 in 26 (16.5%) patients. The demographic characteristics, blood, and laboratory data of the patients are demonstrated in Table 1. The diagnoses of the cases were as follows: pneumonia in 61 (38.6%) patients, cerebrovascular diseases (CVD) in 44 (27.8%) patients, chronic obstructive pulmonary disease (COPD) in 20 (12.7%) patients, Alzheimer's disease in 12 patients, heart failure (HF) in 10 (6.3%) patients, myocardial infarction (MI) in 8 (5.1%) patients, and sepsis in 3 (1.9%) patients (Figure 1).

Table 1: Demographic, clinical, and laboratory characteristics of the patients.

| Parameter | | Value |
|---|---|---|
| **Gender (Male)** | | 84 (53.2) |
| **Co-morbidity** | | 100 (63.3) |
| **Stage** | Stage 1 | 95 (60.1) |
| | Stage 2 | 37 (23.4) |
| | Stage 3 | 26 (16.5) |
| **Age, (year)** | | 75.0 (65-85) |
| **Neutrophil ($10^3\mu L^{-1}$)** | | 10.39 (0.69-14.21) |
| **Lymphocyte ($10^3\mu L^{-1}$)** | | 0.78 (0.54-1.15) |
| **Monocyte ($10^3\mu L^{-1}$)** | | 0.66 (0.57-0.86) |
| **Platelet ($10^3\mu L^{-1}$)** | | 270 (230-450) |
| **MPV (fL)** | | 12.8 (9.9-13.8) |
| **NLR** | | 11.8 (7.1-21.7) |
| **PLR** | | 0.4 (0.2-0.6) |
| **LMR** | | 1.2 (0.7-2.1) |

MVP: Mean Platelet Volume, NRL: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-To-Lymphocyte Ratio. Gender, comorbid diseases, and pressure ulcer stages are given as n (%). Other values are given as median (interquartile range) + (minimum-maximum)

Figure 1: Distribution of patients according to their diagnoses




CVD: Cerebrovascular Disease, COPD: Chronic Obstructive Pulmonary Disease, CHF: Chronic Heart Failure, MI: Myocardial Infarction

Among men, 58.3% were at stage 1, 22.6% were at stage 2, and 19% were at stage 3. For women, 62.2% were at stage 1, 24.3% were at stage 2, and 13.5% were at stage 3. The distribution of PU stages did not show a significant difference by gender ($P$=0.645). Among patients with co-morbidities, 55% were at stage 1, 25% were at stage 2, and 20% were at stage 3. The PU stages did not differ significantly based on the presence of co-morbidities ($P$=0.169).

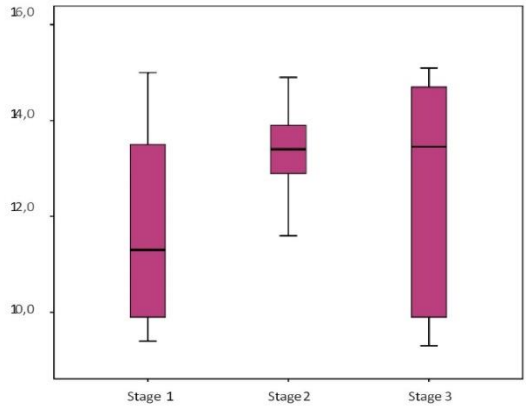
There was a significant difference in mean platelet volume (MPV) between the stages ($P$<0.001). This difference was primarily observed between stage 1 and the other two stages, with the MPV value of stage 1 being lower than the other two stages. No significant differences were found between the stages in terms of age, neutrophils, lymphocytes, monocytes, platelets, NLR, PLR, and LMR ($P$=0.156, $P$=0.613, $P$=0.593, $P$=0.667, $P$=0.360, $P$=0.602, and $P$=0.569, respectively) (Table 2). The relationship between MPV and the pressure stages of the patients is illustrated in Figure 2.

Table 2: Comparison of patient characteristics according to the pressure ulcer stages

| | Stage 1 (n=95) | Stage 2 (n=37) | Stage 3 (n=26) | *P*-value |
|---|---|---|---|---|
| **Gender (male)** | 49 (58.3) | 19 (22.6) | 16 (19) | 0.645* |
| **Co-morbidity** | 55 (55) | 25 (25) | 20 (20) | 0.169* |
| **Age (year)** | 77(65-85) | 76.0 (69-86) | 70 (65-81) | 0.300** |
| **Neutrophil ($10^3\mu L^{-1}$)** | 10.43 (0.64-14.07) | 12.14(8.2-15.34) | 8.39 (6.83-13.37) | 0.156** |
| **Lymphocyte ($10^3\mu L^{-1}$)** | 0.77 (0.51-1.15) | 0.86 (0.62-1.10) | 0.74 (0.56-1.43) | 0.613** |
| **Monocyte ($10^3\mu L^{-1}$)** | 0.67 (0.59-0,85) | 0.62 (0.59-0.82) | 0.63(0.43-0,90) | 0.593** |
| **Platelet ($10^3\mu L^{-1}$)** | 275 (235-425) | 365 (189-463) | 242.0 (236-463) | 0.667** |
| **MPV (fL)** | 1.3 (9.9-13.5) [a] | 13.4 (12.9-13.9)[b] | 13.5 (9.9-14.7)[b] | <0.001** |
| **NLR** | 11.7 (7.1-22.1) | 13.6 (8.4-21.4) | 11.1 (4.3-19.6) | 0.360** |
| **PLR** | 0.4 (0.2-0.5) | 0.4 (0.2-0.6) | 0.3 (0.2-0.6) | 0.602** |
| **LMR** | 1.2 (0.7-2.1) | 1.3 (1.0-1.7) | 1.3 (0.8-2.7) | 0.569** |

MVP: Mean Platelet Volume, NRL: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PLR: Platelet-To-Lymphocyte Ratio, *Chi-squared test **Kruskal-Wallis test. a, b give the groups with difference. Gender, and comorbid diseases are given as n (%). Other values are given as median (interquartile range) (minimum-maximum). $P$<0.05 was considered statistically significant.

Figure 2: Comparison of MPV values according to the compression stage




## Discussion

The development of PU poses numerous challenges, particularly in intensive care and palliative care centers, including worsened clinical conditions, prolonged hospitalization, and increased treatment costs. Therefore, various scales such as the Braden Risk Assessment Scale, Norton Risk Assessment Scale, and Waterlow Risk Assessment Scale are employed to assess multiple risk factors such as physical activity, mental state, incontinence, and skin condition [1]. In this study, we aimed to investigate the impact of hematological parameters on the formation and stages of PUs. Our findings revealed that MPV was lower in stage 1 compared to stages 2 and 3. However, demographic data, hemogram parameters, and values of NLR, PLR, and LMR did not show significant differences among different stages of PUs.

Our study exhibited similarities in terms of age, gender, and co-morbidities compared to previous studies. Adıyeke E and Adıyeke L [3] reported demographic data of patients with and without PUs that aligned with our study. In a 2017 article by Jaul et al. [2], it was stated that the likelihood of PU development is higher in geriatric patient groups due to factors such as diabetes, HF, increased neurodegenerative diseases, immobility, nutritional deficiency, incontinence, and peripheral vascular diseases. Given that our study population consisted of geriatric patients with an average age of 75 years, our findings could not be evaluated based on different age groups.

In our study, 53.2% of the patients were male. Consistent with our findings, the literature does not report a significant gender-related difference in PUs. Shi et al., in their meta-analysis of 65 articles, found that 53% of PU patients were female [4]. Similarly, Dinçer et al. [5] reported that 44.8% of patients with PUs in the palliative unit were female.

In the present study, the most common diagnoses at hospitalization for patients who developed PUs were pneumonia, CVD, and COPD. However, the diagnoses at hospitalization did not significantly impact the stage of PUs. Tissue hypoxia is a major concern in PUs. It is widely recognized that, in addition to pressure, comorbid factors that impede perfusion and oxygenation can predispose individuals to PUs and hinder wound healing under conditions of tissue hypoxia. Our study revealed that pneumonia and COPD, which affect the respiratory system, were significant co-morbidities. As this patient group primarily consisted of geriatric patients, they often require mechanical ventilation support due to impaired oxygenation, tissue hypoxia,

and reduced lung capacity associated with advanced age. The need for mechanical ventilation support results in patient immobilization and prolonged ICU stays. Manzano et al. [6] documented the impact of mechanical ventilation support on PU formation. In a multicenter study involving 13,254 patients, Labeau et al. [7] identified COPD as a risk factor for PUs.

In our study, co-morbidities such as cardiogenic diseases, including heart failure (HF) and MI, played a significant role in forming PUs. Conditions like low cardiac output, hypotension, and rhythm disorders contribute to the development of PUs by reducing tissue perfusion pressure [8]. In a 2017 article by Cox, it was mentioned that inadequate tissue perfusion is a notable risk factor for PUs in MI patients with left ventricular failure caused by reduced ejection fraction (EF) and subsequent decreased cardiac output [9]. HF increases the risk of PU development due to factors such as dehydration (resulting from diuretic use, for example), edema, and decreased cardiac output [10]. While we considered decreased arterial blood flow in the affected extremity due to peripheral arterial diseases as an exclusion criterion in our study, it remains an inevitable risk factor that predisposes individuals to PUs. Lopatina et al. [11] identified diabetes and hypertension as risk factors for post-surgical PUs in patients with cardiogenic diseases. They also demonstrated a significant increase in the likelihood of developing PUs in patients with a high ASA score.

CVDs are another significant factor contributing to the development of PUs. Given that most PU patients are geriatric, the incidence of neurodegenerative diseases such as Alzheimer's tends to be higher. Particularly in the advanced stages of the disease, factors like immobility and malnutrition emerge as risk factors for PU development in these patients. In our study, Alzheimer's disease was observed as a co-morbidity in 12 (6.3%) patients.

Our literature search revealed a scarcity of publications regarding hemogram values, as well as parameters such as NLR, PLR, and LMR, in relation to PUs. The NLR ratio is commonly utilized to assess inflammation and mortality. Therefore, it was expected that the NLR ratio would be higher, particularly in stage 3 and stage 4 PUs. However, our study had no patients with stage 4 PUs. Our investigation solely involved a retrospective review of patients who developed PUs. Consequently, we could not ascertain the difference in NLR between patients with and without PUs. Nonetheless, our findings indicated that NLR did not impact the stage of PUs.

Similar to NLR, MPV is frequently used to indicate inflammation and mortality. Platelets play a crucial role in maintaining a balance between inflammation and hemostasis in patients with PUs. They enhance the efficacy of leukocytes and contribute to wound healing [12]. As the wound site and stage progress, inflammation intensifies, leading to increased production of new platelets to compensate for platelet consumption. Younger platelets are expected to be larger in size. In line with this expectation, our study observed that MPV was higher in stage 2 and stage 3 PUs compared to stage 1, indicating that MPV can serve as an important parameter for evaluating the follow-up and treatment outcomes of PUs.

Adıyake E and Adıyake L [3] conducted a study evaluating PUs and hematological parameters. They found that the NLR was higher in patients with PUs than those without. Additionally, they observed higher MPV values in patients with PUs. Their findings regarding MPV align with our study results. Kutlu et al. examined blood values in bedridden patients, a primary population susceptible to PUs, and demonstrated a significant decrease in MPV values following exercise [13]. This decrease could be attributed to a partial relief of compression in the pressure area and a reduction in tissue hypoxia in parallel with increased blood circulation due to exercise.

Numerous studies have examined whether lymphocyte and monocyte counts, as well as LMR and PLR, can serve as indicators of inflammation and mortality. For instance, Durmuşoğlu et al. [14] conducted studies on ovarian cancers and found that LMR, NLR, and PLR did not impact mortality. Conversely, in his specialized thesis, Dede [15] determined that although LMR is a poor prognostic indicator in COVID-19, it is not effective in predicting mortality. There are limited studies in the literature investigating the effects of LMR and PLR on PUs and their stages. While these studies may have demonstrated an association between these parameters and PUs due to their involvement in inflammation, we lacked data on this matter since our study exclusively focused on patients who developed PUs. Consequently, we could not arrive at a definitive conclusion regarding the staging and/or prognosis of PUs in our study.

**Limitations**

Our study had certain limitations. First, we solely focused on patients who developed PUs, which prevented us from comparing them with patients who did not develop PUs. Second, the study was conducted at a single center, which may limit the generalizability of the findings. Additionally, the small number of patients included in the study is another limitation that should be taken into consideration.

**Conclusion**

Our search revealed that age, pneumonia, COPD, coronary artery diseases, and neurodegenerative diseases, as well as MPV, may influence the risk of development and stage of PU. While we initially hypothesized that MPV could be a contributing factor, we lacked sufficient evidence to support this claim. Further research is needed to explore the role of MPV in PU. Other parameters, apart from MPV, did not demonstrate a significant association with PU. Alongside preventive measures such as proper nutrition, early mobilization, and the use of air mattresses, early treatment of PUs and addressing the underlying factors are crucial in preventing the formation of PUs and potential complications.

## References


1. Firat Kiliç H, Sucudag G. The scales frequently used in patients with the Assessment of Pressure Sores. G.O.P. Taksim E.A.H. JAREN. 2017;3(1):49-54.
2. Jaul E, Barron J, Rosenzweig JP, Menczel J. An overview of co-morbidities and the development of pressure ulcers among older adults. BMC Geriatr. 2018;18(1):305.
3. Adıyeke E, Adıyeke L. Neutrophil to lymphocyte ratio and mean platelet volume may predict the development of the pressure ulcers. J Surg Med. 2020;4(7):578-81.
4. Shi C, Dumville JC, Cullum N. Support surfaces for pressure ulcer prevention: A network meta-analysis. Plos One. 2018;13(2):e0192707.
5. Dincer M, Doger C, Tas SS, Karakaya D. An analysis of patients in palliative care with pressure injuries. Niger J Clin Pract. 2018;21:484-91.
6. Manzano F, Perez-Perez AM, Martinez-Ruiz S, Garrido-Colmenero C, Roldan D, Jiménez-Quintana Mdel M, et al. Hospital-acquired pressure ulcers and risk of hospital mortality in intensive care patients on mechanical ventilation. J Eval Clin Pract. 2014;20:362-8.
7. Labeau SO, Afonso E, Benbenishty J, Blackwood B, Boulanger C, Brett SJ, et al. Prevalence, associated factors and outcomes of pressure injuries in adult intensive care unit patients: the DecubICUs study. Intensive Care Med. 2021;47(2):160-9.
8. Kaitani T, Tokunaga K, Matsui N, Sanada H. Risk factors related to the development of pressure ulcers in the critical care setting. J Clin Nurs. 2010;19(3–4):414–21.

9. Cox J. Pressure Injury Risk Factors in Adult Critical Care Patients: A Review of the Literature. Ostomy Wound Manage. 2017;63(11):30–43.
10. Aloweni F, Ang SY, Fook-Chong S, Agus N, Yong P, Goh MM, et al. A prediction tool for hospital-acquired pressure ulcers among surgical patients: Surgical pressure ulcer risk score. Int Wound J. 2019;16(1):164-75.
11. Lopatina T, Bruno S, Tetta C, Kalinina N, Porta M, Camussi G. Platelet-derived growth factor regulates the secretion of extracellular vesicles by adipose mesenchymal stem cells and enhances their angiogenic potential. Cell Communication and Signaling. 2014;12(1):26–38.
12. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm. 2019;17;2019:9213074.
13. Koca Kutlu A, Diramalı A, Temiz C, Onur E, Miskioğlu M. Effect of exercise on blood values and vital findings in bed-connected patients. Journal Of Ege University Faculty of Nursing. 2011;27(1):25-36.
14. Erben Durmusoglu S, Kiliç F, Unsal M, Aytekin O, Kimyon Comert G, Karalok A, et al. Preoperative neutrophil/lymphocyte, lymphocyte/monocyte and platelet/lymphocyte ratios serous ovarian cancer survival Balikesir Medical Journal. 2021;5(1):43-53.
15. Dede S. In Critical Patients Diagnosed Wıth Covid-19, Platelet Lymphocyte Rate, Monocyte Lymphocyte Rate And Some Others Effect Of Hematological Values On Prognosis. (Master thesis in medicine), Konya, Necmettin Erbakan University 2021.

J Surg Med. 2023;7(8):486-490.
DOI: 10.28982/josam.7847

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Renal dysfunction due to surgical stress and its effects on survival in patients aged 90 and over

**Sevgi Kutlusoy [1], Erdinç Koca [1], Ahmet Aydın [2]**

[1] Department of Anesthesiology and Reanimation Clinic, Malatya Training and Research Hospital, Malatya, Turkey
[2] Department of Anesthesiology and Reanimation Clinic, Malatya Turgut Ozal University, Malatya, Turkey

**ORCID ID of the author(s)**

SK: 0000-0002-8172-5075
EK: 0000-0002-6691-6711
AA: 0000-0003-1836-2061

**Corresponding Author**
Sevgi Kutlusoy
Department of Anesthesiology and Reanimation Clinic, Malatya Training and Research Hospital, Ozalpler, Malatya Turkey
E-mail: stopal70@hotmail.com

**Ethics Committee Approval**
The study was approved by Ethics Committee of Malatya Turgut Özal University (November 7, 2022, number 2022/191).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 25

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Published studies of surgical outcomes in patients aged 90 years and older have mostly focused on specific surgeries such as hip fractures. Unlike previous reports, our study includes all surgical procedures in patient groups aged 90 and over for eight years in our hospital. We aim to be able to predict the responses of an older adult's kidney due to surgical stress by using the values of plasma urea and creatine, which are preoperative and postoperative routine laboratory parameters, and to predict its effect on mortality.

**Methods:** Our study was conducted as a retrospective cohort study with 284 patients whose ages ranged from 90 to 119 and who had undergone a surgical operation. The patients were divided into four groups according to preoperative and postoperative creatinine values: preoperative and postoperative creatinine <1.25 mmol/L RFT-I group; preoperative creatinine <1.25 mmol/L but postoperative creatinine >1.25 mmol/L RFT-II group; preoperative creatinine >1.25 mmol/L but postoperative creatinine <1.25 mmol/L RFT-III group; and preoperative and postoperative creatinine >1.25 mmol/L RFT-IV group.

**Results:** Of the 284 cases, 62% required intensive care after surgery. While 95.4% of the patients were discharged, 4.6% did not survive. No renal dysfunction was observed in the RFT-I group (68.7%, n=195) (preoperative and postoperative creatinine <1.25 mmol/L). In the RFT-II group (17.6%, n=50), renal dysfunction (creatinine >1.25 mmol/L) developed due to postoperative surgical stress (creatinine <1.25 mmol/L). In patients in the RFT-III group (6%, n=17), preoperative renal dysfunction (creatinine >1.25 mmol/L) improved with postoperative care (creatinine <1.25 mmol/L). In the RFT-IV group (7.7%, n=22), preoperative renal dysfunction (creatinine >1.25 mmol/L) did not improve postoperative renal dysfunction despite appropriate perioperative fluid replacement.

**Conclusion:** Our study observed an increase in postoperative urea and creatinine values due to surgical stress in our patient group aged 90 and over, who had limited physiological reserves. However, it has been shown that improvement in renal function tests can be achieved with appropriate fluid replacement and postoperative intensive care treatment in patients with postoperative or preoperative renal dysfunction. Our rates of postoperative renal dysfunction due to surgical stress were lower and did not change mortality.

**Keywords:** geriatrics, acute kidney injury, mortality

How to cite: Kutlusoy S, Koca E, Aydın A. Renal dysfunction due to surgical stress and its effects on survival in patients aged 90 and over. J Surg Med. 2023;7(8):486-490.

## Introduction

Aging encompasses all the functional and structural changes that occur over time at the level of cells, tissues, and systems in the organism. It is an irreversible physiological process [1]. The World Health Organization considers the age of 65 to be the old age limit. However, the transition of people to dependent lives is around the age of 75 [2].

With the decrease in death rates in recent years, life expectancy in our country has increased to 70 years. It is estimated that the number of older people will increase twice in the next 20 years and reach 12 million in 2050 [3]. Diseases and organ dysfunctions increase in the elderly population with age and prolonged life span [4]. Renal blood flow and mass decrease with age, which increases the risk of developing renal failure in elderly patients, especially in the perioperative and postoperative periods, when exposed to nephrotoxic drugs and applications. The reduced capacity to hold water and electrolyte loads makes liquid treatment more critical [5].

With the advancement of anesthesia and surgical techniques, major elective and emergency surgery services are being provided to a larger number of elderly patients; therefore, the life expectancy of the elderly is increasing even more [6]. In the elderly, a limited physiological reserve is sufficient to maintain hemostasis in a normal state, while surgery may result in stress-related insufficiency. However, decreased body mass index and total water and fat ratios change the distribution and elimination of anesthetic drugs [7].

Published studies on surgical outcomes in patients 90 years of age and older have mostly focused on specific surgeries, and most are based on hip fracture cases [8,9]. Plasma creatinine and urea values are the most commonly used preoperative laboratory tests to evaluate kidney function [10].

Patients aged 90 years and older who had been admitted to our hospital with various symptoms over eight years and underwent surgical treatment were included in our study. Our aim is to predict the responses of an elderly person's kidney due to surgical stress by using the values of plasma urea and creatine, which are preoperative and postoperative routine laboratory parameters, and to predict their effects on mortality.

## Materials and methods

Our retrospective cross-sectional study was carried out in accordance with the Declaration of Helsinki after the approval of the Ethics Committee of X University dated November 7, 2022, and numbered 2022/191. The study included 284 patients between the ages of 90 and 119 who presented to our hospital with various symptoms between June 30, 2014, and October 7, 2022, and underwent surgical treatment. The data of the patients included in the study were obtained from the patient files and the hospital's automation system. Patients with chronic renal failure and at risk of severe blood loss were excluded from the study. The age of the patients, comorbidities, and American Society of Anesthesiologists (ASA) scores were recorded. The patients' urea and creatinine values were recorded on the first and second postoperative days. Also, the type of operation and type of anesthesia; the status and duration of hospitalization in the intensive care unit (ICU); whether there was intubation, inotropic, dialysis, and blood transfusion treatment; discharge; and non-survival status were recorded.

In our study, the serum creatinine limit value was accepted as 1.25 mmol/L according to the laboratory parameters in our clinic. The patients included in our study were divided into four groups according to preoperative and postoperative creatinine values: preoperative and postoperative creatinine <1.25 mmol/L RFT-I group; preoperative creatinine <1.25 mmol/L but postoperative creatinine >1.25 mmol/L RFT-II group; preoperative creatinine >1.25 mmol/L but postoperative creatinine <1.25 mmol/L RFT-III group; and preoperative and postoperative creatinine >1.25 mmol/L RFT-IV group.

**Statistical analysis**

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 program was used for statistical analyses. The Kolmogorov-Smirnov test evaluated the conformity of the parameters to the normal distribution, and it was found that the parameters did not show a normal distribution. While evaluating the study data, in addition to descriptive statistical methods (mean [standard deviation], median, frequency), the Kruskal Wallis test was used to compare the quantitative data between the groups, and Dunn's test was used to determine the group that caused the difference. The Chi-Square, Fisher's Exact Chi-Square, and Fisher Freeman Halton Exact Chi-Square tests were used to compare the qualitative data. The significance was evaluated at the level of $P<0.05$.

## Results

The study was conducted with 284 patients ranging in age from 90 to 119. The average age was 93.08 (3.71) years. While only 4.2% of the cases were ASA 2, 95.8% were ASA 3. Hypertension was observed in 63.4% of the patients, neurological diseases in 29.2%, chronic obstructive pulmonary disease (COPD) in 21.8%, congestive heart failure (CHF) in 13.4%, coronary artery disease (CAD) in 12.7%, diabetes in 11.3%, and other comorbidities in 3.5%. Of the cases, 83.1% underwent orthopedic surgery. Of the patients, 85.2% underwent regional anesthesia (Table 1).

A total of 62% of the cases required postoperative intensive care. The most common cause of intensive care hospitalization was respiratory failure (73.9%), followed by delirium (21.6%), hemodynamic follow-up (2.8%), and hypotension (1.7%). Of the cases, 3.9% were intubated, 9.2 received inotropic treatment, 0.7% received dialysis, and 56.7% received blood transfusion treatment. While 95.4% of the patients were discharged, 4.6% did not survive (Table 2).

We accessed the urea and creatinine values of the patients participating in the study on the preoperative and postoperative first and second days but we could not access the urine follow-ups. However, we divided our patients into four groups based on ≥0.3 mg/dl increases in serum creatinine levels within 48 hours according to the KDIGO classification. No renal dysfunction was observed in 68.7% (n=195) of the patients (preoperative and postoperative creatinine <1.25 mmol/L) in the RFT-I group. There was no preoperative renal dysfunction (creatinine <1.25 mmol/L) in the RFT-II group (17.6%, n=50), but renal dysfunction (creatinine >1.25 mmol/L) developed due to postoperative surgical stress. Patients in the RFT-III group

(6%, n=17) had preoperative renal dysfunction (creatinine >1.25 mmol/L), and with postoperative care, these patients saw improved renal dysfunction (creatinine <1.25 mmol/L).

Table 1: ASA scores, comorbidities, operation type and anesthesia type in patients

| | | n | % |
|---|---|---|---|
| **ASA** | 2 | 12 | 4.2 |
| | 3 | 272 | 95.8 |
| **Comorbidities** | Hypertension | 180 | 63.4 |
| | Diabetes Mellitus | 32 | 11.3 |
| | CHF | 38 | 13.4 |
| | COPD | 62 | 21.8 |
| | CAD | 36 | 12.7 |
| | Neurological diseases | 83 | 29.2 |
| | Other diseases | 10 | 3.5 |
| **Operation type** | **Neurosurgery** | 6 | 2.2 |
| | Subdural hemorrhage | 3 | 1.1 |
| | Epidural hematoma | 1 | 0.4 |
| | Kyphoplasty | 2 | 0.7 |
| | **General Surgery** | 17 | 6 |
| | Inguinal hernia | 8 | 2.8 |
| | Malignancy | 3 | 1.1 |
| | Acute cholecystectomy | 2 | 0.7 |
| | Ileus | 2 | 0.7 |
| | Appendectomy | 2 | 0.7 |
| | **Otolaryngology surgery** | 1 | 0.4 |
| | FES | 1 | 0.4 |
| | **Cardiovascular surgery** | 5 | 1.8 |
| | Embolectomy | 4 | 1.4 |
| | Pericardial tamponade | 1 | 0.4 |
| | **Orthopedics surgery** | 236 | 83.1 |
| | Hip fracture | 224 | 78.9 |
| | Radius fracture | 5 | 1.6 |
| | Tibia fracture | 3 | 1.1 |
| | Knee arthroplasty | 2 | 0.7 |
| | Proximal humeral fracture | 1 | 0.4 |
| | Foot amputation | 1 | 0.4 |
| | **Plastic surgery** | 2 | 0.7 |
| | Tissue injury | 2 | 0.7 |
| | **Urology surgery** | 17 | 6 |
| | Prostate hyperplasia | 12 | 4.2 |
| | Ureteroscopy | 3 | 1.1 |
| | Hydrocele | 2 | 0.7 |
| **Anesthesia type** | General anesthesia | 25 | 8.8 |
| | Peripheral nerve block | 12 | 4.2 |
| | Sedation | 5 | 1.8 |
| | Rejyonel anesthesia | 242 | 85.2 |

ASA: The American Society of Anesthesiologists physical status classification, FES: Functional endoscopic sinus surgery, HF: Heart failure, COPD: chronic obstructive pulmonary disease, CAD: Coronary Artery Disease

Table 2: Perioperative treatments, intensive care stay and duration

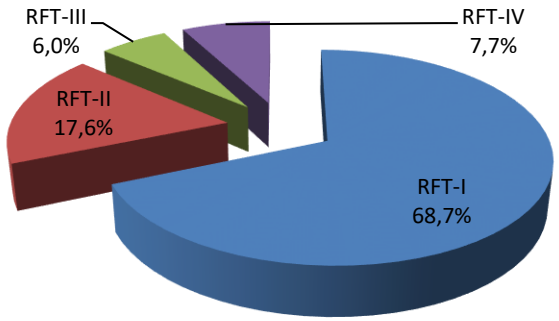
| | | Min-Max | Median |
|---|---|---|---|
| **Length of stay in intensive care** | | 0-91 | 2.18 (6.49) (1) |
| **Duration of hospital stay** | | 2-95 | 11.05 (9.13) (9) |
| | | **n** | **%** |
| **Status of hospitalization in the ICU** | No | 108 | 38 |
| | Yes | 176 | 62 |
| **Reason for hospitalization in ICU (n=176)** | Hemodynamic monitoring | 5 | 2.8 |
| | Delirium | 38 | 21.6 |
| | Hypotension | 3 | 1.7 |
| | Respiratory failure | 130 | 73.9 |
| **Intubation** | No | 273 | 96.1 |
| | Yes | 11 | 3.9 |
| **Inotropic therapy** | No | 258 | 90.8 |
| | Yes | 26 | 9.2 |
| **Leaving the hospital** | Discharge | 271 | 95.4 |
| | Non survivors | 13 | 4.6 |
| **Dialysis therapy** | No | 282 | 99.3 |
| | Yes | 2 | 0.7 |
| **Blood transfusion therapy** | No | 123 | 43.3 |
| | Yes | 161 | 56.7 |

ICU: Intensive care units

In the RFT-IV group (7.7%, n=22), preoperative renal dysfunction (creatinine >1.25 mmol/L) (Figure 1) did not improve postoperative renal dysfunction despite appropriate perioperative fluid replacement.

