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# Retrospective analysis of the relationship between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and glycemic regulation in patients with type 2 diabetes mellitus followed up at an internal medicine outpatient clinic

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**Ethics Committee Approval**
The study was approved by Balıkesir University Faculty of Medicine Clinical Research Ethics Committee (March 22, 2023 and 2023/35). 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.

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## Abstract

**Background/Aim:** Type 2 diabetes mellitus (T2DM) is a common chronic disease with an increasing incidence worldwide and its effects are being seen in many countries. Insulin resistance is the main factor in the pathophysiology. T2DM leads to an increase in mortality and morbidity due to macrovascular and microvascular complications. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are effective parameters in monitoring the inflammatory response. The primary aim of this study was to investigate glycemic control in patients with type 2 diabetes by focusing on their correlation with inflammatory markers, such as NLR and PLR, glycated hemoglobin (HbA1c), and fasting blood glucose levels.

**Methods**: The present study was carried out in 2022 within the purview of the Internal Medicine Clinic at Balikesir İvrindi State Hospital. Data from the initial annual consultations of patients with T2DM, either newly diagnosed or previously diagnosed and visiting for follow-up, were utilized. Our study excluded patients under the age of 18 and those diagnosed with cirrhosis, heart failure, type 1 diabetes mellitus, malignancy, epilepsy, acute infection, pregnancy, or chronic inflammatory disease. We further excluded those on medications including steroids, antivirals, anticonvulsants, antipsychotics, antithyroids, and chemotherapeutic drugs that impact the leukocyte count. Based on their HbA1c levels, patients were systematically categorized into two distinct cohorts: those with controlled blood sugar (HbA1c ≤7%) and those with uncontrolled blood sugar (HbA1c >7%). In the ambit of this study, we incorporated data from 205 patients. We employed a cross-sectional study that retrospectively examined the correlation between NLR, PLR, and glycemic regulation in T2DM patients. SPSS 22.0 software was used to perform statistical calculations.

**Results**: It was observed that patients with poor glycemic control had longer disease durations and this disparity bore statistical significance ($P$=0.005). Patients exhibiting poor glycemic control demonstrated elevated levels of CRP (C-reactive protein), a difference that reached statistical significance ($P$=0.003). The group exhibiting poor glycemic control demonstrated a notable elevation in NLR, indicating statistical significance ($P$=0.001). Although it was not statistically significant, PLR was found to be higher in patients with uncontrolled T2DM ($P$=0.441).

**Conclusion**: This research investigates the correlation between HbA1c levels and inflammatory markers, specifically NLR and TLR, in T2DM patients who exhibit poor control of glycemia. Our findings highlight the potential of these markers as indicators of glycemic control, thus emphasizing the need for integrated strategies for managing inflammation and improving glycemic control in T2DM patients. The novelty of this area of research contributes to the scarcity of available literature, underlining the importance and timeliness of this study. Based on our findings, we suggest an increased focus on regular monitoring of inflammatory markers, for instance NLR and PLR, to assess the glycemic control in T2DM patients. The significant correlation of these markers with HbA1c levels implies that they could potentially serve as useful tools in personalizing diabetes management strategies, leading to improved patient outcomes. Not only does our research contribute to filling this knowledge gap, but it also underscores the potential for utilizing inflammatory markers in tracking disease progression and optimizing treatment efficacy in T2DM.

**Keywords:** neutrophil lymphocyte ratio, platelet lymphocyte ratio, type 2 diabetes mellitus

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## Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that causes multi-organ involvement and dysfunction. The most important feature is that it occurs with insulin resistance [1]. The global incidence of T2DM continues on an upward trend, with projections indicating an estimated prevalence of around 10.4% by the year 2040 [2]. T2DM causes a significant increase in mortality and morbidity due to chronic macrovascular and microvascular complications. Coronary artery disease, peripheral vascular disease, and cerebrovascular disease are prominent as macrovascular complications, while nephropathy, retinopathy, and neuropathy are defined as microvascular complications [3]. Hyperglycemia and insulin resistance cause stimulation of inflammatory processes. Markers of inflammation, specifically C-reactive protein (CRP) and interleukin-6 (IL-6), are noted to be significantly elevated in T2DM [4].