ASA was similar among groups (*P*=0.685). The number of inpatients admitted to the ICU was higher in the RFT-IV group. The number of patients intubated and given inotropic drugs was higher in the RFT-II group, and dialysis was applied to two patients in the RFT-II group. The number of patients who were given blood and did not survive was higher in the RFT-III group. Hospital and intensive care hospitalization periods were longer in the RFT-III group, but these results were not statistically significant (*P*=0.285) (Table 3).

Figure 1: Distribution of groups




There was a statistically significant difference between the groups in terms of preoperative urea levels (*P*=0.001). Preoperative urea levels in the RFT-I group were lower than in the RFT-II, RFT-III, and RFT-IV groups (*P*=0.001). Preoperative urea levels in the RFT-II group were lower than in the RFT-III and RFT-IV groups (*P*=0.001). Preoperative urea levels were similar between RFT-III and RFT-IV groups. There was a statistically significant difference among the groups in terms of postoperative day 1 and day 2 urea levels (*P*=0.001). The postoperative day 1 and day 2 urea levels in the RFT-I group were lower than in the RFT-II, RFT-III, and RFT-IV groups (*P*=0.001). Postoperative day 1 and day 2 urea levels were similar among RFT II, RFT-III, and RFT IV groups (Table 4).

Table 4: Evaluation of groups in terms of laboratory findings

| | RFT-I | RFT-II | RFT-III | RFT-IV | |
|---|---|---|---|---|---|
| | **Mean (SD) (Median)** | **Mean (SD) (Median)** | **Mean (SD) (Median)** | **Mean (SD) (Median)** | ***P-values*** |
| **Preoperative urea mmol/L** | 48.13 (17.54) (45.2) | 57.35 (22.83) (53) | 101.83 (41.36) (98) | 87.41 (29.96) (76) | 0.001 * |
| **Urea on postoperative day 1 mmol/L** | 53.7 (31.1) (50) | 78.49 (36.66) (71) | 70.5 (21.76) (72) | 95.49 (39.06) (94.8) | 0.001 * |
| **Urea on postoperative day 2 mmol/L** | 54.01 (20.4) (51) | 88.84 (33.07) (88.1) | 71.2 (24.97) (71) | 97.21 (29.75) (87) | 0.001 * |

Kruskal Wallis Test, *$P<0.05$

Table 3: Evaluation of perioperative treatments, intensive care stays and durations between groups

| | | RFT-I | RFT -II | RFT-III | RFT-IV | |
|---|---|---|---|---|---|---|
| | | n (%) | n (%) | n (%) | n (%) | *P-values* |
| **ASA** | 2 | 9 (4.6) | 1 (2) | 1 (5.9) | 1 (4.5) | [1]0.685 |
| | 3 | 186 (95.4) | 49 (98) | 16 (94.1) | 21 (95.5) | |
| **Status of hospitalization in the ICU** | No | 76 (39) | 21 (42) | 6 (35.3) | 5 (22.7) | [2]0.449 |
| | Yes | 119 (61) | 29 (58) | 11 (%64.7) | 17 (77.3) | |
| **Intubation** | No | 190 (97.4) | 45 (90) | 16 (94.1) | 22 (100) | [1]0.075 |
| | Yes | 5 (2.6) | 5 (10) | 1 (5.9) | 0 (0) | |
| **Inotropic therapy** | No | 179 (91.8) | 44 (88) | 13 (76.5) | 22 (100) | [1]0.066 |
| | Yes | 16 (8.2) | 6 (12) | 4 (23.5) | 0 (0) | |
| **Leaving the hospital** | Discharge | 188 (96.4) | 47 (94) | 15 (88.2) | 21 (95.5) | [1]0.285 |
| | Non survivors | 7 (3.6) | 3 (6) | 2 (11.8) | 1 (4.5) | |
| **Comorbidities** | Hypertension | 120 (61.5) | 34 (68) | 12 (70.6) | 14 (63.6) | [2]0.771 |
| | Diabetes | 26 (13.3) | 2 (4) | 2 (11.8) | 2 (9.1) | [1]0.279 |
| | CHF | 25 (12.8) | 5 (10) | 3 (17.6) | 5 (22.7) | [1]0.429 |
| | COPD | 41 (21) | 15 (30) | 2 (%11.8) | 4 (18.2) | [1]0.400 |
| | CAD | 22 (11,3) | 9 (18) | 1 (5,9) | 4 (18.2) | [1]0.405 |
| | Neurological diseases | 58 (29.7) | 17 (34) | 5 (29.4) | 3 (13.6) | [2]0.367 |
| **Dialysis therapy** | No | 195 (100) | 48 (96) | 17 (100) | 22 (100) | [1]0.097 |
| | Yes | 0 (0) | 2 (4) | 0 (0) | 0 (0) | |
| **Blood transfusion therapy** | No | 90 (46.2) | 17 (34) | 5 (29.4) | 11 (50) | [2]0.246 |
| | Yes | 105 (53.8) | 33 (66) | 12 (70.6) | 11 (50) | |
| **Anesthesia type** | General anesthesia | 18 (9.2) | 4 (8.0) | 0 (0) | 3 (13.6) | [3]0.350 |
| | Peripheral nerve block | 9 (4.6) | 2 (4.0) | 0 (0) | 1 (4.5) | |
| | Sedation | 2 (1.0) | 1 (2.0) | 0 (0) | 2 (9.1) | |
| | Regional anesthesia | 1666 (85.1) | 43 (86.0) | 17 (100) | 16 (72.7) | |
| **Duration of hospitalization in the ICU (median)** | | 1.94 (6.99) (1) | 2.66 (5.14) (1) | 4.35 (7.84) (1) | 1.45 (1.18) (1.5) | [4]0.609 |
| **Duration of hospital stay (median)** | | 10.87 (9.16) (9) | 11.98 (10.02) (9) | 12.35 (7.42) (11) | 9.5 (8.2) (8) | [4]0.306 |

[1] Fisher Freeman Halton Exact Test, [2] Ki-square test, [3] Fisher's Exact Test, [4] Kruskal Wallis Test

## Discussion

During illness or surgical stress, the kidneys' ability to adapt to changing conditions decreases in older individuals. While young people can easily tolerate such changes, they can cause fluid–electrolyte disorders and kidney failure in the elderly [11].

Our study was conducted retrospectively with 284 patients whose ages ranged from 90 to 119 years and who underwent surgical operations. The patients were divided into four groups according to their preoperative and postoperative creatinine values. With appropriate perioperative fluid replacement and postoperative intensive care treatment, more than half of our patient group's preoperatively existing kidney dysfunction improved. Our rates of postoperative kidney dysfunction were lower and did not affect mortality.

In our study, hypertension and neurological diseases were the most common comorbidities among the groups, and the incidence rates of comorbidities were similar. In a study conducted by Karaman et al. [12] on 255 patients, hypertension and diabetes were the most common comorbidities. In our study, we attribute the more frequent occurrence of neurological diseases to the fact that our age group is more advanced. Hip fractures are an important health problem among the elderly [13]. Most of our patients had hip fractures. The most common type of anesthesia used in our study was regional anesthesia, and it was similar among the groups. Bakı et al. [14] defended the superiority of regional anesthesia over general anesthesia in terms of complications in their study conducted in 2014.

In a study conducted by Stahl et al. [15] on 115 patients over 90 years of age who underwent orthopedic surgery, delirium and respiratory failure were the most common complications. In our study, respiratory failure was the most common complication. The number of inpatients admitted to the ICU was higher in the RFT-IV group. The hospital and intensive care hospitalization periods were longer in the RFT-III group. Our patients' hospital and intensive care hospitalization times were like those of a study conducted by Kassahun et al. [16] in 2017. However, our intensive care hospitalization rates were lower.

Most of the time, it is difficult to clinically evaluate liver function correctly. Two classification systems are helpful in detecting and staging renal function: risk, injury, failure, loss, end-stage renal disease (RIFLE), and acute kidney injury network (AKIN) staging systems. In both systems, creatinine increases, and urine flow measurements are at the forefront [5].

In our study, we determined the urea and creatinine values of the patients on the preoperative and postoperative first and second days. However, we could not access the urine follow-ups, which was one of the restrictive factors of our study. Our patient rates in the RFT-II group were similar to the study conducted by Ghanem et al. [17] in an orthopedic patient group over 90 years of age. In a multicenter comprehensive study conducted by Bell et al. [18], postoperative renal dysfunction rates were lower than the rates in our study. In a study conducted by Bakı et al. [9] on orthopedic patients in 2021, the rates of renal dysfunction were lower than in our RFT-II patient group. This situation depended on the advanced age of our patient group. In the studies conducted by Hobson et al. [19] on patients undergoing surgery, the rates of renal dysfunction were higher than in the RFT-II group in our study. Again, Leistner et al. [20] reported higher rates of renal dysfunction in patients aged 80 years and older who underwent cardiac interventions than in the RFT-II group. We attribute this condition to appropriate perioperative fluid replacement and postoperative intensive care follow-up.

In this age group, the risk of dehydration and preoperative renal dysfunction due to nonsteroidal anti-inflammatory drugs increased. Perregaard et al. [21] found that 11.1% of patients had preoperative renal dysfunction in a study conducted on 3416 patients in 2016. Our preoperative renal dysfunction rates were higher in our patient group. However, renal dysfunction recovered postoperatively in more than half of our patients with appropriate perioperative fluid replacement therapy.

Recent studies conducted on elderly patient groups have shown the relationship between postoperative renal dysfunction and mortality. In extensive studies conducted by Chiang et al. [22], kidney dysfunction was associated with increased mortality. Again, in their 2022 study, Kaşıkara et al. [23] showed that postoperative dysfunction had a higher mortality rate. Similarly, in our study, mortality rates were higher in the group of patients with preoperative and postoperative renal dysfunction than in the group without renal dysfunction. However, the rate was not statistically significant. We attribute this situation to the comprehensive treatments applied in perioperative and postoperative intensive care units in our elderly patient group.

**Limitations**

The fact that our study was conducted in a single center, the relatively small number of patients, and the inability to access patients' urine follow-ups were restrictive factors. We think that future studies need to be done more comprehensively and prospectively. As a result, the rates of postoperative kidney dysfunction due to surgical stress were lower in our group of patients aged 90 and older with limited physiological reserve, who were divided into four groups according to preoperative and postoperative creatinine values, and had no effect on postoperative mortality.

**Conclusions**

Our study observed an increase in postoperative urea and creatinine values due to surgical stress in our patient group aged 90 and over, who had limited physiological reserves. However, it has been shown that improvement in renal function tests can be achieved with appropriate fluid replacement and postoperative intensive care treatment in patients with postoperative or preoperative renal dysfunction. Our rates of postoperative renal dysfunction due to surgical stress were lower and did not change mortality. However, more comprehensive and prospective studies are needed on this subject.

## References


1. Aslan M, Hocaoğlu Ç. Aging and Psychiatric Problems Associated with Aging Period. Journal of Duzce University Health Sciences Institute. 2017;7(1):53-62.
2. Muravchick S. Anesthesia For The Geriatric Patient, In: Barash PG. Cullen BF. Stoelting RK. Clinical Anesthesia. 5th edition, USA. Lipincott Williams&Wilkins; 2006. pp. 1219-1228.
3. Erden AI, Akıncı SB, Pamuk AG, Aycan Öİ, Çelebioğlu B, Aypar Ü. Retrospective evaluation of geriatric patients in the intensive care unit. Turkish Journal of Geriatrics. 2009;12(4):171-6.
4. Vaguhan S. "The Eldery Patient" in High risk patient Ed. By Ian Mc Conachia, Greenwich Medical Media Ltd. Sanfrancisco, USA. 2002. pp. 101-116.
5. Marino ER. Geriatric anesthesia. In: Butterworth JF, Mackey DC, Wasnick JD (Eds). Morgan& Mikhail's Clinical Anesthesiology. 5th edition, Lange, Mc Graw Hill, USA. 2013. pp. 907-917.
6. Türkmen A, Turgut N. Geriatric Anesthesia. Turkish Journal of Geriatrics 2007;10(1):49-56.
7. Cook DJ, Rooke GA. Priorities in Perioperative Geriatrics. Anesth Analg. 2003;96:1823-36.
8. Miric A, Inacio MC, Kelly MP, Namba RS. Are nonagenarians too old for total hip Arthroplasty? An evaluation of morbidity and mortality within a total joint replacement registry. J Arthroplasty. 2015;30:1324-7.
9. Bakı ED, Mazlum M, Uçan E, Gökalp M, Korkmaz H, Parpucu A, et al. Retrospectıve investigation of postoperative renal functions of elderly patients that hip prosthesıs performed. Kocatepe Medical Journal. 2021;22(3):208-12.
10. Roizen MF, Foss JF, Ficsher SP. Preoperative evaluation, In: Miller RD (Ed). Anesthesia. 5th edition, Churchill Livingstone, USA. 2000. pp. 824-883.
11. Altun B. Kidney and aging. Turkish Journal of Geriatrics. 1998;1(2):68-71.
12. Karaman S, Karaman T, Doğru S, Şahin A, Arici S. The effects of anesthsia techniques on mobidity-mortality in geriatric patients underwent orthopedic surgery. Journal of Contemporary Medicine. 2014;4(3):143-50.
13. Berggren M, Stenvall M, Englund U, Olofsson B, Gustafson Y. Co-morbidities, complications and causes of death among people with femoral neck fracture- a three-year follow-up study. BMC Geriatr. 2016; 16:120.
14. Bakı ED, Özcan Ö, Demirboğan ME, Kokulu S, Uzel H, Ela Y, et al. Investigation of the effects of anesthesia techniques on intensive care admission and postoperative mortality in elderly patients undergoing bilateral knee replacement surgery. Turkish Journal of Geriatrics. 2014;17(4):373-81.
15. Stahl CC, Funk LM, Schumacher JR, Zarzaur BL, Scarborough JE. The Relative Impact of Specific Postoperative Complications on Older Patients Undergoing Hip Fracture Repair. Jt Comm J Qual Patient Saf. 2021;47(4):210-6.
16. Kassahun WT, Staab H, Gockel I, Mehdorn M. Factors associated with morbidity and in-hospital mortality after surgery beyond the age of 90: Comparison with outcome results of younger patients matched for treatment. Am J Surg. 2018;216(6):1063-9.
17. Ghanem M, Garthmann J, Redecker A, Ahrberg-Spiegl AB, Fakler JKM, Spiegl UJA. Management of pertrochanteric fractures in patients over 90 years: In-hospital mortality rate, complications and associated risk factors. BMC Musculoskelet Disord. 2021;22(1):799.
18. Bell S, Dekker FW, Vadiveloo T, Marwick C, Deshmukh H, Donnan TP, et al. Risk of postoperative acute kidney injury in patients undergoing orthopaedic surgery development and validation of a risk score and effect of acute kidney injury on survival: observational cohort study. BMJ. 2015;351:5639.
19. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, et al. Cost and Mortality Associated With Postoperative Acute Kidney Injury. Ann Surg. 2015;261(6):1207-14.
20. Leistner DM, Münch C, Steiner J, Erbay A, Riedel M, Gebhard C, et al. Impact of acute kidney injury in elderly (≥80 years) patients undergoing percutaneous coronary intervention. J Interv Cardiol 2018;31(6):792-8.
21. Perregaard H, Damholt MB, Solgaard S, Petersen MB. Renal function after elective total hip replacement. Acta Orthop. 2016;87(3):235-43.
22. Chiang MH, Lee HJ, Kuo YJ, Chien PC, Chang WC, Wu Y, et al. Predictors of In-Hospital Mortality in Older Adults Undergoing Hip Fracture Surgery: A Case-Control Study. Geriatr Orthop Surg Rehabil. 2021;12:21514593211044644.
23. Kaşıkara H, Lafçı A. Evaluation of factors affecting mortality in geriatric hip fracture surgery: A retrospective study. Turkish Journal of Geriatrics. 2022;25(3):452-64.

J Surg Med. 2023;7(8):491-497.
DOI: 10.28982/josam.7906

Research article

**Journal of Surgery and Medicine**
e-ISSN: 2602-2079
https://jsurgmed.com/

# The etiology, risk factors, and clinical features of anaphylaxis: The single-center retrospective cohort study of the tertiary university hospital

**Ceyda Tunakan Dalgıç**

Department of Internal Medicine, Division of Allergy and Clinical Immunology, Ege University Medical Faculty, Izmir, Turkey

**ORCID ID of the author(s)**

CTD: 0000-0002-0318-3135

**Corresponding Author**
Ceyda Tunakan Dalgıç
Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy and Clinical Immunology, Izmir, Turkey
E-mail: dr_ceydat@yahoo.com

**Ethics Committee Approval**
The study was approved by Sivas Cumhuriyet University's non-interventional clinical research ethics committee, with the decision number 2020-01/01, dated January 15, 2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 25

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Anaphylaxis presents in multiple ways, making its diagnosis challenging. Delayed diagnosis can lead to a postponement in administering crucial adrenaline treatment. The prevalence of anaphylaxis varies by geographical region and gender. However, there has been no comprehensive regional analysis of anaphylaxis data within our country. Despite an increasing incidence, our understanding of anaphylaxis etiology, risk factors, and clinical features remains limited, particularly within our nation. This study aims to assess the frequency, etiology, risk factors, and clinical findings of anaphylaxis among patients seen at the allergy clinic of a tertiary university hospital. Additionally, it seeks to compare regional data with existing literature.

**Methods:** This retrospective cohort study reviewed the medical records of 8,295 patients who visited the allergy outpatient clinic at Sivas Cumhuriyet University Hospital between July 2, 2018, and December 10, 2019. The hospital's data system retrospectively analyzed records using the ICD code T78.2 (anaphylaxis). Only cases where patients were prescribed an adrenaline auto-injector were included. The study evaluated anaphylaxis frequency, etiologies, demographics, and clinical features.

**Results:** The study identified 77 patients (n=77) with a mean age of 40.29 (3.77) years, consisting of 47 females and 30 males. The frequency of anaphylaxis among allergy outpatient admissions was less than 1% (0.009%). Single-type atopic diseases included venom allergy (23%), drug allergy (14%), inhalant allergens (n=6), food allergens (n=4), and skin allergic diseases (n=3). Multiple allergic diseases were present in 40% (n=31) of cases. Prick tests were performed on 56 (72%) patients, with 25 (44%) yielding negative results. Among positive prick test cases, venom was the main cause of anaphylaxis (82%), while drug allergy was more prevalent (68.2%) among negative test results ($P$=0.016). Inhalant allergen sensitivity and allergen polisensitivity did not significantly influence the anaphylaxis cause ($P$<0.001). Causes of anaphylaxis included drug allergy (47%), venom allergy (31%), food allergens (16%), food-dependent exercise-induced reactions (n=2), idiopathic cases (n=2), and cold urticaria (n=1). Non-steroidal anti-inflammatory drugs (NSAIDs) (44%) and beta-lactams (10%) were the primary culprits. In cases where neither drugs nor venom were involved, food allergies were the cause ($P$<0.001). With venom allergy, the cause was venom, and without venom, drug allergy was the cause ($P$<0.001). Female patients showed significantly higher drug- and food-related anaphylaxis rates than males ($P$=0.032 and $P$=0.042, respectively). History of *Apis mellifera*-related anaphylaxis was significantly more common than *Vespula vulgaris*-related cases ($P$=0.028). Anaphylaxis severity included grade 2 (30%), grade 3 (48%), and grade 4 (12%) reactions. Recurrent anaphylaxis episodes occurred in 55% (n=42) of patients. Initial hospital administrations involved epinephrine injections in only 25% (n=19) of cases. Cutaneous symptoms were present in 94%, respiratory symptoms in 88%, cardiovascular symptoms in 63%, neurological symptoms in 57%, and gastrointestinal symptoms in 12% of patients.

**Conclusion:** This study identified drug allergy as the leading cause of anaphylaxis in the examined cases. Preventable factors contributing to drug-induced anaphylaxis included insufficient patient and physician knowledge and widespread over-the-counter drug use without medical consultation. Despite 55% of patients experiencing recurrent attacks, only a quarter received epinephrine administration. These findings emphasize the need to educate patients with recurrent anaphylaxis about avoidance strategies and to enhance healthcare providers' understanding of anaphylaxis treatment.

**Keywords:** etiology, frequency, anaphylaxis, hypersensitivity reactions

How to cite: Tunakan Dalgıç C. The etiology, risk factors, and clinical features of anaphylaxis: The single-center retrospective cohort study of the tertiary university hospital. J Surg Med. 2023;7(8):491-497.

## Introduction

Anaphylaxis represents a swiftly advancing and potentially life-threatening systemic allergic reaction. Its immediate diagnosis and prompt treatment are imperative, yet it can be overlooked due to diagnostic challenges. Globally, the prevalence and incidence of allergic diseases are rising [1,2]. The causative factors and clinical manifestations of anaphylaxis exhibit variability. Shortcomings and delays persist in diagnosing and treating this condition within the realm of healthcare providers [2]. Conducting regional and national studies can enhance awareness among healthcare services, physicians, and the general public about anaphylaxis diagnosis and treatment [3,4].

Research on anaphylaxis has predominantly taken place in Western nations, often involving the analysis of hospital records, regional health data, or examining prescriptions for adrenaline auto-injectors [5-7].

The prevalence of anaphylaxis exhibits variations based on geographic regions and genders. However, a comprehensive analysis of anaphylaxis data within our country on a regional level has not been conducted. Our operational area represents a region where allergy immunology experts are not frequently available. The services of the respective specialized branch are only accessible when assigned by the Ministry of Health. If the designated specialist is unavailable, cases are typically referred to other regional hospitals for evaluation following initial treatment in emergency departments. With the recent assignment of an allergist to the Sivas province during the specified period, cases are retained within our region, establishing region-specific records.

Comprehending the causative factors, prevalence, and triggers of anaphylaxis holds significant importance for accurate patient treatment, preventing the recurrence of anaphylactic episodes, and devising preventive measures.

Our study endeavors to comprehensively depict anaphylaxis cases within the northeastern region of our country, meticulously scrutinizing the clinical and demographic attributes, as well as anaphylactic episodes among individuals prescribed adrenaline auto-injectors. Additionally, we seek to discern distinctive regional traits associated with these cases.

## Materials and methods

The medical records of 8295 patients above the age of 16, who sought treatment at the outpatient clinic of the Department of Chest Diseases, Division of Allergy and Clinical Immunology, Sivas Cumhuriyet University Faculty of Medicine, between July 2, 2018, and December 10, 2019, due to anaphylaxis, were analyzed to establish a retrospective cohort using the hospital data system.

In our single-center cohort study, we retrospectively reviewed the hospital data system using the ICD-10 code T78.2 (anaphylaxis). Only instances where patients were prescribed the adrenaline auto-injector were included.

Our study encompassed the hospital records of all individuals who presented at the allergy clinic within the designated timeframe. Periods preceding and succeeding this window were excluded due to the allergist's exclusive association with the relevant center during this period. The EAACI 2021 anaphylaxis guideline (update) served as the basis for determining the inclusion criteria for our cases [2].

To diagnose anaphylaxis, it is necessary to fulfill one of the three primary clinical criteria. The most easily recognizable is the inclusion of one of these systemic presentations (such as respiratory, cardiovascular, neurological, or gastrointestinal symptoms) in conjunction with skin signs like acute onset urticaria, angioedema, and flushing. The second diagnostic criterion entails acute involvement in two systems following exposure to a recognized allergen (involving the skin, respiratory, cardiovascular, neurological, or gastrointestinal systems). The third and final diagnostic criterion involves the onset of acute hypotension after exposure to a known allergen, specifically characterized by a systolic blood pressure reduction to below 90 mmHg or a decrease of more than 30% from baseline in adults [2].

The same allergist evaluated all these patients. Conditions encompassing the differential diagnosis of anaphylaxis were ruled out through comprehensive anamnesis, thorough examinations, and laboratory tests.

However, given that the diagnosis of anaphylaxis was primarily clinical, meticulous attention was dedicated to the differential diagnosis process. This encompassed a comprehensive assessment of potential alternative diagnoses. The complete differential diagnosis included a sequential evaluation of allergic conditions (variants of urticaria, asthma), followed by respiratory and upper respiratory tract conditions (chronic lung disorders and upper respiratory tract diseases), cardiovascular disorders (vasovagal syncope, arrhythmias), endocrine disorders (hypo-hyperthyroidism, hypoglycemia), neuro-psychiatric conditions, toxic factors (such as scombroid poisoning), and pharmacological reactions. This evaluation was supported by various accessible laboratory tests (including complete blood count, liver and kidney function tests, TSH, and blood glucose levels), electrocardiography, abdominal ultrasonography, bidirectional chest X-ray, and pulmonary function tests.

Nonetheless, given that patients were not under direct observation during the episodes of anaphylaxis, diverse approaches were employed for recording, contingent upon the underlying causes. These methods encompassed relying on the patient's verbal account, consulting the records from the emergency department or medical teams, and when patients granted consent, accessing individual electronic medical record systems to gather details regarding their medical history and potential triggers.

Initially, we assessed the prevalence of anaphylaxis within the patient population under study. Subsequently, a comprehensive questionnaire was employed to scrutinize the demographic details found in the hospital records. This encompassed information such as the patient's gender, age, presence of atopic diseases, pre-existing chronic conditions, ongoing medication regimens, clinical manifestations of anaphylaxis, specifics of the triggering agent, clinical indications (about the affected organ systems), duration of hospitalization, and the therapeutic approaches employed. These details were meticulously documented alongside case report forms, which

were gathered from hospital records in a cross-sectional and retrospective manner.

Anaphylaxis was classified into four grades following the Mueller classification [8]. Due to unmet conditions, provocation tests could not be conducted using the triggering agents (e.g., drugs, venom, and foods). Instead, skin prick tests were administered employing standardized allergen extracts of venoms (*Apis mellifera* and *Vespula vulgaris*), foods, inhalant allergens, and latex from ALK–Abelló*.

**Ethics committee approval**

Ethics approval and written informed consent was procured in accordance with ethical standards. The study received approval from the non-interventional clinical research ethics committee of Sivas Cumhuriyet University, under decision number 2020-01/01, dated January 15, 2020.

**Statistical analysis**

The data were presented as frequency (number and percentage) and mean (range) as applicable. Fisher's exact and chi-square tests were employed for 2 × 2 comparisons involving categorical variables. For numerical variables with counts below 30, the Mann-Whitney U and Kruskal-Wallis H tests were utilized for comparisons. All statistical analyses were conducted using SPSS software, version 23 (SPSS Inc., Chicago, IL, USA). Results with a *P*-value below 0.05 were considered statistically significant.

## Results

**Study group and the frequency of anaphylaxis**

The group comprised 8295 patients aged 16 and above who sought treatment at the outpatient allergy clinic of Sivas Cumhuriyet University Faculty of Medicine, specifically within the Department of Chest Diseases, Division of Allergy and Clinical Immunology, during the period between July 2, 2018, and December 10, 2019. This retrospective analysis identified 77 cases (n=77) where adrenaline auto-injectors were prescribed and coded under the ICD-10 designation T78.2, indicating anaphylaxis. Our study revealed that the incidence of anaphylaxis among admissions to the allergy outpatient department was less than 1%, specifically amounting to 0.009%.

**Demographics and characteristics of the patients with anaphylaxis**

A total of 77 patients were included in the evaluation, with a mean age of 40.29 (13.77) years. Of these, 47 were female, and 30 were male. Among the patients, 73 (94%) had atopic diseases. Allergic diseases were categorized as single-type and multiple allergic diseases. Single-type allergic diseases comprised venom allergies (*Apis mellifera* and *Vespula vulgaris*) in 18 cases (23%), drug allergies in 11 cases (14%), food allergies in four cases, respiratory allergies in six cases, and cutaneous allergies in three cases. Multiple allergic diseases were identified in 31 patients (40%) (Figure 1). Among the 77 patients, 39 (51%) reported drug allergies, with predominant sensitizations to NSAIDs (43%) (Table 1).

A total of 32 individuals (41%) had a history of chronic illness,, 24 individuals (31%) reported chronic drug usage, with ten of them (12%) specifically using anti-hypertensive medications (Table 1).

Figure 1: Distribution of atopic diseases among patients with anaphylaxis (shown as number)

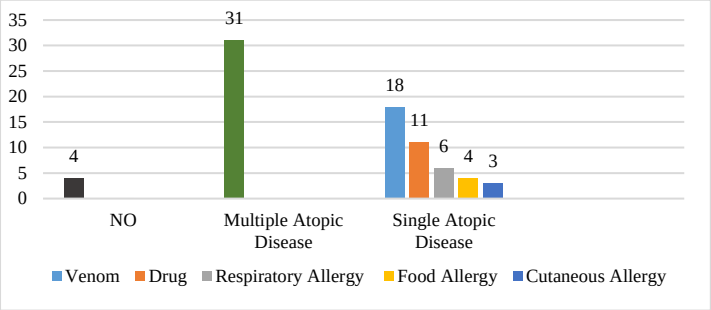


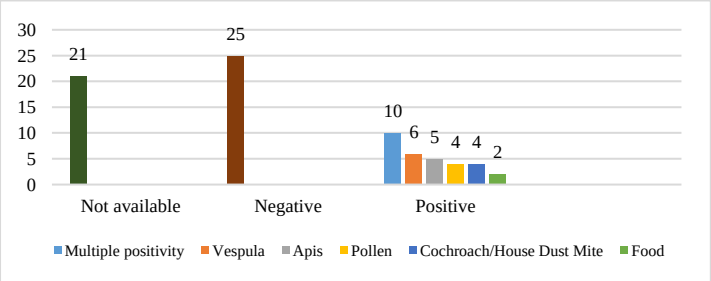

Table 1: General characteristics of patients with anaphylaxis.

| Variables | Number, % |
|---|---|
| **Total number of patients** | 77 |
| **Age, mean (SD) (years)** | 40.29 (13.77) |
| **Gender (female/male)** | 47/30 |
| **Chronic disease** | 32 (41%) |
| **Chronic drug usage** | 24 (31%) |
| **Anti-hypertensive drug usage** | 10 (12%) |
| **Atopic disease** | 73 (94%) |
| **History of drug allergy** | 39 (51%) |
| **History of Food Allergy** | 19 (24%) |
| **Prick test results (+/-/not performed)** | 31 (40%) /25 (32%) /21 (27%) |

SD: Standard deviation

Prick tests were administered to 56 patients (72%), of whom 25 individuals (44%) yielded negative results. Equally observed were sensitivities to pollen, cockroach, and house dust mites, each accounting for four cases. Polysensitization was evident in ten patients; only two exhibited positive food prick test responses. Interestingly, although cases of anaphylaxis stemming from *Apis mellifera* were more numerous than those from *Vespula vulgaris*, the instances of *Vespula vulgaris* reactivity exceeded those of *Apis mellifera* reactivity in prick tests (Figure 2). Regarding prick test positivity, venom accounted for 82% of anaphylactic cases, while for those with prick test negativity, drug allergies were the predominant cause (68.2%) ($P$=0.016). Notably, the presence of sensitivities to inhalant allergens and the presence of multiple allergen sensitivities did not significantly impact the etiology of anaphylaxis ($P$<0.001) (Figure 2).

Figure 2: Prick test results of the patients with anaphylaxis (shown as numbers)




Certain patterns emerge when assessing the relationship between the etiology of anaphylaxis and various atopic diseases, prick test results, and specific prick test outcomes. Notably, when neither drug nor venom allergy is present, anaphylaxis is solely attributed to food allergies (100%) ($P$<0.001). In cases where venom allergy is present, venom is identified as the predominant cause (95%), whereas in the absence of venom allergy, drug allergy assumes an 86% causal association ($P$<0.001).

**Clinical characteristics of the anaphylaxis episodes**

Based on a systematic assessment, cutaneous symptoms were observed in 94% of cases, respiratory symptoms in 88%, cardiovascular symptoms in 63%, neurological symptoms in 57%, and gastrointestinal symptoms in 12% of all patients.

Additionally, 55% of the patients experienced recurrent anaphylaxis episodes (Table 2).

Table 2: Clinical characteristics of anaphylaxis episodes

| Variables | Number, % |
|---|---|
| **Recurrent anaphylaxis** | 43 (55%) |
| **Biphasic anaphylaxis** | 4 (5%) |
| **Symptoms** | |
| Mucocutaneous symptoms | 73 (94%) |
| Respiratory tract symptoms | 68 (88%) |
| Cardiovascular system symptoms | 49 (63%) |
| Neurologic system symptoms | 44 (57%) |
| Gastrointestinal tract symptoms | 10 (12%) |
| Adrenalin administration | 19 (25%) |
| Antihistaminic administration | 77 (100%) |
| Corticosteroid administration | 77 (100%) |

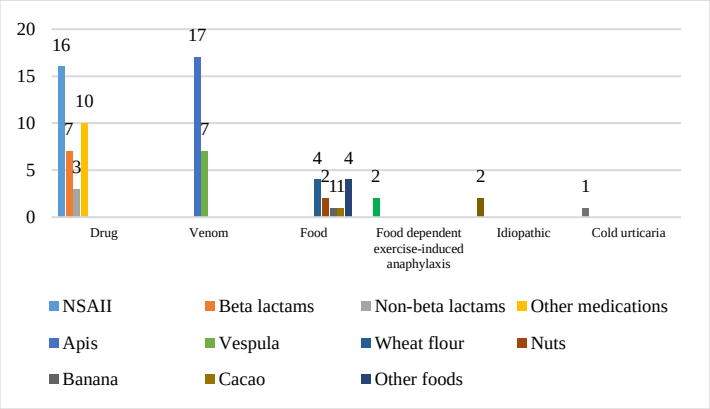
In cases of grade 4 anaphylaxis, cardiovascular and neurological symptoms were observed more frequently (100%) compared to other grades ($P$<0.001). Gastroenterological symptoms were also more prevalent in patients with grade 3 anaphylaxis compared to other grades ($P$=0.002). Furthermore, in situations where cutaneous symptoms were absent, grade 4 anaphylaxis was more prevalent (80%) than grade 2 anaphylaxis ($P$=0.047).

The causes of anaphylaxis included drugs (47%), venom (31%), food (16%), food-dependent exercise-induced reactions (n=2), idiopathic cases (n=2), and cold urticaria (n=1) (Figure 3). A gender-based comparison of anaphylaxis etiology revealed that drug- and food-related anaphylaxis was notably more frequent in women than men ($P$=0.032 and $P$=0.042, respectively). Regarding venom allergies, instances of anaphylaxis linked to *Apis mellifera* were significantly more prevalent than those related to Vespula ($P$=0.028) (Table 3).

Table 3: Etiologies of anaphylaxis according to the gender

| Etiology | Female | Male | *P*-value |
|---|---|---|---|
| **Drug** | 25 | 11 | 0.032 |
| **Food** | 8 | 4 | 0.042 |
| **Wheat flour** | 3 | 1 | |
| **Others** | 5 | 3 | |
| **Venom** | 12 | 12 | >0.05 |
| *Apis mellifera* | 9 | 8 | |
| *Vespula vulgaris* | 3 | 4 | |
| **Idiopathic** | 1 | 1 | >0.05 |
| **Food-dependent exercise-induced** | 0 | 2 | |

Figure 3: The triggers of anaphylaxis are categorized according to the etiologies (The frequencies are given as numbers).

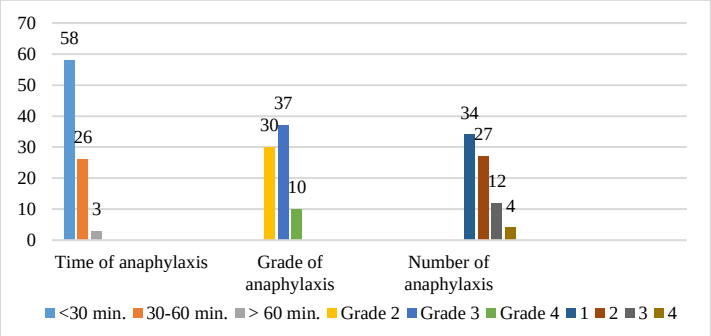



Both cases of food-dependent exercise-induced anaphylaxis were male, and the reaction occurred following mild exercise or even walking within the initial 10 min after eating. In both instances, skin tests yielded negative results. The diagnosis was established through patient history (anamnesis). Given that the suspected allergen could be wheat protein based on existing literature, the diagnosis was confirmed by implementing an elimination diet and restricting exercise for the initial 2 h after meals, leading to the disappearance of the symptoms.

In the emergency room, a patient with cold urticaria received an anaphylaxis diagnosis after presenting with widespread cutaneous manifestations, shortness of breath, palpitations, and dizziness following exposure to extremely cold temperatures during winter. Among instances of drug-related anaphylaxis, the predominant culprits were non-steroidal anti-inflammatory drugs (NSAIDs) (44%) and beta-lactams (10%). In food allergens, anaphylaxis was most frequently associated with wheat flour, although there were also cases triggered by bananas, cacao, and nuts (Figure 3).

Symptoms manifested within 30 min in 62% (n=58) of cases and within 1 h in 33% (n=26) of patients. Following the Mueller scale of anaphylaxis, 38% (n=30) experienced grade 2 reactions, 48% (n=37) had grade 3 reactions, and 12% exhibited grade 4 reactions (Figure 4).

Figure 4: The characteristics of the anaphylaxis episodes are categorized according to the time, grade, and number of the episodes (The frequencies are given as numbers).




**Management of the anaphylaxis episodes**

Merely 25% of cases received epinephrine injections upon arrival at the emergency department, with all individuals also being administered antihistamines and corticosteroids (Table 2).

It is important to note that, in our country, the acquisition of an adrenaline auto-injector necessitated a prescription from allergists; post-emergency service administration, the prescription of adrenaline auto-injector was not feasible.

**Treatments and follow-up of the anaphylaxis patients**

Venom immunotherapy was administered for cases with venom allergies. Oral provocation tests were conducted using alternative medications to identify safe options for those allergic to NSAIDs and antibiotics. Drug skin tests were not feasible due to challenging circumstances and inadequate facilities for patients with drug allergies. In cases of drug sensitivity, oral provocation was predominantly carried out using COX-2 inhibitors for those reacting to COX-1 inhibitors, and non-beta-lactam antibiotics were employed for individuals with beta-lactam antibiotic allergies.

Furthermore, comprehensive drug and food allergy cards were provided to patients, containing detailed information. Guidance was imparted on recognizing the significance of managing food allergies within their social lives. Precautions specific to cold urticaria were also communicated. Given that the city of Sivas, where our study is situated, experiences prolonged sub-zero temperatures during the winter as one of Turkey's coldest cities, individuals in these cases were advised to carry an adrenaline auto-injector. Notably, heightened vigilance was

stressed in instances of cold urticaria due to the inherent risk of anaphylaxis in physical urticaria conditions. Every patient received instruction in the proper use and carriage of adrenaline auto-injectors.

## Discussion

In our study, we conducted a retrospective analysis of anaphylaxis cases admitted to the allergy outpatient department of a tertiary university hospital in the northeast region of Turkey. We determined the frequency of anaphylaxis among patients seeking care at this single center. Our study revealed that anaphylaxis is exceedingly rare among admissions to the allergy outpatient clinic. According to existing literature, the lifetime prevalence of anaphylaxis ranges from 0.5% to 2% [9]. Research conducted in Korea demonstrated that anaphylaxis in adults rose from 8 to 13 cases per 100,000 individuals between 2007 and 2011 [10]. This upward trend in anaphylaxis incidence can be attributed to advancements in diagnostic methods and the increasing frequency of allergic diseases [11].

In a nationwide study conducted by Civelek et al. [12], a total of 843 cases were examined. The study revealed a predominance of females among anaphylaxis cases involving individuals older than 10 years, with venom identified as the primary etiological factor. In our study, drugs emerged as the leading cause of anaphylaxis within the general population. However, when analyzed by gender, drugs were the primary cause of anaphylaxis among women, whereas venom held the top position among men. Nearly 95% of the cases we investigated had a history of allergic disease. Conversely, drug allergies were frequently noted in the existing literature, particularly in cases of adult anaphylaxis, with up to 50% of cases displaying atopic tendencies [10,13,14].

Parallel to our findings, studies from China and Pakistan also identified drugs as prominent culprits in anaphylactic episodes [15,16]. The incidence of venom-induced anaphylaxis displayed significant variation across different populations, ranging from 1.5% to 59% [17]. In our country, venom-related anaphylaxis is particularly prevalent, a phenomenon attributed to the substantial number of individuals engaged in beekeeping and heightened awareness of the condition [18].

Food-induced anaphylaxis in adults is a rarity compared to children, with nuts/peanuts triggering the highest susceptibility, closely trailed by seafood sensitivity [19,20]. Within our study, wheat flour emerged as the leading cause of food sensitivity, although we also identified sensitivities to bananas, cacao, and nuts.

Literature data indicate a greater susceptibility to allergic diseases among female patients. This propensity is attributed to the augmenting role of estrogens in mast cell activation and allergen sensitization, whereas progesterone has been demonstrated to enhance sensitivity within target organs, exhibiting a synergistic impact. Consequently, this interplay leads to a prevailing female presence in non-venom-allergic conditions [21]. In the context of venom allergies, however, a male predominance persists. This phenomenon is primarily ascribed to the fact that men predominantly undertake beekeeping, resulting in a higher frequency of bee stings among the male population [17].

Typically, mucocutaneous manifestations are prevalent; however, cardiovascular and neurological symptoms occur more in grade 4 anaphylaxis cases. While dermatological manifestations are frequently documented in the literature and align with our findings, it's imperative to recognize that anaphylactic reactions can manifest without skin involvement and even with cardiovascular collapse. In instances where skin involvement is lacking, diagnosing anaphylaxis becomes more challenging, resulting in a decrease in the administration of adrenaline when cardiovascular symptoms are present [22,23].

Collapse is less commonly observed in cases of food-related anaphylaxis, with gastrointestinal symptoms taking on a more anticipated role [24]. Conversely, in instances of venom and drug-induced anaphylaxis, cardiovascular symptoms are more likely and have been more frequently linked to fatal outcomes [18].

In a nationwide study, biphasic reactions were documented at 4.3%, while recurrent episodes of anaphylaxis were observed in 60% of cases [12]. In our study, a notable proportion – over 20% – experienced two episodes, and 30% had three separate anaphylactic episodes. Within our study, the incidence of biphasic anaphylactic reactions stood at 5%, recurrent cases were noted in 55%, and adrenalin administration was administered at a rate of 25%. Biphasic reactions frequently arise due to delayed or inadequate administration of adrenaline and are most commonly reported within the initial 8 h. As a standard protocol, individuals presenting with anaphylaxis should undergo at least 8 h of observation within emergency departments [25].

Similar to our own country's experience, the rate of epinephrine prescription spans from 10% to 40%, and referral rates to allergy specialists fluctuate between 10% and 60%, as reported in the literature [26,27]. The prevention of biphasic and recurrent anaphylactic episodes hinges upon enhancing the awareness of healthcare providers regarding accurate diagnosis, effective treatment, and diligent follow-up. The endorsement of prescribing an adrenaline auto-injector holds significance, particularly in outdoor settings where venom allergies or food allergies are pertinent. Nevertheless, when a safe alternative exists for drug allergies, the prescription of an adrenaline auto-injector may not be deemed necessary.

**Limitations**

The principal limitation of our study resides in its limited sample size and retrospective design, coupled with the reliance on patient-reported data. Inherent to our retrospective approach is the potential for documentation bias, while recording patient-reported data introduces the possibility of data collection bias. Aspects such as the grading of anaphylactic reactions and determination of etiology were derived from the electronic patient files, introducing potential recall bias since they stem from patients' recollections. To mitigate this bias, a consistent allergist oversaw each patient and posed standardized inquiries, with the resultant data meticulously entered into the hospital's electronic records system. Notably, a paramount limitation influencing epidemiological data stems from the tendency in our country, akin to global trends, for physicians, patients, and/or caregivers to delay the diagnosis of anaphylaxis unless unmistakable shock-related indicators are evident or, in some

instances, not making the diagnosis at all. In such scenarios, accurate diagnosis remains elusive, and the referral to an allergist becomes unattainable.

Anaphylactic cases triggered by drugs were managed by implementing alternative drug recommendations. This approach is adopted due to physicians' inclination to opt for safe alternative drugs when circumstances for conducting skin tests are not conducive – factors like the absence of secure test sites, time constraints, challenges in describing the suspected drug, or patient use of medications affecting the testing process, among others. Regrettably, diagnostic tests for confirmation or drug provocations to pinpoint the causative drug could not be administered. It's worth noting that provocation tests stand as the benchmark for diagnosing genuine drug allergies and should be conducted under safe conditions. Regarding non-drug origins, standardized allergen extracts were employed for skin prick tests; however, no provocations involving venom or food sources could be conducted.

In addition, basal tryptase could not be measured because laboratory conditions were not possible. An increase of tryptase [(1.2 × baseline tryptase) +2 μg/L)] measured in serum within the first 2 h after the anaphylaxis attack supports the diagnosis [28].

Systemic mastocytosis and mast cell activation syndromes, entities encompassed within the anaphylaxis differential diagnosis, underscore the utility of basal tryptase levels. When evaluating patients' medical history, factors prompting physicians to consider mast cell disorders encompass the recurrence of numerous anaphylactic episodes, instances of idiopathic or grade 4 anaphylaxis, the emergence of direct cardiovascular manifestations devoid of cutaneous signs, and anaphylactic reactions linked with venom allergies [29].

Nevertheless, it is crucial to recognize that tryptase is not exclusively indicative of anaphylaxis. Particularly in instances of mast cell disorders or hereditary alpha tryptazemia, both susceptibility to anaphylaxis and heightened basal tryptase levels (normal basal tryptase <11.5 ng/ml) can manifest. Consequently, when anaphylaxis is suspected, basal tryptase measurements should be taken at least 24 h after induced tryptase measurements. It's important to note that tryptase levels may not consistently rise in children, particularly in anaphylactic episodes characterized by food-related reactions, especially those presenting with gastrointestinal symptoms. In summary, the absence of an elevated tryptase level during an anaphylactic event does not definitively rule out the occurrence of anaphylaxis [30,31].

**Strengths**

Literature reviews have predominantly centered on subgroups of anaphylaxis, conducting subgroup analyses that delve into triggers such as drugs or food. While epidemiological studies on anaphylaxis are within the literature, our country's landscape lacks investigations that ascertain the risk associated with anaphylactic incidents [32]. In the current study, we aimed to ascertain the prevalence and distribution of anaphylaxis triggers across all cases attending a solitary allergy outpatient clinic, thereby illuminating the region's epidemiological insights.

**Future research**

There is a paramount need to educate healthcare providers during their post-graduate training about the diagnosis and treatment protocols for anaphylaxis, ensuring that these essential teachings are reiterated through mandatory annual training sessions. Employing technological reminders such as mobile phones, smart watches, and virtual intelligence systems can effectively enhance early awareness of anaphylactic risks. In laboratory settings, blood samples should be collected under optimal conditions for accurate tryptase measurement to support diagnostic endeavors. The serum must be segregated and appropriately stored if an immediate analysis is unfeasible. Patients should be strongly encouraged to carry a minimum of two auto-injectors, equipping them to recognize anaphylactic symptoms and self-administer them as needed. Organizing group activities –in-person or online – with patients can aid in dispelling misconceptions such as needle apprehensions and concerns regarding adrenaline's side effects.

Strategic social responsibility initiatives, particularly within educational institutions and workplaces, are essential for fostering awareness about triggers such as food allergies and anaphylaxis. These initiatives should emphasize first-response training to equip individuals with the necessary skills to handle anaphylactic emergencies effectively [2].

**Conclusions**

Our study presents the inaugural dataset for analyzing the northeastern region of Turkey. Within the scope of anaphylaxis studies in our country, there has been a notable absence of research into the outcomes of adult cases within this specific region, particularly through the eyes of allergist evaluation.

While allergic diseases tend to exhibit a higher prevalence among females, our anaphylaxis study yielded comparable frequencies between the female and male genders. The prominence of venom allergy as the second leading cause of anaphylaxis etiology, coupled with the observation that nearly all venom-induced allergies occurred in males engaged in beekeeping, appears to have influenced this gender-based distribution. Our findings underscore the enduring prominence of drug-induced anaphylaxis as the primary etiological factor – a preventable trigger that remains at the forefront. Notably, the incidence of recurrent anaphylaxis stood alarmingly high at 55%, shedding light on the insufficient awareness surrounding this matter, particularly in cases where triggers such as drugs and food could be averted with greater knowledge. The recurrent exposure to the same triggers emphasizes the need for heightened understanding. Implementing immediate adrenaline administration is a pivotal preventive measure against biphasic and prolonged anaphylactic episodes. Strikingly, our investigation reveals a concerning statistic: only 25% of anaphylaxis cases in our region receive adrenaline promptly.

NSAIDs and antibiotics stand out as the prevailing culprits in etiology. This observation underscores the imperative for all medical practitioners, pharmacists, and healthcare units to comprehensively understand anaphylactic triggers. By doing so, these stakeholders can effectively heighten vigilance when providing outpatient and inpatient care, including surgical procedures. Furthermore, a compelling need exists to foster

patient awareness concerning drug-induced anaphylaxis – a preventable catalyst in this context.

Sivas, the focal point of our study, assumes a significant role in our nation as a hub for beekeeping and honey production. Despite venom sensitivity emerging as the foremost solitary allergic condition among our admitted patients, it assumes the second position in the hierarchy of anaphylaxis etiology. It remains common knowledge that Venom Immunotherapy (VIT), a treatment regimen extended to our venom-allergic cases, is the exclusive therapeutic approach capable of altering the trajectory of this ailment. Encouragingly, VIT demonstrates both efficacy and safety right from its initial administration.

Furthermore, an exhaustive patient history becomes imperative in instances of anaphylaxis incited by food-dependent exercise – a notably rare yet acknowledged category of anaphylaxis. While these cases remain symptom-free when physical exertion remains below a certain threshold after consuming food, symptoms manifest when exercise coincides with food ingestion. The intricacies of this presentation often render differential diagnosis challenging, even for allergy specialists. Once accurately diagnosed, proactive measures and medical interventions effectively manage the condition, greatly enhancing the affected individuals' quality of life.

Adrenaline administration presents no contraindications when faced with an anaphylactic episode and should be promptly administered without reservation. Within the purview of our study, the intended recipients of this guidance encompass a diverse group of medical practitioners. Among them are clinical allergists, spanning specialists and sub-specialists, and primary care physicians, internists, emergency physicians, anesthesiologists, and intensive care specialists. This directive also extends to nurses, dietitians, and other healthcare professionals. Essential to effective management, the ability to differentially diagnose anaphylaxis falls within the domain of emergency room physicians. In such cases, a swift and accurate diagnostic discernment, based on history and physical examination findings aligning with anaphylaxis, warrants the immediate administration of adrenaline.

In conclusion, our study is noteworthy due to the infrequency of anaphylactic occurrences among cases attending the tertiary allergy immunology outpatient clinic in the northeastern region of Turkey.

Notwithstanding its limitations, our study fills a crucial gap by furnishing insights into a region hitherto unexplored, emphasizing anaphylaxis – a matter of significance for practitioners across various medical disciplines and healthcare sectors. The implications of our findings underscore the essentiality of bolstering awareness surrounding the diagnosis and management of anaphylaxis in both emergency and primary healthcare settings, both prior to and after graduation.

## References


1. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7. doi: 10.1016/j.jaci.2005.12.1303.
2. Muraro A, Worm M, Alviani C, Cardona V, Dunn Galvin A, Garvey LH, et al. European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022 Feb;77(2):357-77. doi: 10.1111/all.15032.
3. Vezir E, Erkoçoğlu M, Kaya A, Toyran M, Özcan C, Akan A, et al. Characteristics of anaphylaxis in children referred to a tertiary care center. Allergy Asthma Proc. 2013 May-Jun;34(3):239-46. doi: 10.2500/aap.2013.34.3654.
4. Erkoçoğlu M, Civelek E, Azkur D, Özcan C, Öztürk K, Kaya A, et al. Knowledge and attitudes of primary care physicians regarding food allergy and anaphylaxis in Turkey. Allergol Immunopathol (Madr). 2013 Sep-Oct;41(5):292-7. doi: 10.1016/j.aller.2012.05.004.
5. Gaspar Â, Santos N, Piedade S, Santa-Marta C, Pires G, Sampaio G, et al. One-year survey of pediatric anaphylaxis in an allergy department. Eur Ann Allergy Clin Immunol. 2015 Nov;47(6):197-205. Erratum in: Eur Ann Allergy Clin Immunol. 2016 Jan;48(1):31.
6. Hoyos-Bachiloglu R, Ivanovic-Zuvic D, Álvarez J, Linn K, Thöne N, de los Ángeles Paul M, et al. Prevalence of parent-reported immediate hypersensitivity food allergy in Chilean school-aged children. Allergol Immunopathol (Madr). 2014 Nov-Dec;42(6):527-32. doi: 10.1016/j.aller.2013.09.006.
7. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. J Allergy Clin Immunol. 2002 Oct;110(4):647-51. doi: 10.1067/mai.2002.127860.
8. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res. 1966 Jun;3(4):331-3. doi: 10.3109/02770906609106941.
9. Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011 Feb;4(2):13-37. doi: 10.1097/WOX.0b013e318211496c.
10. Ye YM, Kim MK, Kang HR, Kim TB, Sohn SW, Koh YI, et al. KAAACI Work Group on Urticaria/Angioedema/Anaphylaxis. Predictors of the severity and serious outcomes of anaphylaxis in Korean adults: a multicenter retrospective case study. Allergy Asthma Immunol Res. 2015 Jan;7(1):22-9. doi: 10.4168/aair.2015.7.1.22.
11. Russell S, Monroe K, Losek JD. Anaphylaxis management in the pediatric emergency department: opportunities for improvement. Pediatr Emerg Care. 2010 Feb;26(2):71-6. doi: 10.1097/PEC.0b013e3181ce2e1c.
12. Civelek E, Erkoçoğlu M, Akan A, Özcan C, Kaya A, Vezir E, et al. The Etiology and Clinical Features of Anaphylaxis in a developing country: A nationwide survey in Turkey. Asian Pac J Allergy Immunol. 2017 Dec;35(4):212-9. doi: 10.12932/AP0752.
13. Alvarez-Perea A, Tomás-Pérez M, Martínez-Lezcano P, Marco G, Pérez D, Zubeldia JM, et al. Anaphylaxis in Adolescent/Adult Patients Treated in the Emergency Department: Differences Between Initial Impressions and the Definitive Diagnosis. J Investig Allergol Clin Immunol. 2015;25(4):288-94.
14. Yang MS, Lee SH, Kim TW, Kwon JW, Lee SM, Kim SH, et al. Epidemiologic and clinical features of anaphylaxis in Korea. Ann Allergy Asthma Immunol. 2008 Jan;100(1):31-6. doi: 10.1016/S1081-1206(10)60401-2.
15. Khan NU, Shakeel N, Makda A, Mallick AS, Ali Memon M, Hashmi SH, et al. Anaphylaxis: incidence, presentation, causes, and Outcome in patients in a tertiary-care hospital in Karachi, Pakistan. QJM. 2013 Dec;106(12):1095-101. doi: 10.1093/qjmed/hct179.
16. Tang R, Xu HY, Cao J, Chen S, Sun JL, Hu H, et al. Clinical Characteristics of Inpatients with Anaphylaxis in China. Biomed Res Int. 2015;2015:429534. doi: 10.1155/2015/429534.
17. Bilò BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. Curr Opin Allergy Clin Immunol. 2008 Aug;8(4):330-7. doi: 10.1097/ACI.0b013e32830638c5.
18. Orhan F, Canitez Y, Bakirtas A, Yilmaz O, Boz AB, Can D, et al. Anaphylaxis in Turkish children: a multi-center, retrospective, case study. Clin Exp Allergy. 2011 Dec;41(12):1767-76. doi: 10.1111/j.1365-2222.2011.03859.x.
19. Jacobs TS, Greenhawt MJ, Hauswirth D, Mitchell L, Green TD. A survey study of index food-related allergic reactions and anaphylaxis management. Pediatr Allergy Immunol. 2012 Sep;23(6):582-9. doi: 10.1111/j.1399-3038.2012.01315.x.
20. Lee AJ, Gerez I, Shek LP, Lee BW. Shellfish allergy--an Asia-Pacific perspective. Asian Pac J Allergy Immunol. 2012 Mar;30(1):3-10.
21. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy. 2008 Nov;63(11):1418-27. doi: 10.1111/j.1398-9995.2008.01880.x.
22. Greenberger PA. Fatal and near-fatal anaphylaxis: factors that can worsen or contribute to fatal outcomes. Immunol Allergy Clin North Am. 2015 May;35(2):375-86. doi: 10.1016/j.iac.2015.01.001.
23. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol. 2009 Feb;123(2):434-42. doi: 10.1016/j.jaci.2008.10.049.
24. Pumphrey RS. Fatal anaphylaxis in the UK, 1992-2001. Novartis Found Symp. 2004;257:116-28; discussion 128-32, 157-60, 276-85.
25. Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunol Allergy Clin North Am. 2007 May;27(2):309-26, viii. doi: 10.1016/j.iac.2007.03.011.
26. Rudders SA, Banerji A, Corel B, Clark S, Camargo CA Jr. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. Pediatrics. 2010 Apr;125(4):e711-8. doi: 10.1542/peds.2009-2832.
27. Campbell RL, Luke A, Weaver AL, St Sauver JL, Bergstralh EJ, Li JT, et al. Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. Ann Allergy Asthma Immunol. 2008 Dec;101(6):631-6. doi: 10.1016/S1081-1206(10)60227-X.
28. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol. 2012;157(3):215-25. doi: 10.1159/000328760.
29. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features, and risk factors in 120 patients. Allergy. 2008;63(2):226-32. doi: 10.1111/j.1398-9995.2007.01569.x.
30. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet. 2016 Dec;48(12):1564-9. doi: 10.1038/ng.3696.
31. Lyons JJ, Chovanec J, O'Connell MP, Liu Y, Šelb J, Zanotti R, et al. Heritable risk for severe anaphylaxis associated with increased α-tryptase-encoding germline copy number at TPSAB1. J Allergy Clin Immunol. 2021 Feb;147(2):622-32. doi: 10.1016/j.jaci.2020.06.035.
32. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med. 2001 January 8;161(1):15-21. doi: 10.1001/archinte.161.1.15.