The ratio was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count in the complete blood count is expressed as the neutrophil-lymphocyte ratio (NLR). It is an easily calculable and low-cost marker. This ratio stands as a crucial marker of systemic inflammatory response [5]. NLR independently prognosticates ventricular dysfunction, and is notably correlated with the severity and mortality outcomes in coronary artery disease [6]. The elevated NLR value has been shown to be correlated with a reduced overall survival duration in many cancers [7]. Moreover, empirical evidence underscores a significant association between NLR and the occurrence of diabetic nephropathy [8]. NLR may increase in T2DM patients, and this increase may indicate the inflammatory burden of T2DM [9]. The ratio of the absolute platelet count divided by the absolute lymphocyte count in the complete blood count is expressed as the platelet-lymphocyte ratio (PLR). PLR may be utilized as an inflammatory marker in rheumatologic diseases and chronic obstructive pulmonary disease [10,11]. There are studies showing that the PLR value can also be used as an inflammatory marker in T2DM patients [12,13]. The high level of inflammation has been observed in uncontrolled T2DM patients, as evaluated in the existing literature. Additionally, it is known that NLR and PLR values are associated with inflammation. The objective of this study is to clarify the association between NLR and PLR values, and reveal their potential influence on glycemic control among patients diagnosed with T2DM.

## Materials and methods

### Study design

This research was conceived as a retrospective, cross-sectional study, in the Internal Medicine Clinic of Balikesir İvrindi State Hospital between January 2022 and December 2022. After obtaining approval from the local ethics committee (2023/35, 22/03/2023), the study was initiated by accessing the patients' records by retrospectively scanning the hospital and laboratory systems. This research was performed with patients who visited the Internal Medicine Outpatient Clinic. All newly diagnosed or previously diagnosed T2DM patients were incorporated into the study. The first application of each patient in 2022 was considered. Patients with diagnoses of cirrhosis, heart failure, type 1 diabetes mellitus, malignancy, epilepsy, acute infection, pregnancy, chronic inflammatory disease, and patients under the age of 18 were excluded from the study. Those using steroids, antivirals, anticonvulsants, antipsychotics, antithyroids, and chemotherapeutic drugs that affect the leukocyte count were also excluded from the study. The total patient count for the study was established at 205. T2DM patients were divided into two groups: those with controlled blood glucose levels (HbA1c ≤7%) and those without (HbA1c >7%). The study was performed ensuring ethical conformity with the principles expounded in the Declaration of Helsinki.

### Participant selection

The sample size calculation was performed utilizing G*Power 3.1, a software program created by Franz Faul at the University of Kiel, Germany. Setting the Type I error rate at 0.05 and confidence level at 90%, it was determined that a minimum sample size of 140 was necessary.

### Data collection

All participants' demographic attributes, clinical details, and laboratory data were accumulated from their individual medical documents. Demographic characteristics and clinical and laboratory data of all participants were obtained from their respective medical records. In addition to their age, gender, T2DM disease duration, biochemical data such as alanine aminotransferase (ALT), fasting blood glucose, aspartate aminotransferase (AST), glycated hemoglobin (HbA1c), CRP, urea, creatinine, total protein, triglyceride (TG), albumin, total cholesterol, globulin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), neutrophil count (NEU), white blood cell (WBC), platelet count (Plt), hemoglobin count (Hgb), lymphocyte count (LYM), iron, ferritin, and total iron binding capacity values were examined. NLR and PLR were evaluated by taking the ratio of the absolute neutrophil count and the absolute platelet count to the absolute lymphocyte count, respectively, from the evaluation of the complete blood count.