J Surg Med. 2023;7(8):498-503.
DOI: 10.28982/josam.7923

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# 25-hydroxy vitamin D levels in patients with myelofibrosis and potential relationships with disease severity: A case-control study

**Yildiz Ipek**

Department of Hematology, Kartal Lutfi Kirdar City Hospital, Istanbul, Turkey

**ORCID ID of the author(s)**

YI: 0000-0003-2952-2286

**Corresponding Author**
Yildiz Ipek
Department of Hematology, Kartal Lutfi Kirdar City Hospital, Cevizli, D-100 Guney Yanyol, Cevizli Mevkii No:47, 34865 Kartal, Istanbul, Turkey
E-mail: dryildizipek@hotmail.com

**Ethics Committee Approval**
The study was approved by the Clinical Research Ethics Committee of Dr. Lütfi Kırdar State Hospital (decision date: December 29, 2021, decision number: 2021/514/216/5).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 29

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Although vitamin D deficiency has been associated with cancer and its prognosis, data is unclear regarding associations with myelofibrosis. This study aimed to measure 25-hydroxy vitamin D levels in patients with myelofibrosis and to evaluate its relationship with prognoses.
**Methods:** This case-control study consisted of 72 patients with myelofibrosis and 75 controls. The Dynamic International Prognostic Scoring System was used to determine prognostic risk groups, and patients were divided into two subgroups: intermediate-1 (low risk) and intermediate-2 (high risk).
**Results:** The median 25-OHD levels were decreased in the myelofibrosis group more so than in the controls (13.05 vs. 23.0 ng/mL, $P<0.001$). A cut-off value of ≤ 16.5 ng/mL yielded a sensitivity of 84.72% and a specificity of 80% for the identification of patients with myelofibrosis. This impact was also evident when adjusted for age and sex, showing that patients with low 25-hydroxy vitamin D (≤16.5) had a 23.787-fold higher probability to have myelofibrosis (OR: 23.787, 95% CI: 9.676-58.479, $P<0.001$). When examined for the two prognostic subgroups, 25-hydroxy vitamin D was found to be significantly lower in the intermediate-2 and high subgroup ($P=0.017$). For a cut-off value of ≤13.7 ng/mL, 25-hydroxy vitamin D level was able to discriminate patients in the intermediate-2 and high subgroup from those with lower risk (sensitivity: 77.8%, specificity: 55.6%).
**Conclusion:** A serum 25-hydroxy vitamin D level may serve as a biomarker associated with myelofibrosis diagnosis and prognosis; however, the discriminatory value for prognostic groups was low, indicating the need for larger and longitudinally-designed studies.

**Keywords:** dynamic international prognostic scoring system, myeloproliferative neoplasm, myelofibrosis, prognosis, vitamin D

How to cite: Ipek Y. 25-hydroxy vitamin D levels in patients with myelofibrosis and potential relationships with disease severity: A case-control study. J Surg Med. 2023;7(8):498-503.

## Introduction

Myelofibrosis is an uncommon hematological neoplasm arising from clonal abnormalities in stem cells, displaying both clinical and biological heterogeneity [1]. It has an incidence between 0.47 and 1.98 per 100,000 individuals, and greatly shortens life expectancy (median survival 5.2–5.9 years) [2,3]. Clinical presentation varies greatly from patient to patient, but typically includes debilitating systemic effects such as weight loss, night sweats, fever, hepatosplenomegaly, and vascular complications. Additionally, myelofibrosis can lead to the development of acute leukemia [3]. Disruption of the JAK/STAT signaling pathway is a recognized mechanism leading to myelofibrosis, resulting in myeloproliferation, cytopenia, cytokine secretion, bone marrow hyper-cellularity, collagen and reticulin fibrosis, bone modification and extramedullary hematopoiesis [4]. Given the high variability in clinical presentation and short survival, it is critical to identify determinants that can be used to guide treatment decisions and act as prognostic indicators.

A pleiotropic, fat-soluble secosteroid hormone with a major regulatory function in calcium and phosphorus homeostasis, vitamin D is recognized as contributing to a wide range of disease conditions [5]. Vitamin D also plays a crucial role in the immune system as an anti-inflammatory, immunomodulatory, anti-fibrotic, and antioxidant molecule, and is also involved in the pathogenesis of various clinical conditions in non-skeletal tissues, including malignancies [6,7]. Vitamin D may inhibit tumorigenesis by modulating inflammatory responses, cellular survival, cell-cell interactions, and angiogenesis –all of which can impact cancer spread and progression [8]. Previous observational studies have found a link between vitamin D deficiency and a higher chance of developing cancer as well as a worse prognosis [9]. To date, there have been case reports examining vitamin D levels in patients with myelofibrosis, but the results are uncertain and information regarding its clinical or prognostic significance is lacking [10]. Therefore, our goal was to measure 25-hydroxy vitamin D levels in myelofibrosis patients and assess any potential associations with the prognosis of the condition.

## Materials and methods

### Study population

This case-control study was carried out between May 2022 and May 2023 in the Department of Hematology of Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey. The study had 72 myelofibrosis patients who were 18 years of age or older and 75 healthy controls. Subjects in the healthy control group were consecutively included among those referred for routine evaluations from primary care physicians, given that they were not referred for any specific suspicion and did not have any comorbidities. The patient group was chosen based on inclusion/exclusion criteria.

Myelofibrosis was diagnosed using the updated World Health Organization 2022 categorization criteria, which were supported by biochemical analysis, cytogenetic testing, and bone marrow biopsies [11]. Participants with a history of chronic or inflammatory diseases, rheumatological disorders, severe liver or kidney disease, and malignancies other than myeloproliferative neoplasms were excluded from the study. Subjects referred for allogenic stem cell transplantation, or participants presenting with acute malignancies such as AML or ALL were also excluded. The control group was comprised of 75 healthy people aged 18 years and older, with no history of malignancies and no known disease. Sex, age, body mass index (BMI), smoking status, type of myelofibrosis, Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of comorbid conditions like ischemic heart failure, hypertension, diabetes mellitus, peripheral arterial hypertension, hypothyroidism, or hepatomegaly were obtained from files and pertinent records. Additionally, spleen size, peripheral blood blasts, presence of constitutional symptoms such as weight loss, night sweats and fever were recorded based on the Dynamic International Prognostic Scoring System (DIPSS). In addition, cytogenetic profiles were examined, including mutations of Janus kinase (JAK) 2, JAK2 exon 12, calreticulin (CALR), and myeloproliferative leukemia virus oncogene (MPL), all of which were collected from the most recent data available for each subject.

The Kartal Dr. Lutfi Kirdar City Hospital's Clinical Study Ethics Committee accepted all study methods. All ethical principles specified in the Declaration of Helsinki (Decision date: 29.05.2023 and Decision number: 2023/514/250/7) were also accepted.

### Prognostic stratification

DIPSS is prognostic risk stratification tool. It is calculated by utilizing five variables: 1 point for age >65 years, 2 points for hemoglobin value <10 g/dL, 1 point for peripheral blood blasts ≥1%, 1 point for presence of constitutional symptoms, and 1 point for white blood cell counts $>25 \times 10^9$/L [4]. Risk groups were as follows: low-risk (0 points), intermediate-1 risk (1 or 2 points), intermediate-2 risk (3 or 4 points), and high-risk (5 or 6 points). All myelofibrosis patients were evaluated using a DIPSS score at the time of the last follow-up. ECOG performance status was employed to evaluate functionality by determining an individual's level of functioning in relation to daily activities and physical capabilities, including work and walking. This assessment was quantified on a scale ranging from 0 to 5 points [12]. A lower ECOG score of 0 and 1 defines fewer activity restrictions, while a higher score indicates elevated disability or mortality. All measurements were carried out by the same clinician with strict measures to ensure reliability and reproducibility.

### Biochemical analysis

Each participant was asked to provide blood samples, which were drawn from the antecubital vein following an overnight fast in preparation for the laboratory analyses. To collect serum, serum separator tubes were centrifuged at 2400 g for 7 minutes. Using a Mindray BC-6800 analyzer (Mindray, China), the full blood count, comprising hemoglobin and the hematocrit levels, mean corpuscular volume (MCV), white blood cell (WBC), and platelet values, were determined. On an Architect c8000 autoanalyzer (Abbott, USA), serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total protein, albumin, and C-reactive protein (CRP) were measured. Using a UniCel DxI

800 (Beckman Coulter, USA), a chemiluminescent enzyme immunoassay was used to measure the levels of 25-hydroxyvitamin D and vitamin B12. Of note, mutation analyses including JAK2, JAK2 exon 12, CALR, and MPL were performed in duplicate at the hospital.

**Statistical analysis**

The data analysis was conducted using IBM SPSS Statistics for Windows, Version 28.0. The normality of distribution was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean (standard deviation) or median (1st quartile-3rd quartile), depending on the normality of distribution. Categorical variables were expressed as frequency (percentage). For normally distributed variables, the Student's t-test was used for analysis, while the Mann-Whitney U test was employed for non-normally distributed variables. Categorical variables were analyzed using chi-square tests or Fisher's exact tests as appropriate. The discrimination performance of 25-hydroxy vitamin D was assessed through the receiver operating characteristic (ROC) curve analysis. The Youden index was used to calculate the best cut-off positions. For the chosen cut-off values, sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Odds ratios (OR) were also computed for the determined cut-off points using logistic regression analysis. The cutoff for statistical significance was *P*-value <0.05.

## Results

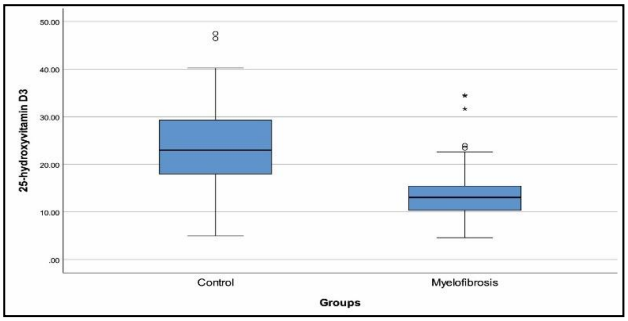
Seventy-two patients diagnosed with myelofibrosis and 75 healthy individuals were enrolled in the study. The mean age in the patient group was 63.71 (7.87) years, and 44 (61.11%) were males. The control group consisted of 40 (53.33%) males, and the mean age was 60.59 (10.21) years. The groups were similar for age and sex distribution. The mean 25-hydroxy vitamin D levels were 13.05 (10.35-15.45) ng/mL in the myelofibrosis group and 23.0 (17.7-29.5) ng/mL in the control group (*P*<0.001) (Table 1, Figure 1).

Table 1: Summary of age, sex and 25-hydroxy vitamin D levels with regard to groups

| | | Groups | | |
|---|---|---|---|---|
| | **Total (n=147)** | **Control (n=75)** | **Myelofibrosis (n=72)** | ***P*-value** |
| **Age, years** | 62.12 (9.24) | 60.59 (10.21) | 63.71 (7.87) | 0.039 |
| **Sex** | | | | |
| **Male, (n/%)** | 84 (57.14%) | 40 (53.33%) | 44 (61.11%) | 0.341 |
| **Female, (n/%)** | 63 (42.86%) | 35 (46.67%) | 28 (38.89%) | |
| **25-hydroxy vitamin D, ng/mL** | 16.12 (12.40-24.30) | 23.00 (17.70-29.50) | 13.05 (10.35-15.45) | <0.001 |

Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

Figure 1: Box-plot of the 25-hydroxy vitamin D with regard to groups



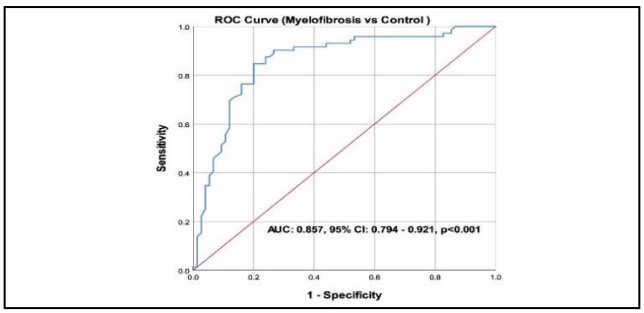

We determined the 25-hydroxy vitamin D level to distinguish between myelofibrosis patients and healthy controls by ROC analysis. The sensitivity and specificity values for the cut-off (≤16.5 ng/mL) were 84.72% and 80%, respectively. Patients with a low 25-hydroxy vitamin D level (≤16.5) had a 23.787-fold higher probability of having myelofibrosis than others after adjusting for sex and age (OR: 23.787, 95% CI: 9.676-58.479, *P*<0.001) (Table 2, Figure 2).

Table 2: Performance of 25-hydroxy vitamin D to discriminate patients with myelofibrosis and healthy controls

| **Cut-off** | **≤16.5** |
|---|---|
| **Sensitivity** | 84.72% |
| **Specificity** | 80.00% |
| **Accuracy** | 82.31% |
| **PPV** | 80.26% |
| **NPV** | 84.51% |
| **AUC (95% CI)** | 0.857 (0.794-0.921) |
| ***P*-value for AUC** | <0.001 |
| **OR (95% CI)** | 22.182 (9.426-52.197) |
| ***P*-value for OR** | <0.001 |
| **Adjusted OR (95% CI) (1)** | 23.787 (9.676-58.479) |
| ***P*-value for adjusted OR** | <0.001 |

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, OR: Odds ratio, (1) Adjusted for age and sex.

Figure 2: ROC curve of the 25-hydroxy vitamin D to discriminate patients with myelofibrosis and healthy controls




ROC: Receiver operating characteristic analysis, AUC: Area under the curve, CI: Confidence interval

The DIPSS risk groups of the patients were as follows: 19 low risk, 17 intermediate-1, 30 intermediate-2, and 6 high risk. The patient population was then further divided into two subgroups: (i) Low and intermediate-1 and (ii) Intermediate-2 and high, with respect to DIPSS risk groups. No significant differences were found between the groups regarding age, sex, BMI, ECOG performance status, smoking status, comorbidities, type of myelofibrosis, the presence of mutations, and hepatomegaly (all, *P*>0.05). Spleen size was greater in the intermediate-2 and high group compared to the low and intermediate-1 group (20.19 [2.94] cm vs. 18.24 [2.85] cm, *P*=0.006) (Table 3).

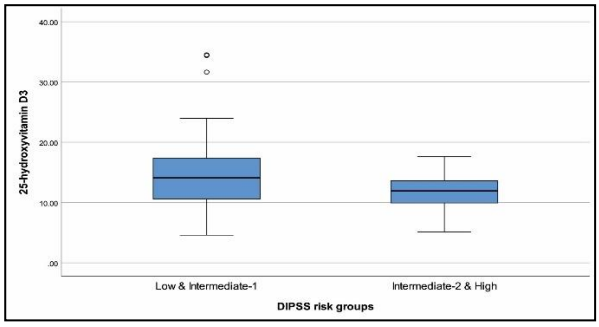
Table 3: Demographics and clinical characteristics with regard to DIPSS risk groups

| | | DIPSS risk groups | | |
|---|---|---|---|---|
| | **Total (n=72)** | **Low & Intermediate-1 (n=36)** | **Intermediate-2 & High (n=36)** | ***P*-value** |
| **Age, years** | 63.71 (7.87) | 64.18 (7.56) | 63.25 (8.24) | 0.621 |
| **Sex** | | | | |
| **Male, (n/%)** | 44 (61.11%) | 23 (63.89%) | 21 (58.33%) | 0.809 |
| **Female, (n/%)** | 28 (38.89%) | 13 (36.11%) | 15 (41.67%) | |
| **Body mass index, kg/m$^2$** | 26.4 (23.4-29.1) | 26.8 (24.0-29.3) | 26.3 (22.8-28.7) | 0.258 |
| **ECOG performance status** | | | | |
| 0, (n/%) | 67 (93.06%) | 34 (94.44%) | 33 (91.67%) | 1.000 |
| 1, (n/%) | 5 (6.94%) | 2 (5.56%) | 3 (8.33%) | |
| **Smoker, (n/%)** | 19 (26.39%) | 11 (30.56%) | 8 (22.22%) | 0.593 |
| **Comorbidities** | | | | |
| Ischemic heart disease, (n/%) | 15 (20.83%) | 4 (11.11%) | 11 (30.56%) | 0.082 |
| Hypertension, (n/%) | 22 (30.56%) | 13 (36.11%) | 9 (25%) | 0.443 |
| Diabetes mellitus, (n/%) | 18 (25%) | 9 (25%) | 9 (25%) | 1.000 |
| Peripheral arterial disease, (n/%) | 3 (4.17%) | 2 (5.56%) | 1 (2.78%) | 1.000 |
| Hypothyroidism, (n/%) | 10 (13.89%) | 5 (13.89%) | 5 (13.89%) | 1.000 |
| **Type of myelofibrosis** | | | | |
| Primary, (n/%) | 24 (33.33%) | 16 (44.44%) | 8 (22.22%) | 0.080 |
| Secondary, (n/%) | 48 (66.67%) | 20 (55.56%) | 28 (77.78%) | |
| **Mutations** | | | | |
| JAK2, (n/%) | 33 (45.83%) | 15 (41.67%) | 18 (50%) | 0.636 |
| JAK2 exon 12, (n=25) (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | N/A |
| CALR, (n=49) (n/%) | 2 (4.08%) | 1 (4.55%) | 1 (3.70%) | 1.000 |
| MPL, (n=49) (n/%) | 0 (0%) | 0 (0%) | 0 (0%) | N/A |
| **Hepatomegaly, (n/%)** | 29 (40.28%) | 18 (50%) | 11 (30.56%) | 0.149 |
| **Size of spleen, cm** | 19.22 (3.04) | 18.24 (2.85) | 20.19 (2.94) | 0.006 |
| **DIPSS risk group** | | | | |
| Low, (n/%) | 19 (26.39%) | 19 (52.78%) | 0 (0%) | <0.001 |
| Intermediate-1, (n/%) | 17 (23.61%) | 17 (47.22%) | 0 (0%) | |
| Intermediate-2, (n/%) | 30 (41.67%) | 0 (0%) | 30 (83.33%) | |
| High, (n/%) | 6 (8.33%) | 0 (0%) | 6 (16.67%) | |

DIPSS: Dynamic International Prognostic Scoring System, ECOG: Eastern Cooperative Oncology Group, JAK: Januse kinase, CALR: Calreticulin, MPL: Myeloproliferative leukemia virus oncogene. Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

25-hydroxy vitamin D levels were found to be 14.1 (10.6-17.35) ng/mL in the low and intermediate-1 subgroup and 11.95 (9.95-13.6) ng/mL in the intermediate-2 and high subgroup ($P$=0.017) (Figure 3). No significant differences were found for vitamin B12, creatinine, AST, ALT, LDH, total protein, albumin, CRP, and MCV and platelet values. WBC, hemoglobin and hematocrit values were significantly lower in the intermediate-2 and high subgroup (all, $P$<0.05) (Table 4).

Figure 3: Box-plot of the 25-hydroxy vitamin D with regard to DIPSS risk groups




DIPSS: Dynamic International Prognostic Scoring System

Table 4: Laboratory measurements with regard to DIPSS risk groups

| | | DIPSS risk groups | | |
|---|---|---|---|---|
| | **Total (n=72)** | **Low & Intermediate-1 (n=36)** | **Intermediate-2 & High (n=36)** | ***P*-value** |
| **25-hydroxy vitamin D, ng/mL** | 13.05 (10.35-15.45) | 14.10 (10.60-17.35) | 11.95 (9.95-13.60) | 0.017 |
| **Vitamin B12, pg/mL (n=49)** | 340.96 (109.47) | 331.92 (126.93) | 351.17 (87.38) | 0.545 |
| **Creatinine, mg/dL** | 0.83 (0.65-1.01) | 0.81 (0.65-0.96) | 0.89 (0.66-1.06) | 0.327 |
| **AST, U/L** | 20 (17-22) | 20 (17-20.5) | 19.5 (17-23.5) | 0.359 |
| **ALT, U/L** | 17 (13-23.5) | 16 (13.5-21) | 20 (12-24.5) | 0.376 |
| **LDH, U/L** | 237 (207-313) | 245.5 (209-294) | 226.5 (192.5-415) | 0.723 |
| **Total protein, g/dL** | 7.00 (6.70-7.45) | 7.00 (6.60-7.50) | 7.05 (6.85-7.30) | 0.236 |
| **Albumin, g/dL** | 4.63 (0.25) | 4.59 (0.27) | 4.67 (0.23) | 0.207 |
| **CRP, g/dL** | 1.27 (0.66-2.28) | 1.23 (0.79-2.28) | 1.28 (0.59-2.34) | 0.951 |
| **White Blood Cell, $10^9$/L** | 8.21 (5.90-10.46) | 9.29 (7.13-14.15) | 7.19 (4.59-8.87) | 0.002 |
| **Hemoglobin, g/dL** | 11.71 (10.06-12.55) | 12.55 (12.00-13.05) | 10.06 (8.71-10.90) | <0.001 |
| **Hematocrit, %** | 34.90 (5.59) | 39.67 (2.37) | 30.14 (3.33) | <0.001 |
| **MCV, Fl** | 90.1 (82.9-101.1) | 86.15 (82.6-99.6) | 91.2 (84.1-103.5) | 0.162 |
| **Platelet (x$10^3$)** | 353 (257.5-502) | 375.5 (286-510) | 334.5 (254-502) | 0.430 |

DIPSS: Dynamic International Prognostic Scoring System, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, MCV: Mean corpuscular volume. Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

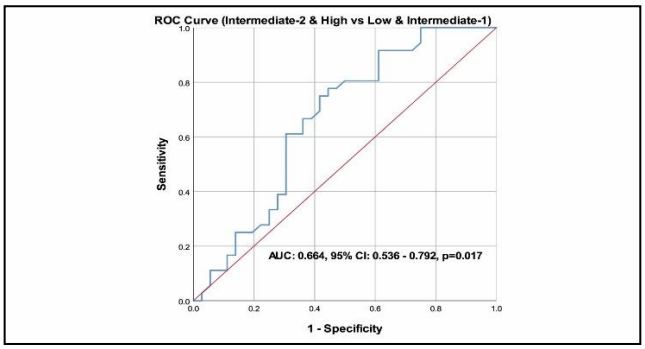
We determined the 25-hydroxy vitamin D level that would allow discrimination of the two subgroups. The cut-off value was <13.7 ng/mL, and resulted in a specificity of 55.6% and sensitivity of 77.8%. Patients with low 25-hydroxy vitamin D (≤13.7) had a 4.695-fold higher likelihood of being categorized in the intermediate-2 and high-risk subgroup, after adjusting for sex and age (OR: 4.695, 95% CI: 1.638-13.459, $P$=0.004) (Table 5, Figure 4).

Table 5: Performance of 25-hydroxy vitamin D to discriminate patients with intermediate-2 & high risk and low & intermediate-1 risk

| **Cut-off** | **≤13.7** |
|---|---|
| **Sensitivity** | 77.78% |
| **Specificity** | 55.56% |
| **Accuracy** | 66.67% |
| **PPV** | 63.64% |
| **NPV** | 71.43% |
| **AUC (95% CI)** | 0.664 (0.536-0.792) |
| ***P*-value for AUC** | 0.017 |
| **OR (95% CI)** | 4.375 (1.571-12.187) |
| ***P*-value for OR** | 0.005 |
| **Adjusted OR (95% CI) (1)** | 4.695 (1.638-13.459) |
| ***P*-value for adjusted OR** | 0.004 |

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, OR: Odds ratio, (1) Adjusted for age and sex

Figure 4: ROC curve of the 25-hydroxy vitamin D to discriminate patients with intermediate-2 & high risk from those with low & intermediate-1 risk




DIPSS: Dynamic International Prognostic Scoring System, ROC: Receiver operating characteristic analysis, AUC: Area under the curve, CI: Confidence interval

## Discussion

The goal of the study was to determine the levels of 25-hydroxy vitamin D in myelofibrosis patients and possibly determine how they relate to the disease's prognosis. With a cut-off value of 16.5 ng/mL that produced good sensitivity and specificity, we discovered that patients with myelofibrosis could be distinguished from controls by having lower 25-hydroxy vitamin D levels. We also showed that lower 25-hydroxy vitamin D levels were linked to a larger chance of having a worse prognostic score, but the ROC analysis reported that accuracy was poor. Notably, after adjusting for gender and age, these associations held true.

Humans require adequate amounts of vitamin D, which can be taken through food sources, including supplements, or produced in the skin by exposure to ultraviolet B rays from sunshine. The 1.25-dihydroxy vitamin D that is produced in the body as a result of hydroxylation occurs in the liver and proximal tubule. By attaching to the vitamin D receptor, this active version performs as a steroid hormone [13]. Hematopoietic stem cells, macrophages, thymocytes, activated lymphocytes, and monocytes all contain the vitamin D receptor. The modulation of many signaling pathways connected to cellular processes like proliferation, differentiation, autophagy, apoptosis, and epithelial-mesenchymal transition is thought to be a function of the vitamin D receptor. Additionally, this affects how cells interact with their surroundings, affecting processes including angiogenesis, oxidative stress, inflammatory response, and both innate and adaptive immunity [14-16]. Adequate levels of vitamin D are essential for normal hematopoiesis. Insufficient vitamin D levels can result in the suppression of bone marrow cell lines, leading to clinical manifestations, such as neutropenia, anemia, and thrombocytopenia [17]. The functional form of vitamin D is not suitable for direct measurement due to its short half-life of 4-6 hours and significantly lower circulating levels compared to the primary storage form, known as 25-hydroxy vitamin D [18]. As a result, the levels of 25-hydroxy vitamin D have been used as a marker of vitamin D shortage in various investigations, including the present study. According to current diagnostic guidelines, vitamin D insufficiency is frequently seen in the general population and is widely evaluated in clinical settings around the world.

It has been reported that a lack of vitamin D raises the risk of certain cancers, including hematological malignancies [19]. In a study of 332 newly diagnosed diffuse large B-cell

lymphoma patients, Chen et al. found that 92.8% of patients had vitamin D deficiency (30 ng/mL) [20]. Although not as common, Shanafelt et al. [21] also showed widespread vitamin D insufficiency in patients with chronic lymphocytic leukemia (30% of 309 patients), and suggested an impact on overall survival. In 97 adult patients with newly diagnosed acute myeloid leukemia who were receiving intensive care, Lee et al. [22] found that 35% of patients had insufficiency (20-30 ng/mL) and 30% had deficiency (20 ng/mL). Additionally, these patients' relapse-free survival was worse than that of patients with normal levels of 25-hydroxy vitamin D. There are limited reports of primary myelofibrosis despite the high prevalence of vitamin D insufficiency. Pardanani et al. [23] showed in 247 primary myelofibrosis patients that 48% and 9% of myelofibrosis patients, respectively, had vitamin D insufficiency and severe deficiency. We repeatedly discovered lower 25-hydroxy vitamin D levels in myelofibrosis patients compared to controls, and that the existence of myelofibrosis could be accurately predicted by a cut-off level of 16.5 ng/mL. To understand if this difference is related to the pathophysiology of myelofibrosis or whether it is an outcome of the condition, more research is necessary. To this end, it can be postulated that inadequate vitamin D levels could impair the immune system and facilitate tumor development and growth. Given the vitamin D deficiency observed in myelofibrosis patients, we believe that it is crucial to assess whether vitamin D supplementation can benefit myelofibrosis patients.

Myelofibrosis can arise either as an idiopathic condition or as a secondary manifestation associated with various conditions. These conditions include chronic kidney failure, hypoparathyroidism, lymphoma, acute lymphoblastic leukemia, neuroblastoma, osteopetrosis, tuberculosis, and systemic lupus erythematosus [24]. A limited number of case-report studies have also reported secondary myelofibrosis caused by vitamin D deficiency, suggesting that it is due to secondary elevation of parathormone or nutritional factors. Balkan et al. [24] presented a case report in a six-month-old infant who developed secondary myelofibrosis and found that myelofibrosis rapidly resolved after vitamin D treatment. Venkatnarayan et al. [25] revealed a ten-month-old rachitic male infant with hepatosplenomegaly and anemia secondary to bone marrow fibrosis, whose clinical characteristics improved following vitamin D treatment. In a study conducted by Yetgin and colleagues [26], they observed that in a group of 12 infants with rickets and anemia, early indications of myelofibrosis were evident through increased reticulin levels. Furthermore, they found that more advanced stages of rickets led to varying degrees of bone marrow myelofibrosis.

Interestingly, increased parathormone levels can also cause bone resorption and deposition through stimulation of osteoblasts and osteoclasts, as well as decrease erythropoietin receptors on erythroid progenitor cells, inducing defective new bone formation and medullary fibrosis [27]. For instance, Stephan et al. [28] demonstrated a relationship between increased PTH level and myelofibrosis in rachitic infants. Furthermore, myelofibrosis associated with vitamin D deficiency can contribute to reduced levels of active vitamin D metabolites. These metabolites play a role in the maturation of megakaryocyte and monocyte precursors. The deficiency of active vitamin D metabolites can lead to impaired collagen breakdown and increased deposition, which are characteristic features of myelofibrosis [29]. These pathways suggest that vitamin D may affect myelofibrosis, and they may also be responsible for the low vitamin D levels found in our patient sample.

In order to choose the best therapeutic approaches for patients, improve their prognosis, and gain a better understanding of the pathophysiology of the disease, it is essential to define the prognostic variables for myelofibrosis. Many prognostic models, such as the mutation-enhanced International Prognostic Scoring System (MIPSS) and DIPSS, have been created to forecast survival in primary and secondary myelofibrosis [30]. As a prognostic predictor, we used DIPSS. A limited number of studies have been published to date, evaluating the correlation between serum 25-hydroxy vitamin D levels and the prognosis of cancer patients, including those with breast and colorectal cancer [31]. However, there is a need to determine whether vitamin D is an effective and beneficial prognostic factor for myelofibrosis patients. We are aware of only one study that looked at 25-hydroxy vitamin D level as a predictive factor. In 247 patients with primary myelofibrosis, Pardanani et al. [10] found no correlation between vitamin D deficiency and overall and disease-free survival. In contrast, we demonstrated that myelofibrosis patients with low 25-hydroxy vitamin D levels tended toward poor prognoses. We discovered that patients with a high prognosis score could be distinguished from those with a poor prognostic score using the 25-hydroxy vitamin D cut-off value of 13.7 ng/mL. Measurement of 25-hydroxy vitamin D levels may not have a reliable role in prognostication, because overall accuracy is too low. However, more research is needed to determine the impact of vitamin D levels on the outlook for myelofibrosis as well as the direction of the association over time.

**Limitations**

The study did have some drawbacks, including a small sample size, a retrospective design originating from a single institution, the heterogeneity of myelofibrosis patients' illness status, and the fact that they received various medications. In addition, we were unable to use different prognostic indicators, as DIPSS was the only scoring system that was used consistently in all patients. Finally, the measurement of 25-hydroxy vitamin D levels are influenced by diet, geographic region, lifestyle, and environmental factors, so these may have contributed to our results [19]. Nonetheless, we adjusted for age and sex to assess whether the relationship between low vitamin D and myelofibrosis persisted, showing that these factors did not alter the demonstrated relationships.

**Conclusions**

We demonstrated that lower serum 25-hydroxy vitamin D level may serve as a reliable biomarker that is closely associated with the presence of myelofibrosis. Additionally, despite far lower accuracy, vitamin D levels also appear to be associated with the prognostic score. The potential role of vitamin D supplementation on prognosis of myelofibrosis and its impact on progression should be addressed with further studies with larger sample sizes and a longer follow-up.

## References


1. Tefferi A, Gangat N, Pardanani A, Crispino JD. Myelofibrosis: genetic characteristics and the emerging therapeutic landscape. Cancer Res. 2022;82(5):749-63.
2. Garmezy B, Schaefer JK, Mercer J, Talpaz M. A provider's guide to primary myelofibrosis: pathophysiology, diagnosis, and management. Blood Rev. 2021;45:100691.
3. Mascarenhas J, Gleitz HF, Chifotides HT, Harrison CN, Verstovsek S, Vannucchi AM, et al. Biological drivers of clinical phenotype in myelofibrosis. Leukemia. 2023;37(2):255-64.
4. Passamonti F, Mora B. Myelofibrosis. Blood. 2023;141(16):1954-70.
5. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, Richards JB. The health effects of vitamin D supplementation: Evidence from human studies. Nat Rev Endocrinol. 2022;18(2):96-110.
6. Carlberg C, Muñoz A, editors. An update on vitamin D signaling and cancer. Semin Cancer Biol; 2022:79:217-30
7. Samadi A, Sabuncuoglu S, Samadi M, Isikhan SY, Chirumbolo S, Peana M, et al. A Comprehensive Review on Oxysterols and Related Diseases. Curr Med Chem. 2021;28(1):110-36.
8. Merchan BB, Morcillo S, Martin-Nunez G, Tinahones FJ, Macias-Gonzalez M. The role of vitamin D and VDR in carcinogenesis: Through epidemiology and basic sciences. J Steroid Biochem Mol Biol. 2017;167:203-18.
9. Liu D, Meng X, Tian Q, Cao W, Fan X, Wu L, et al. Vitamin D and multiple health outcomes: an umbrella review of observational studies, randomized controlled trials, and Mendelian randomization studies. Adv Nutr. 2022;13(4):1044-62.
10. Pardanani A, Drake MT, Finke C, Lasho TL, Rozell SA, Jimma T, et al. Vitamin D insufficiency in myeloproliferative neoplasms and myelodysplastic syndromes: clinical correlates and prognostic studies. Am J Hematol. 2011;86(12):1013-6.
11. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J. 2018;8(2):15.
12. Oken M, Horton D, Davis T, Carbone E. ECoG performance status. Am J Clin Oncol. 1982;5:649-55.
13. Janoušek J, Pilařová V, Macáková K, Nomura A, Veiga-Matos J, Silva DDD, et al. Vitamin D: sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. Crit Rev Clin Lab Sci. 2022;59(8):517-54.
14. Arora J, Wang J, Weaver V, Zhang Y, Cantorna MT. Novel insight into the role of the vitamin D receptor in the development and function of the immune system. J Steroid Biochem Mol Biol. 2022;219:106084.
15. Gabryanczyk A, Klimczak S, Szymczak-Pajor I, Śliwińska A. Is vitamin D deficiency related to increased cancer risk in patients with type 2 diabetes mellitus? Int J Mol Sci. 2021;22(12):6444.
16. Oztas Y, Yalcinkaya A. Oxidative alterations in sickle cell disease: possible involvement in disease pathogenesis. World J Hematol. 2017;6(3):55-61.
17. De Martinis M, Allegra A, Sirufo MM, Tonacci A, Pioggia G, Raggiunti M, et al. Vitamin D deficiency, osteoporosis and effect on autoimmune diseases and hematopoiesis: a review. Int J Mol Sci. 2021;22(16):8855.
18. Acar S, Özkan B. Vitamin D metabolism. In: Özdemir Ö, editor. Vitamin D. London, United Kingdom: IntechOpen; 2021.
19. Ito Y, Honda A, Kurokawa M. Impact of vitamin D level at diagnosis and transplantation on the prognosis of hematological malignancy: A meta-analysis. Blood Advances. 2022;6(5):1499-511.
20. Chen P, Cao Y, Duan X, Li J, Zhao W, Wang H. Bioavailable 25 (OH) D level is associated with clinical outcomes of patients with diffuse large B-cell lymphoma: An exploratory study. Clin Nutr. 2021;40(1):157-65.
21. Shanafelt TD, Drake MT, Maurer MJ, Allmer C, Rabe KG, Slager SL, et al. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. Blood. 2011;117(5):1492-8.
22. Lee HJ, Muindi JR, Tan W, Hu Q, Wang D, Liu S, et al. Low 25 (OH) vitamin D3 levels are associated with adverse outcome in newly diagnosed, intensively treated adult acute myeloid leukemia. Cancer. 2014;120(4):521-9.
23. Pardanani A, Drake MT, Finke C, Lasho TL, Rozell SA, Jimma T, et al. Prognostic Irrelevance of Vitamin D Insufficiency in Myeloproliferative Neoplasms and De Novo Myelodysplastic Syndromes. Am J Hematol. 2011;86:1013-6.
24. Balkan C, Ersoy B, Nese N. Myelofibrosis associated with severe vitamin D deficiency rickets. J Int Med Res. 2005;33(3):356-9.
25. Venkatnarayan K, Gupta A, Adhikari K. Reversible myelofibrosis due to severe Vitamin D deficiency rickets. Med J Armed Forces India. 2018;74(4):404.
26. Yetgin S, Özsoylu Ş, Ruacan Ş, Tekinalp G, Sarialiolu F. Vitamin D-deficiency rickets and myelofibrosis. J Pediatr. 1989;114(2):213-7.
27. Elidrissy A. Myelofibrosis associated, with Rickets, is it hyperparathyroidism the triggering agent or vitamin D and hypocalcemia or hypophosphatemia. Int J Clin Endocrinol Metab. 2016;2(01):019-23.
28. Stephan J, Galambrun C, Dutour A, Freycon F. Myelofibrosis: an unusual presentation of vitamin D-deficient rickets. Eur J Pediatr. 1999;158(10):828.
29. Parikh AC, Singhal T, Upadhyay Z. Vitamin-D Deficiency and Myelofibrosis: A Rare but Reversible Association. J Child Sci. 2021;11(01):e18-e9.
30. Gerds AT, Gotlib J, Ali H, Bose P, Dunbar A, Elshoury A, et al. Myeloproliferative neoplasms, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20(9):1033-62.
31. Torfadottir JE, Aspelund T, Valdimarsdottir UA, Cotch MF, Tryggvadottir L, Harris TB, et al. Pre-diagnostic 25-hydroxyvitamin D levels and survival in cancer patients. Cancer Causes Control. 2019;30(4):333-42.

J Surg Med. 2023;7(8):504-508.
DOI: 10.28982/josam.7905

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Aortic arch repair with extended end-to-side anastomosis in neonates and infants with transverse arch hypoplasia

**Onur Doyurgan [1], Hasan Balık [2]**

[1] Department of Pediatric Cardiac Surgery, Gazi Yasargil Education and Research Hospital, Diyarbakır, Turkey
[2] Department of Pediatric Cardiology, Gazi Yasargil Education and Research Hospital, Diyarbakır, Turkey

**ORCID ID of the author(s)**

OD: 0000-0002-4198-3504
HB: 0000-0002-3373-1585

**Corresponding Author**
Onur Doyurgan
Fetih Mah. 6008 Sok. Kırkkonak Evleri No:4z Sur, Diyarbakır, Turkey
E-mail: onurdoyurgan@gmail.com

**Ethics Committee Approval**
The study was approved by Diyarbakır Gazi Yasargil Training and Research Hospital Ethics Committee (date: May 26, 2023, no: 404). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 28

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** The use of patches to repair the aortic arch is believed to have a positive effect on long-term morbidity. In this study, perioperative and follow-up data of patients who underwent transverse arch repair with a patch were compared with the data of patients who underwent end-to-end anastomosis (ESA).

**Methods**: In this retrospective cohort study, the data of 27 patients (including 18 newborns) who underwent aortic arch repair at the Gazi Yasargil Education and Research Hospital between January 2018 and April 2023 were analyzed. The inclusion criteria included a diagnosis of proximal and distal transverse aortic arch hypoplasia, an age younger than 12 months of age, and the completion of aortic arch repair using cardiopulmonary bypass. Patients who underwent recoarctation repair due to residual obstruction, patients with single ventricular physiology, and patients who underwent aortic arch repair via a lateral thoracotomy without undergoing cardiopulmonary bypass were excluded from the study. The patients were divided into two groups. Group 1 included individuals who underwent aortic anterior wall expansion with autologous pericardium in addition to ESA; Group 2 included patients who underwent ESA only.

**Results**: The median age of the patients was 21 days (range: 6–365 days), and the median body weight of the cohort was 3.5 kilograms (range: 2.4–8.9 kilograms). Enlargement with autologous pericardial patch was applied to 11 patients (40.7%). Surgical procedures performed in addition to arch repair included eight ventricular septal defect closures, six instances of pulmonary banding, three atrial septal defect closures, and one subvalvular pulmonary stenosis repair. The in-hospital mortality rate was 11.1% (n=3). Those three patients died due to sepsis. The median follow-up period was 152 days (range: 10–1316 days). Recoarctation requiring re-intervention did not occur in any of the studied patients. The antegrade selective cerebral perfusion time was statistically significantly longer in patients who underwent aortic arch repair using a patch ($P$=0.03).

**Conclusion**: Repair of the arch with a patch may contribute to a reduction in long-term mortality and morbidity. However, there is a need for more comprehensive and long-term follow-up studies to verify these findings.

**Keywords:** aortic arch, aortic coarctation, congenital heart defects, infant, surgery

How to cite: Doyurgan O, Balık H. Aortic arch repair with extended end-to-side anastomosis in neonates and infants with transverse arch hypoplasia. J Surg Med. 2023;7(8):504-508.

## Introduction

Aortic arch hypoplasia is an anomaly that commonly requires surgical intervention during the neonatal period. The outcomes of aortic arch repair using the extended end-to-side anastomosis (ESA) technique are favorable [1]. Surgical techniques employed for the repair of transverse aortic arch hypoplasia include extended ESA, autologous pericardial patch, and bovine pericardial patch aortoplasty [2-5]. While the relatively shorter duration of surgery for direct anastomosis might be advantageous, it has been argued that recoarctation might occur due to changes in arch geometry [2]. On the other hand, patch aortoplasty preserves the geometry of the arch aorta and reduces tension at the anastomotic site [6,7]. In this study, we compare aortic arch repair results in patients with aortic arch hypoplasia.

## Materials and methods

### Ethical declaration

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Diyarbakır Gazi Yasargil Training and Research Hospital Ethics Committee (Date: May 26, 2023, No: 404).

### Definitions

The transverse aortic arch is the name given to the part of the aorta between the innominate artery and the left subclavian artery. Proximal transverse arch hypoplasia is indicated when the ratio of the outer diameter of the proximal arch to the diameter of the ascending aorta is less than 0.6, and distal transverse arch hypoplasia is defined as a ratio of the outer diameter of the distal arch to the ascending aorta diameter below 0.5 [6,8]. Z-scores of the aortic arch were calculated using transthoracic echocardiography [9]. In postoperative transthoracic echocardiography, recoarctation was diagnosed if a gradient exceeding 20 mmHg was measured at the surgically repaired area [10].

### Patient population

A total of 27 patients diagnosed with transverse arch aortic hypoplasia and aortic coarctation who underwent aortic arch repair from January 2018 to April 2023 at the Gazi Yasargil Education and Research Hospital in Diyarbakır, Turkey were included in the study. Preoperative, intraoperative, and postoperative data were recorded using the hospital's database. Follow-up visits were planned at 1, 3, and 6 months after discharge, every 6 months for the following 18 months, and subsequently annually. Follow-up data were collected by reviewing echocardiography reports from the outpatient clinic system.

The inclusion criteria included a diagnosis of proximal and distal transverse arch aortic hypoplasia, an age younger than 12 months, and completion of aortic arch repair with cardiopulmonary bypass via median sternotomy. Patients undergoing re-coarctation repair due to residual obstruction, those with single ventricle physiology, and those undergoing aortic arch repair via lateral thoracotomy without cardiopulmonary bypass were excluded. Seven of the patients were on preoperative mechanical ventilator support. Milrinone was given to eight patients, and adrenaline treatment was given to three patients. Ten of the patients had undergone preoperative balloon angioplasty. The patients were divided into two groups: Group 1 included individuals who underwent aortic anterior wall expansion with autologous pericardium in addition to ESA; Group 2 included individuals who underwent ESA only. The patients' ages, genders, body weights, diagnoses, accompanying anomalies, antegrade selective cerebral perfusion (ASCP) times, cross-clamp times, cardiopulmonary bypass times, postoperative complications, vasoactive inotrope scores, mechanical ventilation times, length of stay in the intensive care unit, length of hospital stay, follow-up times, and preoperative transverse arch Z-scores were compared.

### Surgical technique

Following median sternotomy, all of the patients underwent a cardiopulmonary bypass via the innominate artery and bicaval venous cannulation. Antegrade selective cerebral perfusion and systemic hypothermia at 28°C were employed. The transverse aortic arch, innominate artery, left carotid artery, left subclavian artery, isthmus, and descending aorta were individually dissected. After clamping the innominate artery, aortic arch branches, and descending aorta, a single dose of 20 ml/kg del Nido cardioplegia solution was administered from the aortic root. The isthmus and proximal descending aorta were divided, and ductus arteriosus tissue on the side of the descending aorta was completely removed. A longitudinal incision was made on the lesser curvature of the aortic arch between the innominate artery and the isthmus. The descending aorta was sutured to the posterior wall of the aortic arch using a continuous suturing technique. In cases where mobilization of the descending aorta was limited and there might be tension at the anastomotic site, the lesser curvature of the transverse arch was widened using an autologous pericardial patch treated with glutaraldehyde. In patients with adequately mobilized descending aorta, the anterior wall of the aorta was sutured to the native aorta using the same suture, completing the anastomosis. After deairing and removing the clamps, full-body perfusion was resumed.

### Statistical analysis

Statistical analyses were performed using SPSS statistical software version 23. The Kolmogorov-Smirnov test was used to assess normality. Descriptive statistics were provided as median (minimum-maximum) for continuous variables and as percentages for categorical variables. The Mann-Whitney U test was used for binary comparisons of continuous variables between independent groups, and the chi-squared test was used for categorical variables. *P*-values less than 0.05 were considered to be statistically significant.

## Results

### Patient characteristics

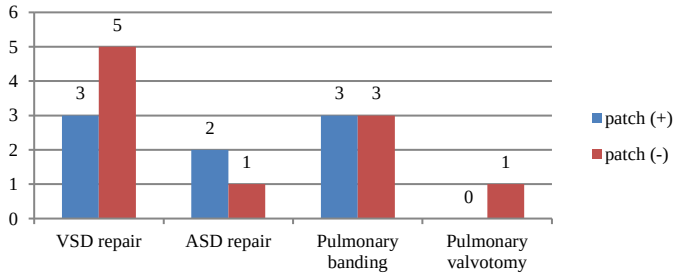
Between January 2018 and April 2023, a total of 27 consecutive patients underwent aortic arch repair surgery at the Gazi Yasargil Education and Research Hospital. Patient information was retrospectively obtained from the hospital's database. Of the 27 patients, 51.8% (14) were male. Eighteen patients (63%) were newborns, and five (18.5%) were premature. The median age of the patients on the day of surgery was 21 days (range: 6–365 days), and the patients' median body weight was

3.5 kilograms (range: 2.4–8.9 kilograms). The demographic characteristics of the patients are listed in Table 1. Sixteen patients (59.2%) were intubated preoperatively. Eleven patients (40.7%) had identified genetic anomalies. The most common genetic anomaly was Down syndrome (n=4, 36.4%), followed by Turner syndrome (n=1, 9.1%) and DiGeorge syndrome (n=1, 9.1%). Other anomalies included genitourinary anomalies, limb anomalies, orofacial anomalies, anal atresia, and a dysmorphic facial appearance (n=5, 45.4%). A bicuspid aortic valve was present in 10 patients (37.1%), persistent left superior vena cava was present in three patients (11.1%), and aberrant right subclavian artery was present in two patients (7.4%).

**Intraoperative and postoperative outcomes**

Sixteen patients (59.3%) underwent direct ESA, and 11 patients (40.7%) underwent ESA with expansion of the anterior wall using an autologous pericardial patch. Additional cardiac surgical procedures other than patent ductus arteriosus ligation and division were performed in 15 patients (55.6%). Those procedures included eight (29.6%) ventricular septal defect closures (using an autologous pericardial patch), six (22.2%) pulmonary bandings, three (11.1%) atrial septal defect closures, and one (3.7%) pulmonary valvotomy (Figure 1). The mean (standard deviation) duration of ASCP was 35.6 (13.3) minutes; the mean (standard deviation) aortic cross-clamp time was 59.2 (26.9) minutes. The mean (standard deviation) cardiopulmonary bypass time was 109.4 (38.1) minutes. Antegrade selective cerebral perfusion time was statistically longer in patients who were repaired using a patch compared with patients in the other group ($P$=0.03).

Figure 1: Additional cardiac surgical procedures performed on patients

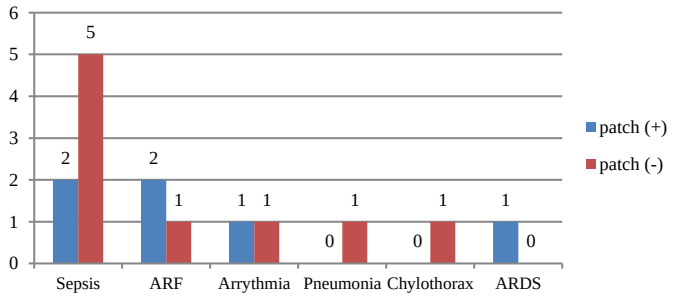



ASD: atrial septal defect, VSD: ventricular septal defect

**Postoperative hospital mortality**

Postoperative hospital mortality was recorded for three patients (11.1%). Two patients succumbed to sepsis during the early postoperative period (0–30 days), and one patient who understand a prolonged intensive care unit stay due to fungal sepsis passed away in the late postoperative period (after one month). Sepsis was the most common complication and was observed in seven patients (25.9%). Four of those patients were successfully treated with appropriate antibiotic therapy. Other complications included acute renal failure requiring peritoneal dialysis (n=3, 11.1%), arrhythmia (n=2, 7.4%), acute respiratory distress syndrome (n=1, 3.7%), pneumonia (n=1, 3.7%), and chylothorax (n=1, 3.7%). The postoperative complications are shown in Figure 2. The median follow-up duration for all of the patients was 152 days (range: 10–1316 days). No recoarctation was detected on echocardiography at discharge or during follow-up, and no interventions were required. The patients' perioperative data are listed in Table 2.

Figure 2: Postoperative complications




ARF: Acute renal failure, ARDS: Acute respiratory distress syndrome

Table 1: Demographic and preoperative data

| Patient characteristics | ESA + patch (n=11) | ESA (n=16) | *P*-value |
|---|---|---|---|
| **Gender n, (%)** | | | |
| Female | 5 (45.5%) | 8(50%) | 0.81 ᵠ |
| Male | 6 (54.5%) | 8(50%) | |
| **Age at surgery (days), median (min-max)** | 24(10-365) | 21(6-120) | 0.31 ᵘ |
| **Weight at surgery (kg), median (min-max)** | 4 (2.86-8.90) | 2.87 (2.41-7.78) | 0.07 ᵘ |
| **Neonates n, (%)** | 6 (54.5%) | 12(75%) | |
| **Preoperative LVEF (%), median (min-max)** | 65(40-78) | 65(40-74) | 0.48 ᵘ |
| **Transvers arch Z score, median (min-max)** | -4.7 ([-9.1]-[-3.6]) | -5.1 ([-8.2]-[-3.6]) | 0.44 ᵘ |

ESA: End-to-side anastomosis, LVEF: Left ventricular ejection fraction, min-max: minimum-maximum, ᵘ: Mann-Whitney U test, ᵠ: Chi-squared test

Table 2: Perioperative findings of the patients

| Parameters | ESA + patch (n=11) | ESA (n=16) | *P*-value |
|---|---|---|---|
| **CPB time (min), median (min-max)** | 113(62-192) | 105(40-152) | 0.34 ᵘ |
| **ACC time (min), median (min-max)** | 53(30-112) | 46(18-105) | 0.55 ᵘ |
| **ASCP time (min), median (min-max)** | 37(26-65) | 30(16-70) | 0.03 ᵘ |
| **Postoperative gradient (mmHg), median (min-max)** | 5(3-28) | 6(3-39) | 0.71 ᵘ |
| **ICU stay (days), median (min-max)** | 11(5-40) | 14(5-64) | 0.21 ᵘ |
| **Mechanical support time (h), median (min-max)** | 5(1-12) | 5.5(2-26) | 0.24 ᵘ |
| **In-hospital time (days), median (min-max)** | 17(9-86) | 18.5(7-70) | 0.74 ᵘ |
| **Vasoactive inotropic score, median (min-max)** | 12(7-27) | 11(7-20) | 0.43 ᵘ |
| **In-hospital mortality (0-30 days) *n*** | 1 | 1 | 0.78 ᵠ |
| **Follow-up time (days), median (min-max)** | 167.5(10-1164) | 123(17-1316) | 0.69 |

ESA: End-to-side anastomosis, ACC: Aortic cross-clamp, ASCP: Antegrade selective cerebral perfusion, CPB: Cardiopulmonary bypass, min-max: minimum-maximum, ᵘ: Mann-Whitney U test, ᵠ: Chi-squared test

## Discussion

The goal of surgically treating patients with aortic coarctation in conjunction with arch hypoplasia is to achieve the least number of repeat interventions and ensure adequate arch growth over the long term [11-13]. To this end, the arch geometry should be restored as close to normal as possible. Surgical repair with extended ESA in the segment between the innominate artery and the left common carotid artery, where proximal arch hypoplasia is present, can be relatively challenging [12-14]. Researchers have differing viewpoints as to the most appropriate repair strategy for this part of the hypoplastic arch. Some centers prefer repairing the arch with median sternotomy and a cardiopulmonary bypass; others opt for a posterolateral thoracotomy without stopping the heart [11,15,16]. However, aortic repair using cardiopulmonary bypass necessitates consideration of its potential harmful effects. In our study, aortic arch repair was performed in all patients after median sternotomy with cardiopulmonary bypass and ASCP.

The use of transverse aortic arch repair using ESA is debated in the literature. Some studies have demonstrated favorable and positive results with ESA in cases of proximal transverse arch hypoplasia [16,17]. However, satisfactory results could not be obtained with ESA in some patients with a large anastomotic area [2,18]. Reducing tension at the anastomotic site is crucial for preventing postoperative recoarctation and is the most significant factor in the treatment of transverse arch hypoplasia [18,19]. In patients with pronounced distance between the hypoplastic segment of the transverse arch and the descending aorta, creating an anastomosis without tension may not always be possible [3]. Additionally, tension at the anastomotic site can lead to late recoarctation [3,18]. Reducing anastomotic tension and creating a smooth arch geometry can be achieved with patch aortoplasty. The use of a patch can sufficiently expand the hypoplastic segment to prevent recoarctation and achieve a relatively normal geometry [18,20]. In a study comparing ESA and patch aortoplasty techniques, a lower incidence of recoarctation was reported in the patch group [21]. Li et al [21] reported that the ESA method was preferable to patch aortoplasty in patients for whom ESA was suitable (i.e., individuals in which descending aorta mobilization was not limited and aortic arch geometry was normal). The authors noted that the ESA method was associated with fewer procedures and a shorter ASCP time. Among our patients, 11 (40.7%) had a relatively long distance between the narrow segment and the descending aorta (Group 1). Therefore, we enlarged the lesser curvature of the aorta using an autologous pericardial patch to reduce tension at the anastomotic site. Antegrade selective cerebral perfusion times were statistically significantly longer in those patients than in Group 2 patients.