### Statistical analysis

Data compiled during the investigation were recorded using the IBM SPSS 22.0 (SPSS INC, Chicago, IL, USA) software, and further statistical analyses were then conducted. In terms of descriptive statistics, continuous variables were denoted as mean (standard deviation), while categorical variables were presented as percentages. The normality of distribution within the groups was examined using both the Kolmogorov-Smirnov and Shapiro-Wilk tests. When comparing the two groups, numerical data following a normal distribution were assessed via the Student's t-test, while the Mann-Whitney U test was employed for numerical data exhibiting a non-normal distribution. The Chi-square test was applied to compare independent groups with categorical variables. Spearman's correlation analysis was deployed to identify linkages between continuous variables. Findings with *P*-values less than 0.05 were interpreted as statistically significant.

## Results

Eighty-four cases with controlled blood sugar (HbA1c ≤%7) and 121 cases with uncontrolled blood sugar (HbA1c >%7) were used in this research. Table 1 presents the

demographic characteristics and laboratory parameters of the enrolled cases. The mean age of controlled T2DM patients was 64.6 (11.9) and the average age of uncontrolled T2DM patients was 65.5 (9.7). This distinction was determined to be statistically inconsequential (*P*=0.573). Fifty-eight (69%) of the controlled T2DM patients were female, while 26 (31%) were male; 79 (65.3%) of the uncontrolled T2DM patients were female, while 42 (34.7%) were male. No statistically significant difference was observed among controlled and uncontrolled patients in terms of gender (*P*=0.574). The mean duration of T2DM was determined to be 4.9 (3.2) years for controlled patients and 6.1 (3.2) years for uncontrolled patients. It was determined that the detected difference was statistically significant (*P*=0.005). A comparative analysis of fasting blood sugar values revealed an average of 140.7 (44.4) for the controlled group and an average of 228.8 (103.2) for the uncontrolled group (*P*<0.001). CRP values were determined to be an average of 1.04 (1.9) in the controlled group and 1.2 (1.8) in the uncontrolled group. Statistical analysis revealed that this discrepancy was significant (*P*=0.003). When compared to controlled T2DM patients, uncontrolled T2DM patients demonstrated significantly elevated NLR levels. This difference was found to carry statistical significance upon evaluation (*P*=0.001). TLR was lower in controlled T2DM patients compared to uncontrolled patients; however, this observation did not reach the threshold of statistical significance (*P*=0.441).

Table 1: Demographic characteristics and laboratory parameters of the study population

| Parameter | Controlled T2DM (HbA1c ≤%7) (n=84) Mean (SD) | Uncontrolled T2DM (HbA1c >%7) (n=121) Mean (SD) | *P*-value |
|---|---|---|---|
| **Age** | 64.6 (11.9) | 65.5 (9.7) | 0.573 |
| **Gender (Female/Male) n(%)** | 58 (69%)/26 (31%) | 79 (65.3%)/42 (34.7%) | 0.574 |
| **Duration of T2DM (years)** | 4.9 (3.2) | 6.1 (3.2) | 0.005 |
| **FPG (mg/dl)** | 140.7 (44.4) | 228.8 (103.2) | <0.001 |
| **AST (U/L)** | 20.6 (12.9) | 20.5 (12.9) | 0.703 |
| **ALT (U/L)** | 18.7 (9.3) | 19.3 (10.6) | 0.918 |
| **Urea (mg/dl)** | 39 (18.2) | 39 (21.4) | 0.828 |
| **Creatinine (mg/dl)** | 1.1 (0.7) | 1.1 (0.7) | 0.806 |
| **Total Protein (g/dl)** | 7.6 (0.5) | 7.5 (0.7) | 0.401 |
| **Albumin (g/dl)** | 4.2 (0.3) | 4.2 (0.4) | 0.795 |
| **Globulin (g/dl)** | 3.3 (0.4) | 3.3 (0.5) | 0.999 |
| **Triglycerides (mg/dl)** | 165.6 (99.7) | 182.1 (100.7) | 0.173 |
| **Total Cholesterol (mg/dl)** | 201 (41.3) | 208.6 (48.3) | 0.503 |
| **LDL (mg/dl)** | 111 (33.9) | 116.7 (38.5) | 0.492 |
| **HDL (mg/dl)** | 57.4 (16.2) | 57.1 (16.3) | 0.908 |
| **CRP (mg/dl)** | 1.04 (1.9) | 1.2 (1.8) | 0.003 |
| **Iron (mg/dl)** | 65.1 (32.4) | 72.3 (46.6) | 0.580 |
| **TIBC (mg/dl)** | 336 (70.4) | 349.2 (70.4) | 0.304 |
| **Ferritin (ng/ml)** | 72.5 (163.8) | 80.3 (155.5) | 0.349 |
| **Hgb (g/dl)** | 13.2 (1.8) | 13.6 (1.9) | 0.056 |
| **WBC (10^3/µL)** | 8.1 (2.5) | 8.2 (2.5) | 0.717 |
| **NEU (#)** | 5.4 (2.0) | 5.8 (2.3) | 0.182 |
| **LYM (#)** | 1.7 (0.7) | 1.5 (0.6) | 0.007 |
| **PLT (10^3/µL)** | 251.6 (74.7) | 231.1 (75.7) | 0.060 |
| **NLR** | 3.3 (1.7) | 4.5 (4.0) | 0.001 |
| **TLR** | 164.7 (104.3) | 171.3 (102.1) | 0.441 |