The relationship between transverse arch hypoplasia and intracardiac defects has been described by Rudolph et al [22]. Those authors found that intracardiac defects may lead to decreased blood flow in the aortic arch, resulting in underdevelopment. Furthermore, Conte et al [23] reported that one-stage repair yielded better outcomes than two-stage repair in 307 newborns with aortic coarctation and accompanying complex cardiac defects. The feasibility and superiority of simultaneous repair of intracardiac defects with arch repair have been reported by other studies as well [24,25]. In our investigation, 70.4% of patients with transverse aortic arch hypoplasia had one or more accompanying intracardiac defects. At our center, we perform simultaneous (one-stage) repair procedures for patients with aortic coarctation/hypoplasia associated with perimembranous ventricular septal defect (VSD). For patients with multiple VSDs, midmuscular VSD, or atrioventricular septal defects, we prefer the arch repair and pulmonary banding (two-stage) procedure.

### Limitations

The retrospective nature of our study, its small sample size, and its limited follow-up duration are its most significant limitations. Furthermore, our investigation was a single-center study. Therefore, increasing the number of cases, supporting the study's findings with prospective comparative research, and investigating long-term outcomes with extended follow-up are necessary.

### Conclusions

Repairing the aortic arch in newborns and infants with transverse arch hypoplasia using extended ESA is a safe, effective, and promising procedure with low rates of early reintervention and favorable short-term outcomes. It allows for the repair of accompanying intracardiac defects and preserves the growth potential of the aortic arch via tissue-on-tissue reconstruction. Aortic arch repair can be done with or without a patch. However, the use of a patch on the anterior aortic wall of the aorta in aortic arch repair reduces tension on the anastomotic line, protects the growth of the aortic arch, and helps prevent recoarctation.

## References


1. Poncelet AJ, Henkens A, Sluysmans T, Moniotte S, de Beko G, Momeni M, et al. Distal aortic arch hypoplasia and coarctation repair: a tailored enlargement technique. World J Pediatr Congenit Heart Surg. 2018;9:496-503.
2. Murtuza B, Alsoufi B. Current readings on surgery for the neonate with hypoplastic aortic arch. Semin Thoracic Surg. 2017;29:479-85.
3. Gray WH, Wells WJ, Starnes VA, Kumar SR. Arch augmentation via median sternotomy for coarctation of aorta with proximal arch hypoplasia. Ann Thorac Surg. 2018;106(4):1214-9.
4. Bernabei M, Margaryan R, Arcieri L, Bianchi G, Pak V, Murzi B. Aortic arch reconstruction in newborns with an autologous pericardial patch: contemporary results. Interact Cardiovasc Thorac Surg. 2013;16(3):282-5.
5. Wen S, Cen J, Chen J, Xu G, He B, Teng Y, et al. The application of autologous pulmonary artery in surgical correction of complicated aortic arch anomaly. J Thorac Dis. 2016;8(11):3301-6.
6. Brown JW, Rodefeld MD, Ruzmetov M. Transverse aortic arch obstruction: when to go from the front. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2009;66-9.doi: 10.1053/j.pcsu.2009.01.024.
7. Walhout RJ, Lekkerkerker JC, Oron GH, Hitchcock FJ, Meijboom EJ, Bennink GB. Comparison of polytetrafluoroethylene patch aortoplasty and end-to-end anastomosis for coarctation of the aorta. J Thorac Cardiovasc Surg. 2003;126:521-8.
8. Zannini L, Gargiulo G, Albanese SB, Santorelli MC, Frascaroli G, Picchio FM, et al. Aortic coarctation with hypoplastic arch in neonates: a spectrum of anatomic lesions requiring different surgical options. Ann Thorac Surg. 1993;56(2):288-94.
9. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr. 2008;21(8):922-34.
10. Turek JW, Conway BD, Cavanaugh NB, Meyer AM, Aldoss O, Reinking BE, et al. Bovine arch anatomy influences recoarctation rates in the era of the extended end-to-end anastomosis. J Thorac Cardiovasc Surg. 2018;155(3):1178-83.
11. Lee MG, Brink J, Galati JC, Rakhra SS, Konstantinov IE, Cheung MM, et al. End-to-side repair for aortic arch lesions offers excellent chances to reach adulthood without reoperation. Ann Thorac Surg. 2014;98(4):1405-11.
12. Kaushal S, Backer CL, Patel JN, Patel SK, Walker BL, Weigel TJ, et al. Coarctation of the aorta: midterm outcomes of resection with extended end-to-end anastomosis. Ann Thorac Surg. 2009;88(6):1932-8.
13. McElhinney DB, Yang SG, Hogarty AN, Rychik J, Gleason MM, Zachary CH, et al. Recurrent arch obstruction after repair of isolated coarctation of the aorta in neonates and young infants: is low weight a risk factor? J Thorac Cardiovasc Surg. 2001;122(5):883-90.
14. Wright GE, Nowak CA, Goldberg CS, Ohye RG, Bove EL, Rocchini AP. Extended resection and end-to-end anastomosis for aortic coarctation in infants: results of a tailored surgical approach. Ann Thorac Surg. 2005;80(4):1453-9.
15. Elgamal MA, McKenzie ED, Fraser CD Jr. Aortic arch advancement: the optimal one-stage approach for surgical management of neonatal coarctation with arch hypoplasia. Ann Thorac Surg. 2002;73(4):1267-72.
16. Dharmapuram AK, Ramadoss N, Verma S, Vejendla G, Ivatury RM. Early outcomes of modification of end to side repair of coarctation of aorta with arch hypoplasia in neonates and infants. Ann Pediatr Cardiol. 2018;11(3):267-74.

17. Liu JY, Jones B, Cheung MM, Galati JC, Koleff J, Konstantinov IE, et al. Favourable anatomy after end-to-side repair of interrupted aortic arch. Heart Lung Circ. 2014;23(3):256-64.
18. Rakhra SS, Lee M, Iyengar AJ, Wheaton GR, Grigg L, Konstantinov IE, et al. Poor outcomes after surgery for coarctation repair with hypoplastic arch warrants more extensive initial surgery and close long-term follow-up. Interact Cardiovasc Thorac Surg. 2013;16(1):31-6.
19. Mery CM, Guzmán-Pruneda FA, Carberry KE, Watrin CH, McChesney GR, Chan JG, et al. Aortic arch advancement for aortic coarctation and hypoplastic aortic arch in neonates and infants. Ann Thorac Surg. 2014;98(2):625-33; discussion 633.
20. Seo DM, Park J, Goo HW, Kim YH, Ko JK, Jhang WK. Surgical modification for preventing a gothic arch after aortic arch repair without the use of foreign material. Interact Cardiovasc Thorac Surg. 2015;20(4):504-9.
21. Li C, Ma J, Yan Y, Chen Ho, Shi G, Chen Hu, et al. Surgical options for proximal and distal transverse arch hypoplasia in infants with coarctation. Transl Pediatr. 2022;11(3):330-9.
22. Rudolph AM, Heymann MA, Spitznas U. Hemodynamic considerations in the development of narrowing of the aorta. Am J Cardiol. 1972;30(5):514-25.
23. Conte S, Lacour-Gayet F, Serraf A, Sousa-Uva M, Bruniaux J, Touchot A, et al. Surgical management of neonatal coarctation. J Thorac Cardiovasc Surg. 1995;109(4):663-74, discussion 74-5.
24. Gaynor JW, Wernovsky G, Rychik J, Rome JJ, DeCampli WM, Spray TL. Outcome following single-stage repair of coarctation with ventricular septal defect. Eur J Cardiothorac Surg. 2000;18(1):62-7.
25. Planche C, Serraf A, Comas JV, Lacout-Gayet F, Bruniaux J, Touchot A. Anatomic repair of transposition of great arteries with ventricular septal defect and aortic arch obstruction. One-stage versus two-stage procedure. J Thorac Cardiovasc Surg. 1993;105(5):925-33.

J Surg Med. 2023;7(8):509-513.
DOI: 10.28982/josam.7930

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Effect of macrocytosis on erlotinib response in metastatic non-small cell lung cancer

**Seher Nazlı Kazaz [1], Mustafa Emre Duygulu [2]**

[1] Department of Medical Oncology, Istinye University, School of Medicine, Istanbul, Turkey
[2] Department of Medical Oncology, Karadeniz Technical University, School of Medicine, Trabzon, Turkey

**ORCID ID of the author(s)**

SNK: 0000-0002-8181-000X
MED: 0000-0001-5113 6782

**Corresponding Author**
Seher Nazlı Kazaz
Istinye University, Faculty of Medicine, Department of Oncology, Medical Park Karadeniz Hospital, Trabzon, Turkey
E-mail: drnazli@gmail.com

**Ethics Committee Approval**
The study was approved by Karadeniz Technical University Ethic Committee, 07/07/2022, with protocol number 20224/158.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 31

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Numerous studies have assessed the relationship between macrocytosis and responses to chemotherapeutic agents and TKIs such as sunitinib and imatinib. However, there is limited data in the literature regarding the prognostic or predictive value of macrocytosis in using erlotinib. If a relationship is detected, early response/resistance assessment can be performed before imaging time in the follow-up of treatments, and a more cost-effective, non-invasive method can be employed for response monitoring. This study aimed to elucidate the effect of macrocytosis on response rates in patients treated with erlotinib for non-small cell lung cancer.

**Methods:** Seventy-five individuals diagnosed with non-small cell lung cancer (NSCLC) and admitted to our institution were enrolled in this retrospective cohort study. Baseline demographics, time of diagnosis, previous treatment, and the initiation or cessation of erlotinib were recorded. Data of patients with and without macrocytosis were analyzed. Stable disease, partial and complete response rates, and progressive disease response were evaluated separately as response rates. Progression-free survival between drug initiation and discontinuation due to progression was interpreted using Kaplan-Meier curves.

**Results:** The distribution of the overall survival (OS) and progression-free survival (PFS) evaluations revealed that 84% (n=63) of the patients were deceased, and the progression rate was 94.7% (n=71). The median OS of the patients was 18 months, and the median PFS was 11 months. There was a statistically significant difference in overall survival in females, with a median OS of 25 months (95% CI 17–32 months) and a median OS of 13 months in males (95% CI 9–20 months) ($P$=0.008). PFS was 14.5 months (95% CI 11–21 months) in women and six months (95% CI 4–17 months) in men, and there was a statistically significant difference ($P$=0.02). A statistically significant difference was achieved between MCV values measured during diagnosis and the third month between age groups ($P$=0.044).

**Conclusion:** The outcomes of this research suggest a statistically significant difference between the MCV values measured at the time of diagnosis and the third month regarding age groups. Both OS and PFS in women were statistically significantly higher than in men.

**Keywords:** erlotinib, macrocytosis, non-small cell lung cancer

How to cite: Kazaz SN, Duygulu ME. Effect of macrocytosis on erlotinib response in metastatic non-small cell lung cancer. J Surg Med. 2023;7(8):509-513.

## Introduction

The mean corpuscular volume (MCV) is one of the most prevalent hematological laboratory parameters. Macrocytosis (identified by MCV >100 fl) is commonly associated with deficiencies in vitamin B12 and/or folic acid, hypothyroidism, alcoholism, and myelodysplastic syndromes. Recently, tyrosine kinase inhibitors (TKIs) have gained increasing employment in cancer treatment. These inhibitors target the ATP binding site of one or more constitutively activated tyrosine kinases within cancer cells [1]. The elevation in MCV induced by sunitinib and imatinib can be attributed to the inhibition of stem cell factor (c-KIT). Furthermore, various drugs bring about macrocytosis through distinct mechanisms [2].

In recent years, there has been a growing exploration of the prognostic and predictive implications of MCV in diverse solid tumors. Numerous studies have highlighted the prognostic and predictive significance of MCV in conditions such as colorectal cancer (CRC), advanced breast cancer, and esophageal cancer.

Macrocytosis can also manifest based on the therapeutic agents administered. While numerous mechanisms have been proposed, the underlying cause remains unidentified in most cases. Several studies have examined the correlation between macrocytosis and reactions to chemotherapeutic agents and TKIs like sunitinib and imatinib [3-7]. Certain studies have indicated that the utilization of capecitabine and/or bevacizumab is associated with macrocytosis [8]. Nevertheless, the outcomes concerning its predictive role in treatment could benefit from greater consistency [9].

Tracking tumor markers in the blood aids in this endeavor, although a definitive standard biomarker for lung cancer has not yet been established. The potential to forecast early resistance and progression lies in the ability to monitor patient responses through straightforward blood tests, such as MCV. While TKIs can yield sustainable responses, swift progression can emerge due to resistance, resulting in rapid deterioration. Patient assessments occur at 3-month intervals through imaging modalities. Nevertheless, an uncomplicated, cost-effective, and minimally invasive approach is still lacking for monitoring treatment response [10]. This study examines macrocytosis's impact on response rates among patients undergoing erlotinib treatment.

## Materials and methods

In this retrospective cohort study, 75 individuals aged 18 and above who applied to our institution, underwent erlotinib treatment for a minimum of 3 months, and were diagnosed with NSCLC were included. At the commencement of the treatment, patients presenting macrocytosis due to alternative causes (e.g., alcoholism, hypothyroidism, megaloblastic anemia) were excluded.

Baseline demographics, time of diagnosis, previous treatments, and the initiation or discontinuation of erlotinib were recorded. MCV values were documented at the initiation of erlotinib and the third month of treatment. Data from patients with and without macrocytosis were subjected to analysis. Treatment outcomes included response rates, progression-free survival (PFS), and overall survival (OS). Response assessment was based on the RECIST (Response Evaluation Criteria In Solid Tumors) criteria (version 1.1) [11], categorizing responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Kaplan-Meier curves assessed PFS from drug initiation to discontinuation due to progression.

The procedures adhered to the ethical standards set by the responsible committee on human experimentation (institutional) and aligned with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Karadeniz Technical University Medical Faculty Scientific Research Ethics Committee on 07/07/2022 under protocol number 20224/158.

**Statistical analysis**

The data underwent analysis using IBM Statistical Package for the Social Sciences (SPSS) version 29.0 for macOS (IBM Corp., Armonk, NY) and MedCalc statistical software version 12.7.0.0 package programs (MedCalc Software, Ostend, Belgium). Categorical data were presented as frequencies and percentages. Descriptive statistics for continuous data included mean, standard deviation, median, minimum, and maximum. The normality of variables was assessed using the Kolmogorov-Smirnov test.

For normally distributed variables, the Paired Sample T-test evaluated differences between dependent measurements. Non-normally distributed variables were assessed using the Wilcoxon Test. The comparison of categorical variables employed either Fisher's Exact Test or the Chi-Square test.

The repeated measurements analysis of variance (ANOVA) test was performed to analyze the variation in MCV measurements between diagnosis and the third month. Gender-based assessments of overall and PFS utilized the Log-rank test, with plotting Kaplan-Meier curves. Results with a *P*-value below 0.05 were considered statistically significant.

## Results

As part of the study, 75 patients were evaluated, comprising 53.3% (n=40) females and 46.7% (n=35) males. The patients' ages ranged from 27 to 82 years, with a mean age of 65 years. Table 1 presents the distribution of demographic and clinical findings among the patients.

The distribution of laboratory measurements, taken both at the time of diagnosis and at the third month, is outlined in Table 2. Analysis revealed no statistically significant differences between the laboratory parameters measured at diagnosis and those measured at the third month. Specifically, the parameters including hemoglobin, MCV, platelets, lymphocytes, neutrophils, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio yielded P values of 0.802, 0.775, 0.081, 0.467, 0.326, 0.318, and 0.447, respectively.

The distribution of patients' OS and PFS evaluations is displayed in Table 3. The median OS and PFS for the patients were 18 (14.4–21.6) months and 11 (6.8–15.2) months, respectively. Notably, the 6-month OS and PFS rates reached 81.3% and 64%, respectively (Figures 1 and 2).

Figure 1: OS and PFS data of the study group.

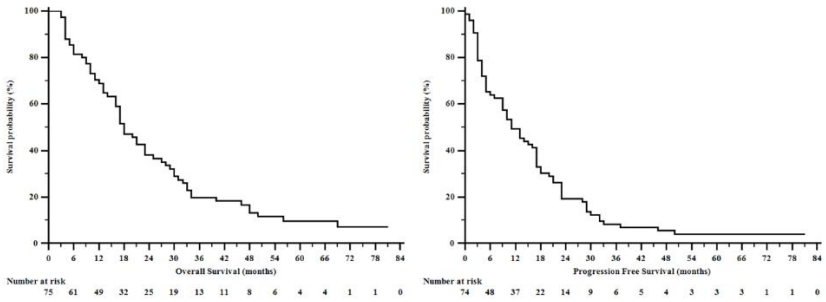



Figure 2: OS and PFS distribution by gender of the patients.

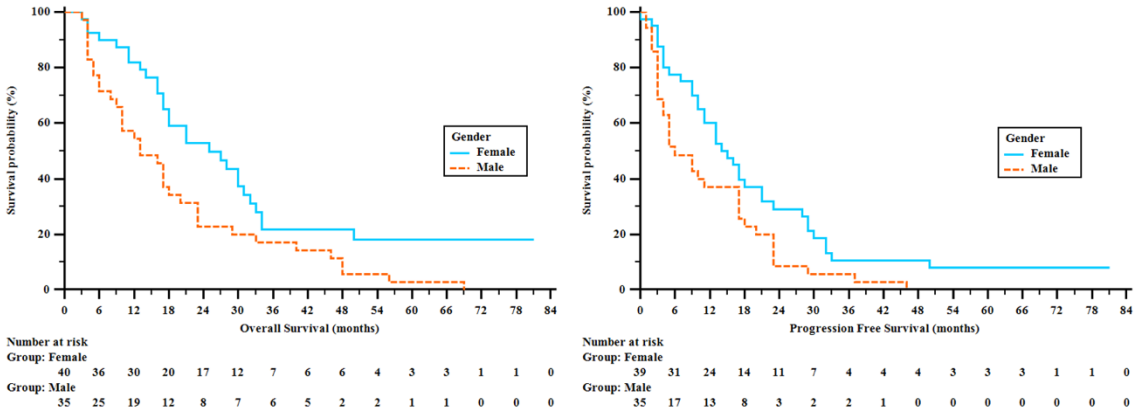



Table 1: Distribution of demographic and clinical findings of patients.

| Variables | |
|---|---|
| **Age (years), mean (SD)** | 62 (12) |
| **Median (Min–Max)** | 65 (27–82) |
| | **n (%)** |
| Age <65 | 37 (49.3) |
| Age ≥65 | 38 (50.7) |
| **Gender** | |
| Female | 40 (53.3) |
| Male | 35 (46.7) |
| **Histological subtype** | |
| Adenocarcinoma | 63 (84) |
| Squamous cell carcinoma | 8 (10.7) |
| NOS | 4 (5.3) |
| **Smoking** | |
| Non-smoker | 51 (68) |
| Quit | 4 (5.3) |
| Smoking | 2 (2.7) |
| Unknown | 18 (24) |
| **Alcohol consumption** | |
| None | 49 (65.3) |
| Quit | 0 (0) |
| Drinking | 0 (0) |
| Unknown | 26 (34.7) |
| **Mutation** | |
| Exon 19 | 15 (20) |
| Exon 21 | 13 (17.3) |
| Unknown | 43 (57.3) |
| Negative | 3 (4) |
| Other | 1 (1.3) |
| **Progression** | 71 (94.7) |
| **Deceased** | 63 (84) |
| **Treatment response** | |
| Stable disease | 26 (34.7) |
| Progression | 24 (32.0) |
| Partial response | 14 (18.7) |
| Complete response | 7 (9.3) |
| Unknown | 4 (5.3) |

SD: Standard Deviation

Table 2: Distribution of diagnosis and third month laboratory measurements of the patients.

| Laboratory | Mean (SD) | Median (Min-Max) | *P*-value |
|---|---|---|---|
| **Hemoglobin (at diagnosis)** | 12.1 (1.8) | 11.9 (8.8–17.7) | 0.802 |
| **Hemoglobin (3rd month)** | 12.1 (1.5) | 12.2 (8.4–14.8) | |
| **MCV (at diagnosis)** | 90.7 (6.2) | 89.8 (77–112.9) | 0.775 |
| **MCV (3rd month)** | 90.6 (5.6) | 90 (78.7–106.4) | |
| **PLT (at diagnosis), $\times 10^3$** | 249.7 (98.9) | 245.0 (61.0–558.0) | 0.081 |
| **PLT (3rd month), $\times 10^3$** | 267.6 (97.3) | 253.0 (65.0–554.0) | |
| **Lymphocyte (at diagnosis)** | 1.8 (0.9) | 1.7 (0.3–5.8) | 0.467 |
| **Lymphocyte (3rd month)** | 1.8 (1.3) | 1.6 (0.2–10.8) | |
| **Neutrophil at diagnosis)** | 5.3 (3) | 4.5 (1–13.5) | 0.326 |
| **Neutrophil (3rd month)** | 5.9 (3.8) | 4.3 (1.6–21.2) | |
| **NLR (at diagnosis)** | 4.1 (3.9) | 2.7 (0.5–23.6) | 0.318 |
| **NLR (3rd month)** | 4.0 (3.0) | 3.2 (0.4–16.4) | |
| **PLR (at diagnosis), $\times 10^3$** | 186.3 (146.1) | 150.4 (24.2–936.7) | 0.447 |
| **PLR (3rd month), $\times 10^3$** | 207.4 (220.0) | 162.0 (16.0–1825.0) | |

SD: Standard Deviation, MCV: Mean Corpuscular Volume, PLT: Platelet, NLR: neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio

Table 3: Progression-free survival and overall survival.

| | Total Events / n | Total |
|---|---|---|
| **Overall Survival (OS)** | 63/75 | |
| **Median (95% CI), month** | | 18.0 (14.4–21.6) |
| **6 months overall survival rate** | | 81.3% |
| **12 months overall survival rate** | | 68.9% |
| **24 months overall survival rate** | | 38.1% |
| **36 months overall survival rate** | | 19.8% |
| **Progression-free survival (PFS)** | 71/75 | |
| **Median (95% CI), months** | | 11.0 (6.8–15.2) |
| **6 progression-free survival rate** | | 64.0% |
| **12 progression-free survival rate** | | 49.3% |
| **24 progression-free survival rate** | | 19.3% |
| **36 progression-free survival rate** | | 8.3% |

Table 4 illustrates patients' demographic and clinical characteristics based on their treatment responses and progression status in the third month. Upon analysis of the table, it was observed that no statistically significant correlation existed between treatment response and the development of progression concerning demographic and clinical variables, including age ($P$=0.997), gender ($P$=0.092), histological subtype ($P$=0.131), smoking status ($P$=0.290), and driver mutations ($P$=0.290).

A statistically significant discrepancy in OS was evident between females and males, with females exhibiting a median survival of 25 months (95% CI 17–32 months), while males displayed a median survival of 13 months (95% CI 9–20 months,

*P*=0.008). In terms of PFS, women experienced a PFS of 14.5 months (95% CI 11–21 months), whereas men had a PFS of six months (95% CI 4–17 months), demonstrating a statistically significant distinction (*P*=0.02).

Table 4: Response rates of patients and distribution of demographic and clinical findings.

| | Stable + Partial + Complete Response | Progression | *P*-value |
|---|---|---|---|
| | n (%) | n (%) | |
| **Age** | | | 0.997 |
| <65 | 22 (46.8) | 12 (50) | |
| ≥65 | 25 (53.2) | 12 (50) | |
| **Gender** | | | 0.092 |
| Female | 29 (61.7) | 9 (37.5) | |
| Male | 18 (38.3) | 15 (62.5) | |
| **Histological subtype** | | | 0.131 |
| Adenocarcinoma | 42 (89.4) | 17 (70.8) | |
| Squamous cell carcinoma | 3 (6.4) | 5 (20.8) | |
| NOS | 2 (4.3) | 2 (8.3) | |
| **Smoking** | | | 0.290 |
| Non-smoker | 34 (72.3) | 14 (58.3) | |
| Quit | 1 (2.1) | 3 (12.5) | |
| Smoking | 1 (2.1) | 1 (4.2) | |
| Unknown | 11 (23.4) | 6 (25) | |
| **Mutation** | | | 0.192 |
| Exon 19 | 9 (19.1) | 6 (25) | |
| Exon 21 | 11 (23.4) | 2 (8.3) | |
| Unknown | 24 (51.1) | 15 (62.5) | |
| Negative | 3 (6.4) | 0 (0) | |
| Other | 0 (0) | 1 (4.2) | |

No statistically significant difference was observed between the MCV measurements at the time of diagnosis and the third month concerning factors such as gender, histological subtype, smoking status, and mutation types.

The MCV value at the time of diagnosis decreased from 91.0 to 89.7 in individuals aged <65 years by the third month, while in individuals aged ≥65 years, it increased from 90.4 to 91.4. Although no statistically significant difference emerged in MCV measurements (*P*=0.775), a significant contrast was evident in MCV values between the diagnosis and the third month concerning different age groups (*P*=0.044). Notably, there was only one patient with macrocytosis (MCV >100) and no other underlying causes who also displayed a baseline MCV >100.

## Discussion

Tyrosine kinases constitute a subgroup of protein kinases primarily responsible for facilitating the transfer of phosphate groups, typically derived from ATP, to target proteins. This process induces functional modifications within the protein structure. These molecules play a pivotal role in instigating tumor growth through diverse mechanisms. These mechanisms encompass cell proliferation, stromal expansion, angiogenesis, and tissue invasion. Genetic mutations leading to activating the pathways above are frequently identified in tumors. Instances encompass the overexpression of growth factors or hormones, their receptors, or the activation of tyrosine kinase receptors.

TKIs operate by impeding the signaling pathways of growth factors through various means. During chronic cancer treatment, the evolution of resistance mechanisms in cancer cells entails secondary mutations in the target site, the activation of alternative signaling pathways, and evasive maneuvers against the immune system. Among these mechanisms, the most prevalent is the occurrence of point mutations at the tyrosine kinase's binding site, resulting in a diminished affinity for TKIs. Given that TKIs necessitate prolonged administration, non-compliance with the prescribed treatment regimen is one of the foremost reasons for diminished efficacy [12].

Erlotinib is employed in treating non-small cell lung cancer (NSCLC) characterized by epidermal growth factor receptor (EGFR) mutations. The prevalent mutations comprise exon 19 deletion (del19) and exon 21 (L858R) substitution. Among the frequently encountered and controllable side effects are skin-related toxicities like rash, muscle and joint discomfort, diarrhea, and cough. In rare instances, more severe side effects may manifest, encompassing interstitial pneumonitis, gastrointestinal perforation, stroke, and corneal ulceration. The emergence of these side effects can be attributed to the inhibitory effects on EGFR.

MCV is a non-invasive, convenient, and cost-effective indicator for assessing red blood cells. This indicator can be readily obtained through a comprehensive analysis of the complete blood count. Macrocytosis, an emerging and frequent laboratory side effect, has been associated with prolonged treatment using the widely utilized TKI sunitinib [13]. The precise mechanism underlying sunitinib-induced macrocytosis remains elusive. Investigations have ruled out alternative causes such as vitamin B12 or folic acid deficiency, liver disease, or nutritional inadequacies. According to Rini et al. [13], sunitinib might directly trigger macrocytosis. A plausible explanation posits that sunitinib induces macrocytosis by inhibiting the c-KIT receptor of progenitor cells within the bone marrow. The restoration of MCV to normal levels following the discontinuation of the agent underscores the transient and reversible nature of this phenomenon. In contrast, sorafenib, a multikinase inhibitor with a potent impact on vascular endothelial growth factor (VEGF), does not affect MCV in renal cell carcinoma (RCC) patients due to its limited effect on c-kit [14].

In this investigation, no differences were detected in gender, histological subtype, smoking habits, or mutation types when comparing MCV measurements taken at the time of diagnosis and those obtained in the third month. However, variations in MCV values were noted between measurements taken solely at the diagnosis and those at the third month, stratified by age groups. Among individuals below the age of 65, the MCV value decreased at the time of diagnosis, while in the third month, an increase was observed among those aged 65 or older. Existing research has demonstrated that generally healthy individuals' MCV values rise with age [15]. Nonetheless, the observed MCV elevation in our study did not meet the criteria for macrocytosis. It is reasonable to consider that this outcome may not be linked to the treatment regimen.

The research conducted by Schallier et al. [16] revealed a notable elevation in mean MCV values from baseline with the administration of sunitinib and imatinib. They noted that neither sorafenib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, nor erlotinib, an EGFR inhibitor, exhibited an impact on MCV. The progression of macrocytosis was characterized by a gradual increase over time, a sustained elevation that remained statistically significant, and eventual plateauing after 6 months, all observed under the standard dose of sunitinib. However, our study lacked the necessary long-term patient follow-up to perform analyses spanning 6 months.

The underlying mechanism behind macrocytosis in TKI treatment remains elusive, though it is speculated to be linked to the inhibition of c-KIT in red blood cell progenitors within the bone marrow. This hypothesis is reinforced by the absence of macrocytosis when administering sorafenib, which exhibits a lower affinity for c-KIT. Nevertheless, it's plausible that inhibiting additional signaling pathways might also contribute to the emergence of macrocytosis [16,17]. Prior research has indicated that hematological progenitors are involved in regulating normal cell proliferation and differentiation within the bone marrow, displaying inherent signaling activity. Furthermore, the effects of newly developed signal transduction inhibitors warrant investigation [16].

Macrocytosis was identified in nearly half (42%) of gastrointestinal stromal tumors (GIST) patients undergoing treatment with the c-KIT inhibitor imatinib [18].

Limited literature exists investigating macrocytosis's potential prognostic or predictive significance in erlotinib usage. The discovery of any such correlation could pave the way for more extensive studies, enabling early assessment of treatment response/resistance prior to imaging and facilitating the adoption of a cost-effective and non-invasive method for monitoring treatment outcomes. The macrocytosis observed using TKIs is primarily believed to be associated with c-kit inhibition. Notably, erlotinib functions as an EGFR inhibitor without any known impact on c-kit. Hence, an inquiry was conducted to determine whether macrocytosis could emerge through unidentified mechanisms. Nonetheless, upon examining these findings, it was ascertained that erlotinib did not lead to the development of macrocytosis.

In this study, we additionally observed that gender exerted an influence on OS and PFS, with females exhibiting statistically significant superiority over males. Existing literature supports the notion that response rates are most prominent in cases of nonsquamous histology, particularly among women with no smoking history [19].

**Limitations**

The retrospective nature of our study constitutes a primary limitation, leading to inherent heterogeneity within the examined subgroups. Moreover, our analysis was confined to the third-month measurements due to the absence of extended follow-up data for certain patients. The potential for MCV elevations to manifest over an extended follow-up period is an additional constraint in our study. Consequently, assessing longer-term outcomes would hold significance and provide a more comprehensive understanding of the phenomenon.

**Conclusion**

Considering the outcomes of this study, in contrast to certain other TKIs like imatinib and sunitinib, there was no observed increase in MCV values at the third-month measurement. This finding supports the notion that macrocytosis associated with TKI usage can be attributed to c-kit inhibition, a mechanism not applicable to erlotinib. Distinct disparities in MCV values were noted between measurements taken at diagnosis and those at the third month, stratified by age groups. Notably, within the third month, MCV levels increased among individuals aged 65 and above, yet macrocytosis did not manifest. Furthermore, OS and PFS were more favorable in female patients than their male counterparts. In conclusion, this study suggests a lack of correlation between erlotinib use and the occurrence of macrocytosis, but it highlights the greater benefit experienced by female patients undergoing erlotinib treatment. It is important to note that these conclusions should be considered within the context of long-term follow-up results.

## References


1. Buszka K, Ntzifa A, Owecka B, Kamińska P, Kolecka-Bednarczyk A, Zabel M, et al. Liquid Biopsy Analysis as a Tool for TKI-Based Treatment in Non-Small Cell Lung Cancer. Cells, 2022;11(18):2871.
2. Tommasi C, Scartabellati G, Giannarelli D, Giorgi U, Brighi N, Fornarini G, et al.. The role of mean corpuscular volume and red cell distribution width in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors: the MARECAP retrospective study. Ther Adv Urol. 2023;15:17562872231187216.
3. Roskoski R Jr. Properties of FDA-approved small molecule protein kinase inhibitors: A 2023 update. Pharmacol Res. 2023;187:106552.
4. Shen F, Li F, Ma Y, Song X, Guo W. Identification of novel stemness-based subtypes and construction of a prognostic risk model for patients with lung squamous cell carcinoma. Curr Stem Cell Res Ther. 2023;10.2174/1574888X18666230714142835.
5. Liu SY, Zhang JT, Zeng KH, Wu YL. Perioperative targeted therapy for oncogene-driven NSCLC. Lung Cancer. 2022;172:160-9.
6. Burger JA. Bruton Tyrosine Kinase Inhibitors: Present and Future. Cancer J. 2019;25(6):386-93.
7. Murugesan S, Murugesan J, Palaniappan S, Palaniappan S, Murugan T, Siddiqui SS, et al. Tyrosine Kinase Inhibitors [TKIs) in Lung Cancer Treatment: A Comprehensive Analysis. Curr Cancer Drug Targets. 2021;21(1):55-69.
8. Dellapasqua S, Bagnardi V, Bertolini F, Sandri MT, Pastrello D, Cancello G, et al. Increased mean corpuscular volume of red blood cells predicts response to metronomic capecitabine and cyclophosphamide in combination with bevacizumab. Breast. 2012;21(3):309-13.
9. Shinde A, Panchal K, Katke S, Paliwal R, Chaurasiya A. Tyrosine kinase inhibitors as next generation oncological therapeutics: Current strategies, limitations and future perspectives. Therapie. 2022;77(4):425-43.
10. Thomson RJ, Moshirfar M, Ronquillo Y. Tyrosine Kinase Inhibitors. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 18, 2023.
11. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Correct study group. regorafenib mono-therapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomise placebo-controlled, phase 3 trial.Lancet 2013;381(9863):303-12.
12. Reed JP, Chung J, Banerjee N. A Case of Cobalamin Deficiency and Macrocytic Anemia Secondary to Sunitinib. Cureus. 2019;11(3):e4310.
13. Rini BI, Choueiri TK, Elson P, Khasawneh MK, Cotta C, Unnithan J, et al. Sunitinib-induced macrocytosis in patients with metastatic renal cell carcinoma. Cancer. 2008;15;113(6):1309-14.
14. Aliberti S, Grignani G, Allione P, Vormola R, Bucci AS, Porrino G, et al. Erythrocyte macrocytosis is a rather common apparently uneventful yet unexplained finding in GIST imatinib (I) chronic therapy. Proc ASCO. 2005;827S:9045.
15. Lee JY, Choi H, Park JW, Son BR, Park HJ, Jang LC, et al. Age-related changes in mean corpuscular volumes in patients without anaemia: An analysis of large-volume data from a single institute. J Cell Mol Med. 2022;26(12):3548-56.
16. Schallier D, Trullemans F, Fontaine C, Decoster L, De Greve J. Tyrosine kinase inhibitor-induced macrocytosis. Anticancer Res. 2009;29(12):5225-8.
17. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res. 2003;9(1):327-37.
18. Aliberti S, Grignani G, Allione P, Vormola R, Bucci A, Porrino G, et al. Erythrocyte macrocytosis is a rather common, apparently uneventful yet unexplained finding in GIST imatinib chronic therapy. J Clin Oncol 2005;23(16S):9045. ASCO Annual Meeting Proceedings.
19. Reck M, van Zandwijk N, Gridelli C, Baliko Z, Rischin D, Allan S, et al. Erlotinib in advanced non-small cell lung cancer: efficacy and safety findings of the global phase IV Tarceva Lung Cancer Survival Treatment study. J Thorac Oncol. 2010;5(10):1616-22.

J Surg Med. 2023;7(8):514-517.
DOI: 10.28982/josam.7933

Research article

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Predisposal factors leading to early re-amputation among diabetic patients who underwent minor amputation

**Onur Gürsan [1], Mustafa Çeltik [2], Cihangir Türemiş [3]**

[1] Department of Orthopedic Surgery, Dokuz Eylül University, Izmir, Turkey
[2] Kağızman State Hospital, Kars, Turkey
[3] Çeşme Alper Çizgenakat State Hospital, Izmir, Turkey

**ORCID ID of the author(s)**

OG: 0000-0002-6356-3834
MÇ: 0000-0002-0517-6684
CT: 0000-0002-5794-6652

**Corresponding Author**
Onur Gürsan
Department of Orthopedic Surgery, Dokuz Eylül University, Izmir, Turkey
E-mail: onur_84_gursan@hotmail.com

**Ethics Committee Approval**
The study was approved by Dokuz Eylül University Non-Interventional Research Ethics Committee (Reference number: 2022/37-03, date: November 23, 2022).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 30

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

**Background/Aim:** Prolonged wound complications and the possibility of reoperations are significant outcomes following minor amputations. As time progresses after the initial surgery, re-amputations become more prevalent. Contrary to prevailing beliefs, the incidence of early amputations remains consistent. Additionally, it is widely acknowledged that the first 6 months following the initial surgery pose the highest risk period for reoperation. This retrospective clinical study aims to investigate the risk factors contributing to ipsilateral re-amputation procedures within 6 months of the initial minor amputation.

**Methods:** A retrospective cohort study was conducted involving amputee patients from 2008 to 2020. Patients with traumatic events, musculoskeletal tumors, prior major amputations, and those who underwent soft tissue procedures such as debridement, incision, drainage, or secondary closure were excluded. Patients who had undergone preoperative lower limb arterial Doppler ultrasound and whose initial preoperative laboratory records were accessible were included. The total cohort comprised 168 patients, comprising 57 women and 109 men. The mean follow-up duration was 1.5 years (range: 1.1–3.2 years). Patients who underwent ipsilateral re-amputation were categorized into two groups based on the timing of the subsequent surgery. The first group comprised 110 (65.5%) patients who underwent ipsilateral re-amputation 6 months after the initial amputation, while the second group encompassed 58 (34.5%) patients who underwent ipsilateral re-amputation within 6 months of the initial amputation.

**Results:** Among the 168 patients, 58 (34.5%) experienced ipsilateral re-amputation within 6 months of their initial minor amputations, while 64.5% underwent re-amputation surgery after the initial 6 months. The absence of peripheral arterial disease was not linked to early re-amputations ($P$=0.001). Although the mean C-reactive protein values (80.30 mg/dL and 84.26 mg/dL for groups 1 and 2, respectively) did not display significance between the groups ($P$=0.40), the group undergoing amputation within 6 months demonstrated significance with elevated serum white blood cell mean levels (10.44 mcL and 11.96 mcL for groups 1 and 2, respectively; [$P$=0.004]). Moreover, lower hemoglobin levels (11.41 g/dL and 10.77 g/dL for groups 1 and 2, respectively) were associated with re-amputation within the initial 6 months following the initial surgery ($P$=0.024).

**Conclusion:** The study underscores that the incidence of re-amputation after minor amputations in diabetic patients is comparably high, as has been reported in recent literature. While the selection of the initial amputation level remains pivotal, and not all patient-specific factors were examined in this study, the research brings attention to specific laboratory values and the vascular status of the diabetic limb as crucial considerations for surgeons prior to the initial surgery.

**Keywords:** minor amputation, re-amputation, diabetic foot

How to cite: Gürsan O, Çeltik M, Türemiş C. Predisposal factors leading to early re-amputation among diabetic patients who underwent minor amputation. J Surg Med. 2023;7(8):514-517.

## Introduction

Recently, there has been a surge in the incidence of lower extremity diabetic amputations. Among these amputations, those that arise due to diabetes predominantly involve minor procedures, encompassing the removal of toes or portions of the foot up to the ankle [1-4].

Indeed, the choice of a minor amputation harms the quality of life and can lead to prolonged wound complications. What's even more concerning is that minor amputation often paves the way for subsequent re-amputations [5]. In a retrospective analysis of forefoot amputations involving 81 patients, the average period between the primary and subsequent amputation was 10.9 months. This group conducted 23 out of 29 major amputations within two months following the forefoot amputation [6]. Beaulieu et al. [7] documented 94 instances of re-amputation out of 100 readmissions in a cohort of 152 transmetatarsal amputations. A decade-long observational study by Izumi et al. [8] revealed that the greatest risk for a patient to undergo further amputation of the same limb occurs 6 months after the initial minor amputation. Their data indicates a re-amputation rate of 60% over 5 years.

Numerous descriptive studies have reported risk factors, including infection, peripheral arterial disease, chronic renal disease, and Hemoglobin A1c (HbA1c) levels associated with re-amputation. Alongside these variables, modifications in human serum parameters influence the necessity and timing of re-amputation [2,9-11]. This study focused on investigating the risk factors that lead to ipsilateral re-amputation procedures within 6 months after the initial amputation. We hypothesize that patients affected by malnutrition, peripheral arterial issues, and renal disease are predisposed to undergoing early re-amputation procedures.

## Materials and methods

A retrospective study was conducted on patients with amputations between 2008 and 2020. Approval from the local ethics committee was obtained under the reference number 2022/37-03. The amputations were carried out following a multidisciplinary approach to determine the appropriate level of amputation. Patients with amputations resulting from traumatic events, musculoskeletal tumors, previous major amputations, or those who had undergone soft tissue surgeries such as debridement, incision, drainage, or secondary closure were excluded from the study.

The study involved the assessment of records from 249 patients who had undergone at least one minor ipsilateral re-amputation. The analysis was carried out by excluding sixty-eight patients who did not have lower limb arterial Doppler ultrasonography performed within a month before the initial surgery. The peripheral arterial disease (PAD) diagnosis was exclusively confirmed for patients who had undergone Doppler ultrasonography. Patients exhibiting monophasic Doppler signals at the ankle level were included in the PAD category. From the remaining pool of 181 patients, thirteen individuals lacking serum hemogram, creatinine, and C-reactive protein (CRP) values within 2 days prior to the initial surgery were subsequently excluded. HbA1c values were recorded monthly following the initial surgery [5,12-14]. The American Society of Anesthesiologists (ASA) physical status classification was employed to categorize participants based on their physical condition prior to the anesthesia for the initial amputation. The ASA values of the 163 patients were segregated into groups according to their preoperative scores.

The total patient count is 168, comprising 57 women and 109 men. The average follow-up duration was 1.5 years (1.1 to 3.2 years). Patients who underwent ipsilateral re-amputation were categorized based on the timing of their subsequent surgeries. The initial group encompasses 110 (65.5%) patients who experienced ipsilateral re-amputation 6 months after the primary amputation. Meanwhile, the second group comprises 58 (34%) patients who underwent ipsilateral re-amputation within 6 months of their initial amputation. An investigation was conducted on these two groups, focusing on serum hemoglobin, white blood cell (WBC) count, albumin levels, CRP levels, creatinine levels, HbA1c levels, ASA scores, smoking habits, and PAD. Due to incomplete documentation on peripheral neuropathy presence and infection progression, these parameters were excluded from the analysis.

**Statistical analysis**

The study findings underwent statistical analysis utilizing IBM SPSS Statistics, version 22 (IBM SPSS, Armonk, NY). The normal distribution of parameters was evaluated through the Shapiro-Wilk test, a widely employed technique for assessing data normality. Statistical evaluations encompassed Wilcoxon rank sum tests for continuous variables, Pearson's chi-squared tests and Fisher's exact tests for categorical variables. These analyses considered diverse attributes such as hemoglobin levels, presence of PAD, gender distribution, WBC count, HbA1c levels, CRP levels, serum albumin levels, creatinine levels, and ASA scores.

The study further undertook an analysis aimed at identifying factors linked to the occurrence of PAD. To assess the relationships between these characteristics and the presence of PAD, odds ratios (ORs), confidence intervals (CIs), and *P*-values were calculated. The significance threshold was established at $P < 0.05$.

## Results

The initial group comprised 110 patients with a mean age of 58 (53.62), while the second group consisted of 58 patients with an initial mean age of 56 (52.59). The age parameter exhibited no significant difference between the two groups ($P=0.30$). The distribution of male and female participants' percentages is detailed in Table 1, revealing no statistical disparity between genders ($P=0.70$). The percentages of smokers and non-smokers are presented in Table 1 as well, indicating no statistically significant distinction between the two groups ($P=0.60$).

In the initial group, 30 patients underwent PAD determination in accordance with our study protocol. Within the second group, comprising patients who underwent amputation within 6 months, 23 cases were identified with PAD. The absence of PAD did not correlate with early re-amputations. A statistically significant disparity between the two groups was observed ($P=0.001$).

Age was uniformly distributed both between the groups and among genders. The mean hemoglobin value was 10.77 (1.73) in the second group and 11.41 (1.78) in the first group. The group subjected to re-amputation within 6 months exhibited notably lower serum hemoglobin levels than group one, with a statistically significant difference ($P$=0.024).

The initial mean WBC values were 10.44 (4.01) for group 1 and 11.96 (3.81) for group 2. The early amputation group (Group 2) displayed significantly higher values than the first group, with a $P$-value of 0.004. As an indicator of malnutrition, the mean serum albumin levels were 3.18 (0.66) for group 1 and 3.17 (0.70) for group 2. However, statistical analyses regarding serum albumin values did not reveal any significant difference between the two groups ($P$=0.50).

CRP levels (80.30 [72.93] for group 1 and 84.26 [67.53] for group 2) and HbA1c values (8.51 [2.07] for group 1 and 8.59 [1.50] for group 2) were higher in the second group. Nonetheless, the two groups did not have a statistically significant difference in CRP levels ($P$=0.40) and HbA1c values ($P$=0.40).

The mean serum creatinine levels were 1.38 (0.98) for group 1 and 1.77 (1.75) for group 2. These higher levels were observed in the early amputation group (Group 2), although no significant values were obtained (Table 1). Percentages of participants within each ASA category were presented in Table 1, showing no significant difference between the groups ($P$=0.70).

Table 1: Demographic findings, comorbidities and serum parameter values of both groups

| Variable | Re-amputation after 6 months n=110 Mean (SD) n (%) | Re-amputation within 6 months n=58 Mean (SD) n (%) | *P*-value |
|---|---|---|---|
| **Age** | 58.31 (8.18) | 56.88 (6.31) | 0.30 |
| **Gender** | | | 0.70 |
| Male | 72 (65%) | 36 (62%) | |
| Female | 38 (35%) | 22 (38%) | |
| **Smoking** | | | 0.60 |
| Smokers | 24 (22%) | 15 (26%) | |
| Non-smokers | 86 (78%) | 43 (74%) | |
| **Peripheral Arterial Disease (PAD)** | | | 0.001 |
| PAD (+) | 30 (%27) | 35 (%60) | |
| PAD (-) | 80 (%73) | 23(%40) | |
| **Hemoglobin (g/dL)** | 11.41 (1.78) | 10.77 (1.73) | 0.024 |
| **White Blood Cells (mcL)** | 10.44 (4.01) | 11.96 (3.81) | 0.004 |
| **HbA1c (mmol/mol)** | 8.51 (2.07) | 8.59 (1.50) | 0.40 |
| **CRP (mg/dL)** | 80.30 (72.93) | 84.26 (67.53) | 0.40 |
| **Albumin (g/dL)** | 3.18 (0.66) | 3.17 (0.70) | 0.50 |
| **Creatinine (mg/dL)** | 1.38 (0.98) | 1.77 (1.75) | 0.40 |
| **ASA (n=163)** | | | 0.70 |
| 1 | 9 (8.6%) | 2 (3.4%) | |
| 2 | 57 (54%) | 35 (60%) | |
| 3 | 23 (22%) | 12 (21%) | |
| 4 | 16 (15%) | 9 (16%) | |

## Discussion

In this retrospective analysis, our objective was to determine the rate of ipsilateral re-amputation and identify the factors contributing to early re-amputation. Our findings indicate that the percentage of ipsilateral re-amputation 6 months after the initial amputation is 34.5%. Interestingly, the absence of PAD is not correlated with early re-amputations. While CRP values did not exhibit significant differences between the groups, we speculate that there might exist a propensity for early re-amputation in the patient group with higher WBC levels.

In their study focusing on diabetic patients, specifically examining six-month readmissions and re-amputations, Ratliff et al. reported an ipsilateral re-amputation rate of 24%. They observed a higher incidence of more proximal-level amputations following minor amputations [15]. In a population-based cohort study, the prevalence of ipsilateral re-amputation after a minor amputation was documented at 10.7% [16]. Murdoch et al. [17] found that within 1 year after the initial amputation, 60% of all individuals underwent subsequent amputations, 21% required a third amputation, and 7% needed a fourth. Comparatively, our observed rate of ipsilateral re-amputation over 6 months is higher. This could be linked to evolving trends, particularly in determining amputation levels.

Inadequate selection of the initial amputation level can lead to suboptimal debridement and subsequent re-amputations. Moreover, a proclivity to preserve extremity length by favoring more distal amputations might contribute to the escalation in the re-amputation rate. Skoutas et al. [9] suggest a considerable likelihood of re-amputation in diabetic foot conditions, especially within the first 6 months following the index amputation, primarily due to poorly informed choices regarding the amputation level, ostensibly aimed at retaining extremity length.

The presence of PAD was assessed through physical examinations (including peripheral pulse palpation or ankle-brachial index measurements) or diagnostic tools such as angiography or Doppler ultrasonography. Re-amputation rates can escalate to as much as 60% over 5 years when associated with PAD [2,18]. A recent study investigating the risk of major amputation after an initial minor amputation found that individuals with both PAD and diabetes faced a higher risk of subsequent major and minor amputations compared to patients with only one of these conditions. Notably, around half of the cases of limb loss occurred approximately 1 year following the initial minor amputation. The rate of subsequent minor amputations stood at 16% for cases with both PAD and diabetes, as opposed to 15.2% for those with only PAD and 12.2% for patients with diabetes [19]. However, this study did not provide information regarding the laterality of the amputations (ipsilateral or contralateral).

In our study, over 6 months following the initial minor amputation in diabetic patients, we did not find any statistically significant difference related to PAD. Moreover, any combination of comorbidities with PAD did not show significance in cases of re-amputation within 6 months. Nevertheless, we speculate that patients without PAD may have undergone ipsilateral minor amputations less frequently than those diagnosed with PAD within 1 year of the index surgery. Our vascular disease determinations relied solely on Doppler ultrasonography; including records involving angiography, ankle-brachial index measurements, or the degree of vascular occlusion could have yielded more substantial analyses.

Various combined parameters, encompassing initial serum levels of CRP, hemoglobin, WBC, HbA1c, and renal disease, have been explored in existing literature [20]. A recent study identified HbA1c, CRP, WBC, and creatinine levels as upper reference bounds for predicting re-amputation. Additionally, lower levels of albumin were linked to increased amputation rates. The study emphasized the significance of HbA1c levels as highly sensitive indicators for anticipating the likelihood of re-amputation [21].

In our study, only lower serum hemoglobin levels and higher WBC values demonstrated significance. These differences did not yield statistically significant outcomes despite observing higher serum HbA1c and creatinine levels and lower albumin levels in the re-amputation group within the 6-month timeframe. Notably, a mere 1 mg/dl difference in hemoglobin levels was observed between the two groups, yet both values fell below those of healthy individuals.

**Limitations**

The retrospective nature of data collection is this study's primary limitation. Notably, the specific levels of amputations performed were not detailed; all instances were categorized as minor amputations. This classification doesn't account for the variability from toe to heel amputations, which could have introduced differences in the analyses. While the timing of subsequent surgeries was factored into the group categorization, patient-specific comorbidities and prior peripheral vascular conditions were regrettably not considered. Noteworthy unmeasured variables include sensitivity analysis and the progression of infections, both of which could exert significant influence. Despite these limitations, the study holds value in its focused inclusion of exclusively ipsilaterally reamputated minor amputations.

**Conclusion**

The study reveals that re-amputation following minor amputations in diabetic patients is strikingly consistent with the rates reported in recent literature. While acknowledging that the selection of the initial amputation level is pivotal and certain patient-specific factors were not addressed in this study, this research underscores the need for surgeons to pay particular attention to laboratory parameters and the vascular condition of the diabetic limb prior to the initial surgical intervention. To advance our understanding, future cohort studies should strive for greater homogeneity within the groups and should encompass an algorithm for guiding decisions regarding amputation levels.

## References


1. Malay DS, Margolis DJ, Hoffstad OJ, Bellamy S. The incidence and risks of failure to heal after lower extremity amputation for the treatment of diabetic neuropathic foot ulcer. J Foot Ankle Surg. 2006 Nov-Dec;45(6):366-74.
2. Thorud JC, Jupiter DC, Lorenzana J, Nguyen TT, Shibuya N. Reoperation and reamputation after transmetatarsal amputation: a systematic review and meta-analysis. J Foot Ankle Surg. 2016;55:1007–12
3. Van Damme H, Limet R. Amputation in diabetic patients. Clin Podiatr Med Surg. 2007;24:569-82.
4. Harding JL, Pavkov ME, Gregg EW, Burrows NR. Trends of nontraumatic lower extremity amputation in end-stage renal disease and diabetes: United States, 2000–2015. Diabetes Care. 2019;42:1430-5.
5. Nerone VS, Springer KD, Woodruff DM, Atway SA. Reamputation after minor foot amputation in diabetic patients: risk factors leading to limb loss. J Foot Ankle Surg. 2013 Mar-Apr;52(2):184-7.
6. Snyder DC, Salameh JR, Clericuzio CP. Retrospective review of forefoot amputations at a Veterans Affairs hospital and evaluation of post-amputation follow-up. Am J Surg. 2006 Nov;192(5):e51-4.
7. Beaulieu RJ, Grimm JC, Lyu H, Abularrage CJ, Perler BA. Rates and predictors of readmission after minor lower extremity amputations. J Vasc Surg. 2015 Jul;62(1):101-5.
8. Izumi Y, Lee S, Satterfield Y, Harkless L. Risk of reamputation in diabetic patients stratified by limb and level of amputation. Diabetes Care. 2006;29:566e70.
9. Skoutas D, Papanas N, Georgiadis GS, Zervas V, Manes C, Maltezos E, et al. Risk factors for ipsilateral reamputation in patients with diabetic foot lesions. Int J Low Extrem Wounds. 2009 Jun;8(2):69-74.
10. Stone PA, Back MR, Armstrong PA, Flaherty SK, Keeling WB, Johnson BL, et al. Midfoot amputations expand limb salvage rates for diabetic foot infections. Ann Vasc Surg. 2005 Nov;19(6):805-11.
11. Newhall KA, Bekelis K, Suckow BD, Gottlieb DJ, Farber AE, Goodney PP, et al. The relationship of regional hemoglobin A1c testing and amputation rate among patients with diabetes. Vascular. 2017 Apr;25(2):142-8.
12. Nather A, Bee CS, Huak CY, Chew JL, Lin CB, Neo S, et al. Epidemiology of diabetic foot problems and predictive factors for limb loss. J Diabetes Complications. 2008;22:77–82.
13. Nasri H, Rafieian-Kopaei M. Diabetes mellitus and renal failure: Prevention and management. J Res Med Sci. 2015 Nov;20(11):1112-20.
14. Faglia E, Clerici G, Clerissi J, Gabrielli L, Losa S, Mantero M, et al. Early and five-year amputation and survival rate of diabetic patients with critical limb ischemia: data of a cohort study of 564 patients. Eur J Vasc Endovasc Surg. 2006;32:484–90.
15. Ratliff HT, Shibuya N, Jupiter DC. Minor vs. major leg amputation in adults with diabetes: Six-month readmissions, reamputations, and complications. J Diabetes Complications. 2021 May;35(5):107886.
16. Birmpili P, Li Q, Johal AS, Atkins E, Waton S, Chetter I, et al. Outcomes after minor lower limb amputation for peripheral arterial disease and diabetes: population-based cohort study. Br J Surg. 2023 Jul 17;110(8):958-65.
17. Murdoch DP, Armstrong DG, Dacus JB, Laughlin TJ, Morgan CB, Lavery LA. The natural history of great toe amputations. J Foot Ankle Surg. 1997 May-Jun;36(3):204-8; discussion 256.
18. Joyce A, Yates B, Cichero M. Transmetatarsal amputation: a 12-year retrospective case review of outcomes. Foot 2020;42(July):101637.
19. Lin JH, Jeon SY, Romano PS, Humphries MD. Rates and timing of subsequent amputation after initial minor amputation. J Vasc Surg. 2020 Jul;72(1):268-75.
20. Liu R, Petersen BJ, Rothenberg GM, Armstrong DG. Lower extremity reamputation in people with diabetes: a systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2021 Jun;9(1):e002325.
21. Gülcü A, Etli M, Karahan O, Aslan A. Analysis of routine blood markers for predicting amputation/re-amputation risk in diabetic foot. Int Wound J. 2020 Dec;17(6):1996-2004.

J Surg Med. 2023;7(8):518-520.
DOI: 10.28982/josam.7549

Case report

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Inguinal herniation associated with hydrocele

**Kasalović Mladen [1,2], Igrutinović Gojko [1,2], Jakovljević Aleksandar [1,2], Miljković Nikola [1,2], Milentijević Milica [1,2]**

[1] Clinical Hospital Center Kosovska Mitrovica, Serbia
[2] Faculty of Medicine University of Prishtina-Kosovska Mitrovica, Serbia

**ORCID ID of the author(s)**

KM: 0000-0002-6634-1380
IG: 0000-0003-0040-8383
JA: 0000-0001-5906-0655
MN: 0000-0002-5513-4781
MM: 0000-0002-1788-4856

**Abstract**

An inguinal hernia is a condition characterized by the protrusion of the intestine through an opening in the abdominal wall into the inguinal canal. There are various techniques available for the surgical repair of inguinal hernias, including open and laparoscopic approaches. On the other hand, a hydrocele refers to the accumulation of fluid within the scrotum and is often referred to as a "water hernia." In adults, hydroceles can be caused by factors such as injury, infection, or radiation therapy. Definitive treatment typically involves a surgical approach, which has an excellent prognosis. This case report presents the clinical scenario of a 58-year-old male patient, who presented with pain in the right inguinal region that radiated to the right scrotum. Upon examination, mild swelling was observed in the right inguinal region, along with significant edema of the right scrotum, which was tender to touch. Following admission, the patient underwent surgical treatment. The purpose of this case presentation is to enhance understanding of inguinal hernias and hydroceles, facilitating their identification and diagnosis.