T2DM: Type 2 diabetes mellitus HbA1c: glycated hemoglobin FBG: fasting blood glucose AST: aspartate aminotransferase ALT: alanine aminotransferase LDL: low-density lipoprotein HDL: high-density lipoprotein CRP: C-reactive protein TIBC: total iron binding capacity Hgb: hemoglobin count WBC: white blood cell count NEU: neutrophil count LYM: lymphocyte count PLT: platelet count NLR: neutrophil-to-lymphocyte ratio TLO: platelet-to-lymphocyte ratio

The correlation rates between HbA1c and other parameters are shown in Table 2. A high level of relationship was discerned between fasting blood sugar and HbA1c, and a low level of a relationship was discerned between NLR and HbA1c. This difference was found to carry statistical significance upon evaluation (Rho=0.642, *P*<0.001; Rho=0.177, *P*=0.011). A moderate level of correlation was found between TLR and HbA1c, but this was statistically insignificant (Rho=0.400, *P*=0.567). An inverse correlation of moderate strength between lymphocyte count and HbA1c was statistically validated (Rho=-0.207, *P*=0.003).

A high level of association was noted between NLR and TLR, and this was statistically validated (Rho=0.697, *P*<0.001). A low level of a link could be seen between NLR and fasting blood sugar, which was confirmed to be statistically meaningful. (Rho=0.235, *P*=0.001). A correlation of lower magnitude was additionally found between TLR and fasting blood sugar, but this was statistically insignificant (Rho=0.132, *P*=0.060). A low level of correlation was found between fasting blood sugar and triglycerides, and a moderate level of correlation was observed between age and duration of T2DM, and these were statistically significant (Rho=0.257, *P*<0.001; Rho=0.398, *P*<0.001).