**Keywords:** inguinal hernia, hydrocele, Winkelmann, Liechtenstein

## Introduction

Inguinal hernias can be categorized into different types, including congenital and acquired, as well as direct and indirect hernias. An indirect hernia occurs when there is weakness in the muscles and supporting structures of the inguinal canal, allowing the intestine to protrude through the internal and external inguinal rings and descend towards the scrotum. This type of hernia is often congenital or acquired and can occur bilaterally in about 30% of cases in men. In women, the hernia is located within the round ligament of the uterus.

On the other hand, a direct hernia is always acquired and is more common in middle-aged and older men. It occurs in Hesselbach's triangle, which is medial to the lower epigastric blood vessels [1]. Unlike an indirect hernia, a direct hernia is not located within the spermatic cord but can extend along the entire length of the inguinal canal to the scrotum. The lifetime prevalence of inguinal hernias is higher in men (27%) compared to women (3%) [2].

The primary symptom of an inguinal hernia is typically a painless lump in the groin area [3]. However, some patients may experience discomfort or a burning sensation in the inguinal region due to nerve compression. In addition to pain, complications such as obstruction and intestinal ischemia can occur [4]. Surgical treatment is the recommended approach for all hernias unless there are contraindications. Conservative management is not curative. There are several surgical methods available, including the tension method (introduced by Eduardo Basini) and the Lichtenstein method, which is considered the gold standard in modern surgery and involves the placement of a mesh (prosthetic material) to reinforce the area.

**Corresponding Author**
Kasalović Mladen
Clinical Hospital Center Kosovska Mitrovica, Serbia
E-mail: kasalovicm2105@gmail.com

**Informed Consent**
The authors stated that the written consent was obtained from the patient presented with images in the study.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 5

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

How to cite: Mladen K, Gojko I, Aleksandar J, Nikola M, Milica M. Inguinal herniation associated with hydrocele. J Surg Med. 2023;7(8):518-520.

A hydrocele is characterized by the collection of fluid inside the scrotum, following the processus vaginalis [5]. The processus vaginalis is a protrusion of abdominal tissue into the scrotum and follows the spermatic ducts within the inguinal canal. Hydroceles are often benign and do not have significant health consequences, but large hydroceles can exert pressure on the testicles, potentially leading to atrophy and sterility. In adults, hydroceles can occur due to injury, infection, or radiation therapy.

Most hydroceles do not cause symptoms, but they may result in painless enlargement of one or both scrotums. Patients may experience discomfort or pressure on the affected side. If an inguinal hernia coexists with a hydrocele, pain may be present.

In adults, it occurs in every hundred patients. The majority of hydroceles do not cause any symptoms. Painless enlargement of one or both scrotums occurs most often [5]. Patients may complain of a feeling of discomfort or pressure on the side where the hydrocele is located.

Definitive treatment for hydroceles usually involves a surgical approach, such as the Winkelmann method, which entails excising the hydrocele sac through an inguinal approach [6,7]. This approach is typically performed when a hydrocele is associated with an inguinal hernia.

## Case presentation

A 58-year-old male patient presented with swelling and pain in the right inguinal region, along with pain spreading to the right hemiscrotum. The intensity of the pain was low a week before admission but became more intense immediately before seeking medical attention. Upon examination, there was swelling in the right inguinal region and right hemiscrotum, and the patient experienced significant pain sensitivity upon palpation. The patient was admitted to a surgery department, where preoperative preparation was conducted. Basic laboratory and biochemical analyses were performed, including white blood cell count (WBC), neutrophil percentage (NE), C-reactive protein (CRP), albumin, proteins, sodium (Na), potassium (K), calcium (Ca), and liver function tests (AST, ALT, ALP, and gGT), all of which were within the reference values. Additionally, the patient underwent a chest X-ray and an ECG, both of which yielded normal findings. An internist and an anesthesiologist were consulted to ensure appropriate medical care. After adequate preoperative preparation, the patient underwent operative treatment under OET anesthesia, while being positioned in a supine, horizontal position. During the surgery, a classic inguinal hernia incision was made in the right inguinal region to access the inguinal canal. Upon dissection of the hernia sac, an expansion resembling a sac was observed (Figure 1), which increased in size when pressure was applied to the right hemiscrotum. Further preparation revealed the presence of a hydrocele associated with the inguinal hernia (Figure 2).

Figure 1: Bridled funiculus, saccular dilatation observed

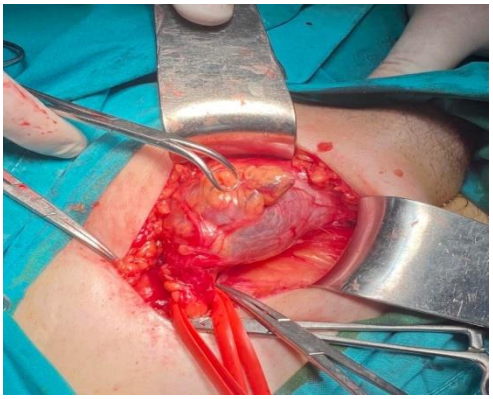
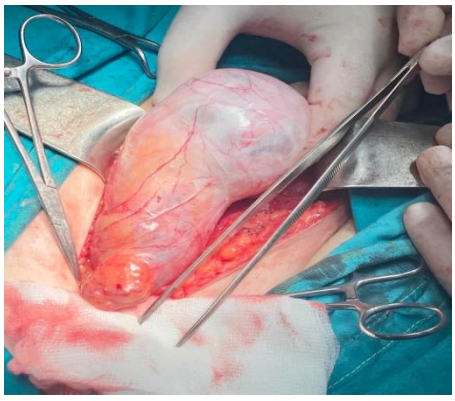


Figure 2: Prepared hydrocele



After dissection of the hernia sac, it is repositioned in the abdomen and reconstruction is performed. We evacuate the clear liquid content (about 50ml) from the hydrocele through an incision and approach the Winkelmann technique.

We return the testicle to the scrotum (Figure 3) and place the drain in the scrotal sac. After that, we perform reconstruction of the inguinal canal according to Lichtenstein (Figure 4, 5).

Figure 3: Condition after Winkelmann, the testicle

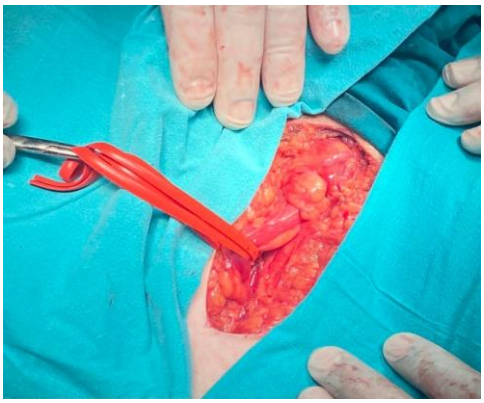


Figure 4: Reconstruction of the inguinal canal returned to the scrotum according to Lichtenstein

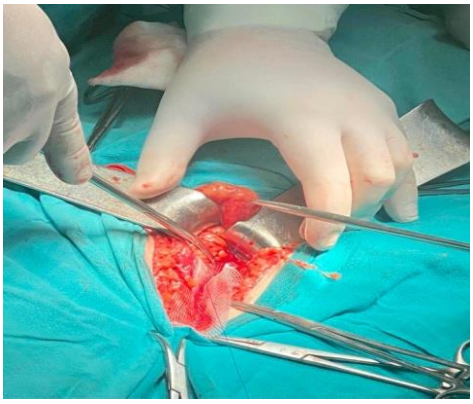
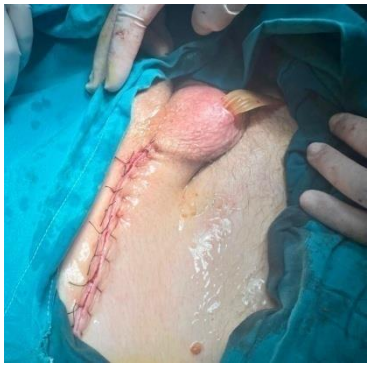


Figure 5: Placed drain in the right hemiscrotum



## Discussion

Hernias are a common surgical condition, and their repair is one of the most frequently performed surgical procedures worldwide. Inguinal or groin hernias account for approximately 75% of all hernias, with indirect inguinal hernias comprising 50% and direct inguinal hernias comprising 25% of cases. Inguinal hernias are more prevalent in men, and they occur more frequently on the right side than on the left. Previous experience and research have shown favorable results in the management of hernias and hydroceles. The technique described in this case, accessing the hydrocele through the inguinal canal, is in line with previous studies that have reported successful outcomes and prevention of recurrence [8]. Elective surgeries under general anesthesia, often performed as "day surgery," are common in the treatment of hernias and hydroceles. Inguinal hernias associated with hydroceles are relatively uncommon, except in cases of incarcerated hernias where immediate surgery is necessary to prevent damage to the organs within the hernia sac due to compromised blood supply. Surgical approaches such as the Bestenstion method, characterized by proper tension adjustment during hernioplasty, have demonstrated advantages such as reduced postoperative pain, faster recovery, and quicker return to daily activities compared to open-tension hernioplasty [9]. A conservative approach may be considered for patients with minimally symptomatic inguinal hernias. In cases where hydroceles develop later in life, it is important to identify the underlying pathology as prognosis can vary depending on the specific cause. Overall, surgical intervention remains the definitive treatment for hernias and hydroceles, providing successful outcomes and alleviating symptoms for patients.

### Conclusion

The presented case of a patient with an inguinal hernia associated with a hydrocele highlights a rare occurrence of these two conditions coexisting. While inguinal hernias and hydroceles individually are commonly encountered in clinical practice, their combined presentation is relatively uncommon. This case report serves to enhance understanding and awareness of this particular entity among healthcare professionals.

## References


1. Radovanović S, Radovanović B. Kile prednjeg trbušnog zida, Beograd, 1988
2. Shakil A, Aparicio K, Barta E, Munez K. Inguinal hernias: Diagnosis and management. Am Fram Physician. 2020 Oct 15;(8):487-92. PMID: 33064426
3. Berndsen MR, Gudbjartsson T, Berndsen FH. Inguinal hernia – review. Laeknabladid. 2019 Sep;105(9):385-91. doi: 10.17992/lbl.2019.09.247
4. Techapongsatorn S, Tansawet A, Kasetsermwiriya W, Pattanaprateep O, Thakkinstian A. Mesh fixation technique for inguinal hernia repair: protocol for an umbrella review with integrated and updated network meta-analysis. BMJ Open. 2019 Oct 28;9(10):e031742. doi: 10.1136/bmjopen-2019-031742
5. Huzaifa M, Moreno MA. Hydrocele. StatPearls. 2022 Jan. Bookshelf ID: NBK559125
6. Xu W, Ko J, Fernandez N, Koyle M, Canning DA, Kurzrock EA. Abdominoscrotal hydrocele: excision of sac may not be necessary. J Pediatr Urol. 2020 Aug;16(4):494.e1-494.e5. doi: 10.1016/j.jpurol.2020.06.027
7. Spessoto Sr LCF, Fontes RF, Beigin G, Spasseto ACN, Facio MFW, Júnior FNF. Giant abdominoscrotal hydrocele in adult: A rare entity. Cureus. 2021 Aug 30;13(8):e17562. doi: 10.7759/cureus.17562
8. Latenstein CSS, Thunnissen FM, Harker M, Groenewoud S, Noordenbos MW, Atsma F, et al. Variation in practice and outcomes after inguinal hernia repair: a nationwide observational study. BMC Surg. 2021 Jan 20;21(1):45. doi: 10.1186/s12893-020-01030-0
9. Bökkerink WJV, Koning GG, Vriens PWHE, Mollen RMHG, Harker MJR, Noordhof RK, et al. Open preperitoneal inguinal hernia repair, TREPP versus TIPP in a randomized clinical trial. Ann Surg. 2021 Nov 1;274(5):698-704. doi: 10.1097/SLA.0000000000005130.

J Surg Med. 2023;7(8):521-523.
DOI: 10.28982/josam.7276

Case report

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

# Pediatric ANCA-associated vasculitis presented with various clinical findings mimicking IgA Vasculitis and IgG4-related disease: Two cases

**Mehmet Ali Oktay [1], Selin Akyüz Oktay [1], Bahriye Uzun Kenan [2], Emine Nur Sunar Yayla [3], Betül Öğüt [4], Bahar Büyükkaragöz [2], Deniz Gezgin Yıldırım [3], Sevcan A. Bakkaloğlu [3]**

[1] Gazi University, Department of Pediatrics, Ankara, Turkey
[2] Gazi University, Department of Pediatric Nephrology, Ankara, Turkey
[3] Gazi University, Department of Pediatric Rheumatology, Ankara, Turkey
[4] Gazi University, Department of Pathology, Ankara, Turkey

**ORCID ID of the author(s)**

MAO: 0000-0002-7116-5828
SAO: 0000-0003-4324-6361
BUK: 0000-0002-8248-0436
ENSY: 0000-0003-1646-2341
BÖ: 0000-0003-1646-2341
BB: 0000-0002-6342-1975
DGY: 0000-0002-4823-2076
SAB: 0000-0001-6530-9672

**Corresponding Author**
Mehmet Ali Oktay
Gazi University Faculty of Medicine, Department of Pediatrics, Ankara, Turkey
Emniyet, Mevlana Boulevard, No: 29, Yenimahalle, Ankara, Turkey
E-mail: malii-71@hotmail.com

**Informed Consent**
The authors stated that the written consent was obtained from the parents of the patients presented with images in the study.

**Conflict of Interest**
No conflict of interest was declared by the authors.

**Financial Disclosure**
The authors declared that this study has received no financial support.

**Published**
2023 August 5

**Copyright © 2023 The Author(s)**
**Published by JOSAM**
**This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND 4.0) where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.**

## Abstract

Granulomatous polyangiitis (GPA) is the most common anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), characterized by necrotizing inflammation of small and medium-sized vessels. It can affect various organs, particularly the lung, kidneys, upper respiratory tract, ears, and skin. Diagnosis of AAV poses significant challenges due to its diverse clinical features. This report presents two interesting cases of GPA: one with rare ocular involvement, who subsequently developed end-stage kidney disease (ESKD), and the other with palpable purpura mimicking immunoglobulin A vasculitis, who relapsed with mastoiditis while in renal remission. Early and effective treatment can improve patient prognosis, highlighting the importance of increasing disease awareness during initial diagnosis and in pediatric AAV patients experiencing relapses.

**Keywords:** ANCA, vasculitis, IgG4, IgA, case report

## Introduction

Anti-neutrophil cytoplasmic antibody- (ANCA) associated vasculitis (AAV) is a small vessel vasculitis characterized by pauci-immune necrotizing inflammation of small vessels. Constitutional symptoms and multiple organ/system manifestations, including recurrent epistaxis, chronic sinusitis, subglottic stenosis, hemoptysis, pulmonary nodules (involving the upper and lower respiratory tract), hematuria, proteinuria, renal impairment (crescentic glomerulonephritis), skin rash, red eye, arthritis, mastoiditis, and hearing loss, among others, may be observed [1].

Consequently, the diagnosis of AAV poses significant diagnostic challenges, and delays in diagnosis are common. This report presents two interesting cases of GPA: one with ocular involvement and mild renal impairment that progressed to end-stage kidney disease (ESKD), and the other with palpable purpura mimicking immunoglobulin A vasculitis (IgAV), who subsequently relapsed with mastoiditis while in renal remission.

How to cite: Oktay MA, Oktay SA, Kenan BU, Yayla ENS, Öğüt B, Büyükkaragöz B, Yıldırım DG, Bakkaloğlu SA. Pediatric ANCA-associated vasculitis presented with various clinical findings mimicking IgA Vasculitis and IgG4-related disease: Two cases. J Surg Med. 2023;7(8):521-523.

## Case presentation

### Case 1

A 14-year-old female patient was admitted to our hospital two years ago with complaints of swelling and redness on the skin of her left upper eyelid (Figure 1A). Her family history was unremarkable. Physical examination was normal except for left eyelid edema and hypertension (blood pressure: 180/100 mmHg). Laboratory tests revealed a creatinine level of 2.64 mg/dL, 24-hour urine protein excretion of 5415 mg/day, C-reactive protein (CRP) level of 1.32 mg/L (normal range: 0–5), erythrocyte sedimentation rate (ESR) of 67 mm/h, antinuclear antibody (ANA) by IFA of +2, and anti-MPO-ANCA of +1.

It was noted that the patient's creatinine level at her first admission for eye complaints a year ago was 1.1 mg/dL. Additionally, her ESR was 68 mm/h, CRP was 52.31 mg/L, and urinalysis showed +3 protein and +3 blood reaction. Orbital magnetic resonance (MR) imaging revealed an orbital pseudotumor and dacryoadenitis in the left eye.

Kidney biopsy showed moderate tubular atrophy/interstitial fibrosis and cellular crescent formation in 1/8 glomeruli, while the remaining glomeruli had global glomerulosclerosis. The patient was diagnosed with GPA with renal and orbital involvement, and treatment was initiated with pulse methylprednisolone (MPZ) (1 g daily for 3 days) followed by 60 mg/day of prednisolone.

The patient received five sessions of therapeutic plasma exchange (TPE) and six monthly intravenous pulse cyclophosphamide courses. The prednisolone dose was gradually tapered, and azathioprine was prescribed for maintenance therapy. At 6 months of treatment, the creatinine level was 3.31 mg/dL, and proteinuria was 828 mg/day. Hemodialysis was initiated on the 18th month of treatment due to pericardial effusion development when the creatinine level was 4.8 mg/dL.

Kidney transplantation from a living donor was performed 16 months later. Currently, the patient is in remission with a well-functioning allograft, and the parents have given written consent to publish this report and the image.

### Case 2

A 12-year-old male patient presented to a local hospital complaining of pain and swelling in his wrists, ankles, and knees, red-purple purpuric rashes on his palms and ankles, and darkening of his urine. Laboratory tests revealed a CRP level of 200 mg/L (normal range: 0–5), ESR of 105 mm/h, a 24-hour urine protein level of 1200 mg, a C3 level of 145 mg/dL, a C4 level of 30 mg/dL, and normal creatinine levels. He was diagnosed with IgA vasculitis (Henoch-Schönlein purpura), and oral corticosteroid therapy was initiated.

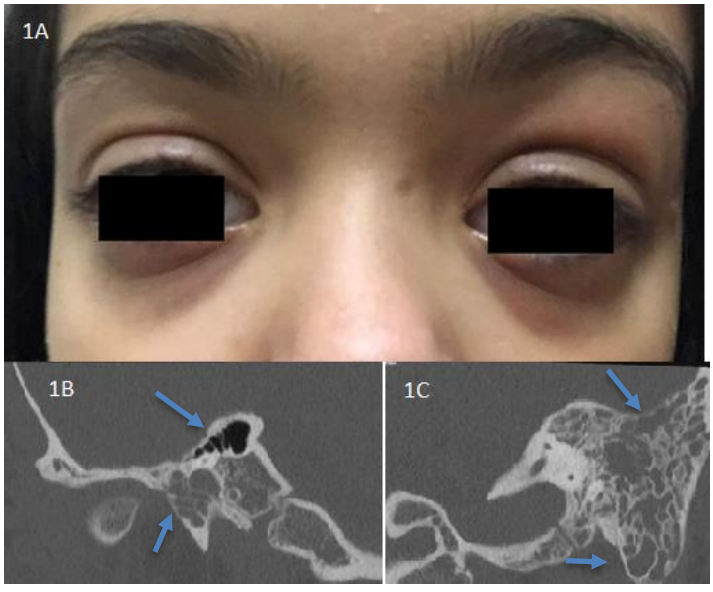
The patient was referred to our hospital for further evaluation when his creatinine level increased. His past medical and family histories were unremarkable. On physical examination, the only finding was purpuric rashes on the lower extremities. Laboratory tests revealed a serum creatinine level of 2.4 mg/dL and a 24-hour urine protein level of 3184 mg. C-ANCA was 2+, p-ANCA was negative, ANA was negative, anti-ds DNA was negative, and the anti-glomerular basement membrane (GBM) antibody was negative.

Kidney biopsy showed pauci-immune diffuse necrotizing crescentic glomerulonephritis with the cellular crescent formation in 20/36 glomeruli. Thorax and paranasal computed tomography (CT) scans were normal. The patient was diagnosed with GPA. Three days of pulse methylprednisolone (MPZ) therapy followed by 60 mg oral prednisolone with gradual tapering, six doses of monthly pulse cyclophosphamide, and seven sessions of therapeutic plasma exchange (TPE) were administered due to severe renal involvement.

The creatinine level decreased to 1.17 mg/dL. On follow-up, four doses of rituximab (375 mg/m$^2$) one week apart were given due to persistent nephrotic-range proteinuria (5610 mg/day). The patient was prescribed mycophenolate mofetil as maintenance therapy, and serum creatinine and urinary protein levels returned to normal. While in remission, the patient presented with hearing loss in the left ear in the 24th month of treatment. Temporal CT showed pneumatized petrous apex on the right, soft tissue densities in the petrous apex, mastoid air cells, epitympanum, and mesotympanum in the middle ear cavity consistent with mastoiditis (Figure 1B and C).

Laboratory tests showed that serum creatinine level had risen to 1.16 mg/dL, CRP was 76.5 mg/L, ESR was 76.5 mm/h, and proteinuria was 1366 mg/day, with c-ANCA being positive. This was accepted as disease exacerbation, and the patient's symptoms improved with the initiation of 60 mg/day prednisolone and the second course of rituximab treatment, resulting in a significant response. The patient's parents have given their written consent to publish this report and the image.

Figure 1: A: Proptosis, upper lid swelling, mild ptosis and hyperemia in the left periorbital area (Case 1). B: The decreasing aeration of the mastoid cells and hypodense soft tissue densities in the mastoid cells in the computer tomography imaging (Right mastoid) (Case 2). C: The absence of middle ear aeration and increased soft tissue densities in the mastoid cells, epitympanum, and mesotympanum mastoid in the computer tomography imaging (Left mastoid).




## Discussion

Childhood AAV patients may present with a wide variety of clinical symptoms, and diagnosing AAV can be challenging for clinicians because it can mimic other diseases. Orbital involvement may be the first or only clinical presentation in 30% of GPA patients. Orbital GPA is difficult to diagnose because its clinical manifestations often overlap with other inflammatory disorders, such as IgG4-related disease [2]. The clinical

manifestations of ocular GPA result from inflammation of ocular structures, including orbital fat, orbital nerves, extraocular muscles, lacrimal glands, and optic nerve. Patients may present with ocular pain, erythema and edema of the eyelids, nasolacrimal duct obstruction, epiphora, limited extraocular muscle movements, proptosis, diplopia, and vision loss [3,4]. ANCA titers are positive in only 50-65% of these patients [3].

In our first case, we observed eyelid edema, proptosis, and erythema, and MRI revealed orbital pseudotumor and dacryoadenitis. Accompanying proteinuria and hematuria were also noted at the patient's admission to our clinic, and GPA was confirmed with a kidney biopsy. Periorbital biopsy was not performed, and therefore IgG4 staining was not available. This case of GPA is presented to emphasize that ocular involvement, albeit rare, might be the initial finding and that systemic evaluation is extremely important.

In a large study conducted in Canada of children with GPA, 43% of those with the multisystem disease had ophthalmic complications [5]. In a European study, this rate was half as common, at 21%, and the median time to progression to ESKD was 12.9 years, while the median time to diagnosis was one month. No statistical correlation was found between the time of diagnosis and the risk of ESKD [6]. Therefore, GPA should be considered in the differential diagnosis of protracted eyelid edema and redness.

Palpable purpura in the lower extremities, which is the main finding of IgAV, can also be observed in GPA, as in our Case 2 [7], which underscores the importance of differential diagnosis. Some patients present with recurrent otitis or mastoiditis that does not respond to medical and surgical treatment and are subsequently diagnosed with GPA [8,9]. In previous reports, sensorineural hearing loss was observed in 10% and otitis/mastoiditis in 17% of patients with GPA with multisystem involvement [5,10]. However, mastoid involvement is less common in pediatric patients than in adults with GPA.

After induction therapy, one or more disease recurrences may occur in half of the patients in remission with maintenance therapy [9]. The most common disease recurrences are in the kidney, lung, and upper respiratory tract [5]. In Case 2, the patient relapsed with mastoiditis while following up under remission with low-dose steroids and mycophenolate mofetil. Although pediatric patients with GPA presenting with mastoiditis have been reported [1], to our knowledge, this is the first reported case of a pediatric patient relapsing with mastoiditis. The success of surgical treatment is limited in cases of mastoiditis and otitis due to GPA, and immunosuppressive therapy is the mainstay of treatment in these patients [8,9]. Indeed, mastoid involvement was successfully treated with steroids and rituximab in our case.

Early diagnosis and prompt treatment in patients with GPA are critical for improving prognosis. Combination therapy with corticosteroids plus cyclophosphamide or corticosteroids plus cyclophosphamide and TPE is recommended for induction therapy in pediatric AAV patients [5]. Corticosteroids combined with rituximab can also be used in induction therapy [3]. Both of our cases received combination therapy. However, one had progressed to ESKD and subsequently received a kidney allograft. On the other hand, the other patient relapsed with mastoiditis while on maintenance therapy and was successfully treated with a combination of steroids and rituximab.

**Conclusion**

Since AAV mimics various clinical entities, it should be considered in pediatric patients who visit hospitals repeatedly for specific reasons. Taking the patient's history carefully, performing a detailed physical examination, and closely monitoring the patient can lead to a proper diagnosis. We believe that increasing awareness of the disease in the initial diagnosis and in relapses in pediatric AAV patients is critical for achieving early and effective treatment and improving patient prognosis.

## References


1. Almaani S, Fussner LA, Brodsky S, Meara AS, Jayne D. ANCA-associated vasculitis: an update. Journal of Clinical Medicine. 2021;10(7):1446.
2. Boncoraglio MT, Prieto-González S, Fernandes-Serodio J, Corral-Molina JM, Solé M, Hernández-Rodríguez J. Simultaneous presentation of granulomatosis with polyangiitis (GPA) and immunoglobulin G4-related disease (IgG4-RD). Leaving an open question: widening the spectrum of a single disease or real overlap? Modern Rheumatology Case Reports. 2021;5(1):108-12.
3. Muller K, Lin JH. Orbital granulomatosis with polyangiitis (Wegener granulomatosis): clinical and pathologic findings. Archives of Pathology and Laboratory Medicine. 2014;138(8):1110-4.
4. Drobysheva A, Fuller J, Pfeifer CM, Rakheja D. Orbital granulomatosis with polyangiitis mimicking IgG4-related disease in a 12-year-old male. International journal of surgical pathology. 2018;26(5):453-8.
5. Cabral DA, Canter DL, Muscal E, Nanda K, Wahezi DM, Spalding SJ, et al. Comparing presenting clinical features in 48 children with microscopic polyangiitis to 183 children who have granulomatosis with polyangiitis (Wegener's): an ARChiVe cohort study. Arthritis & Rheumatology. 2016;68(10):2514-26.
6. Sacri A-S, Chambaraud T, Ranchin B, Florkin B, Sée H, Decramer S, et al. Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study. Nephrology Dialysis Transplantation. 2015;30(suppl_1):i104-i12.
7. Gajic-Veljic M, Nikolic M, Peco-Antic A, Bogdanovic R, Andrejevic S, Bonaci-Nikolic B. Granulomatosis with polyangiitis (Wegener's granulomatosis) in children: report of three cases with cutaneous manifestations and literature review. Pediatric Dermatology. 2013;30(4):e37-e42.
8. Moussa AE-M, Abou-Elhmd KA. Wegener's granulomatosis presenting as mastoiditis. Annals of Otology, Rhinology & Laryngology. 1998;107(7):560-3.
9. Qaisar H, Shenouda M, Shariff M, Cheema A, Tang X, Kaplan A. Granulomatosis with Polyangiitis Manifesting as Refractory Otitis Media and Mastoiditis. Archives of Iranian medicine. 2019;22(7):410-3.
10. James KE, Xiao R, Merkel PA, Weiss PF. Clinical course and outcomes of childhood-onset granulomatosis with polyangiitis. Clinical and experimental rheumatology. 2017;35(Suppl 103):202.