Table 2: Correlation analysis between HbA1c and laboratory parameters

| | HbA1c | |
|---|---|---|
| | **Rho** | ***P*-value** |
| **Age** | -0.002 | 0.98 |
| **FPG (mg/dl)** | 0.642 | <0.001 |
| **NLR** | 0.177 | 0.011 |
| **TLR** | 0.400 | 0.567 |
| **Duration of T2DM (years)** | 0.114 | 0.103 |
| **AST (U/L)** | -0.117 | 0.930 |
| **ALT (U/L)** | -0.056 | 0.421 |
| **Urea (mg/dl)** | -0.011 | 0.881 |
| **Creatinine (mg/dl)** | 0.026 | 0.716 |
| **Total protein (g/dl)** | -0.044 | 0.548 |
| **Albumin (g/dl)** | -0.034 | 0.636 |
| **Globulin (g/dl)** | 0.014 | 0.850 |
| **Triglycerides (mg/dl)** | 0.136 | 0.053 |
| **Total cholesterol (mg/dl)** | 0.066 | 0.353 |
| **LDL (mg/dl)** | 0.024 | 0.733 |
| **HDL (mg/dl)** | 0.013 | 0.852 |
| **CRP (mg/dl)** | -0.031 | 0.666 |
| **Iron (mg/dl)** | 0.025 | 0.752 |
| **TIBC (mg/dl)** | 0.066 | 0.412 |
| **Ferritin (ng/ml)** | 0.020 | 0.824 |
| **Hgb (g/dl)** | 0.082 | 0.242 |
| **WBC (10^3/µL)** | 0.046 | 0.510 |
| **NEU (#)** | 0.127 | 0.700 |
| **LYM (#)** | -0.207 | 0.003 |
| **PLT (10^3/µL)** | -0.135 | 0.540 |

HbA1c: glycated hemoglobin FBG: fasting blood glucose NLR: neutrophil-to-lymphocyte ratio TLR: platelet-to-lymphocyte ratio AST: aspartate aminotransferase ALT: alanine aminotransferase LDL: low-density lipoprotein HDL: high-density lipoprotein CRP: C-reactive protein TIBC: total iron binding capacity Hgb: hemoglobin count WBC: white blood cell count NEU: neutrophil count LYM: lymphocyte count PLT: platelet count

## Discussion

Recently, several reports have shown that the progression of T2DM is significantly impacted by the presence of chronic inflammation [14]. Chronic inflammation plays a pivotal role in the pathogenesis of T2DM and metabolic syndrome, exerting its influence through immunological inflammatory mechanisms and contributing to the advancement of the disease [15,16]. The excessive secretion of some mediators (IL-1, IL-6, TNF-a, and CRP) and damage to the endothelium cause the complications of T2DM [17]. T2DM causes microvascular and macrovascular complications. These complications are the most important factors in increasing mortality and morbidity [18]. Blood glucose control is crucial in preventing complications. For many adult patients without pregnancy, the glycemic target in blood sugar control is set at HbA1c ≤7 [19].

There are many studies showing that glycemic control worsens as the duration of T2DM increases. The main reasons for this include the lack of regular follow-ups, failure of patients to pay attention to their diets, and poor medication adherence [20]. There are also studies on the worsening of glycemic control with the diagnosis of T2DM at a young age and the length of disease duration [21,22]. In the scope of our research, we

discerned a correlation that holds statistical significance between the length of T2DM affliction and poor glycemic control. CRP elevation is often observed in relation to inflammation. As glycemic control deteriorates, CRP levels increase [23]. Our investigation demonstrated a statistically significant correlation between an augmentation in CRP levels and compromised glycemic control. There are studies showing a linear relationship between high triglyceride levels and high HbA1c levels [24]. In addition to its relationship with glycemic control, high HbA1c levels are also considered to be an effective indicator of lipid profile [25]. Although not statistically significant, our study showed that the group with poor glycemic control had high levels of triglycerides and LDL.

NLR can be used as a non-invasive, easy, and economical indicator in the evaluation of systemic inflammation. This indicator can be easily obtained through complete blood count analysis. Some studies have shown a relationship between NLR and T2DM [26]. Others have shown that as glycemic control deteriorates, NLR levels increase [27]. In our investigation, a statistically meaningful increase in NLR was noted in T2DM patients lacking effective glycemic control.

Research has suggested that T2DM patients have inadequate lymphocyte proliferation. One study indicated that there may be an increase in NLR due to a decrease in lymphocyte count caused by hyperglycemia [28]. In our study, the lymphocyte count was lower in T2DM patients with uncontrolled disease, and this was statistically significant. Several research investigations have identified a positive association between HbA1c and WBC counts in patients afflicted with T2DM [29]. Other studies suggest that elevated WBC counts are associated with impaired insulin sensitivity in T2DM patients [30]. In our study, WBC count was found to be higher in uncontrolled T2DM patients; however, this difference did not reach the threshold of statistical significance.

Research has shown an increase in TLR ratio in relation to increased platelet count in T2DM patients [31]. Our study found that TLR was high in patients with poor glycemic control, but this was determined to be statistically insignificant.

**Limitations**

There are some limitations in the current study. First, the possibility of error cannot be ruled out, since laboratory measurements were made only once. Second, because the study design was retrospective, patients could not be reached to measure height, weight, and body mass index, which affect NLR and other parameters. Third, the single center where the study was conducted is a factor limiting the external validity of those measured. In addition, sampling sizes and sampling groups were obtained from only one region; therefore, data from different situations and larger sampling groups need to be validated before the outcomes of this research can be generalized to a larger sample.

**Conclusion**

T2DM is a chronic, multisystemic disease whose impact extends beyond hyperglycemia to a broader range of complications including inflammatory pathologies. The association of inflammation with T2DM underscores the relevance of inflammatory markers, such as NLR and TLR, as potential indicators of glycemic control in individuals with T2DM. Our study illuminates a possible relationship between the levels of HbA1c and values of NLR and TLR, particularly in patients presenting poor glycemic control. This association amplifies the significance of managing inflammation alongside improving glycemic control as integral strategies in T2DM management. Given the relatively novel nature of research within this area, there is a noticeable paucity of studies exploring these relationships. Thus, our findings fill a critical gap in the existing literature, serving as a robust platform for further investigations. In light of these insights, it becomes increasingly evident that integrating the monitoring of inflammatory markers into the treatment regimen could provide a more comprehensive understanding of disease progression and treatment efficacy in T2DM. As such, we anticipate that future research endeavors will further elucidate the mechanistic links between inflammation, NLR and TLR values, and glycemic control, thereby refining therapeutic strategies for T2DM and mitigating its associated complications.

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# The anxiety level of healthcare professionals and hospital support staff during the COVID-19 pandemic

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**Ethics Committee Approval**
The study was approved by Erzincan University clinical research ethics committee (05/24). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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## Abstract

**Background/Aim:** The coronavirus 2019 (COVID-19) pandemic has placed a significant psychological burden on healthcare professionals. This study aims to identify the anxiety levels of healthcare professionals and non-healthcare personnel during the pandemic.

**Methods:** This cross-sectional study was conducted on healthcare professionals during the pandemic, and we attempted to reach all personnel without setting a specific sample size. Participants completed a survey that included demographic information and the State-Trait Anxiety Inventory (STAI). We compared anxiety scores and working conditions between healthcare and non-healthcare personnel during the pandemic.

**Results:** Our study included 204 personnel, with 45.1% being healthcare professionals and 54.9% non-healthcare professionals. The mean state anxiety score for all participants was 44.7 (10.3). Female professionals, those working in intensive care, and personnel who believed they lacked sufficient protection training had significantly higher mean anxiety scores ($P$=0.001, $P$=0.006, $P$<0.001, respectively). Participants with mild or no problems initiating and maintaining sleep and waking up early had lower mean anxiety scores ($P$<0.001). There was no statistically significant difference between healthcare professionals and non-healthcare personnel in mean scores ($P$=0.59).

**Conclusion:** Our study found that all personnel experienced medium-level anxiety during the pandemic, indicating an increased risk for hospital staff. The fact that non-healthcare personnel had similar anxiety scores to healthcare professionals highlights the need for psychosocial interventions to support all hospital staff, regardless of their role in patient care.

**Keywords:** healthcare professionals, anxiety, hospital support staff, pandemic

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## Introduction

The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus in Wuhan, China, on December 31, 2019, quickly led to the global coronavirus disease 2019 (COVID-19) pandemic [1]. The first case of COVID-19 in Turkey was reported on March 11, 2020.

Coronaviruses are zoonotic, meaning they can be transmitted from animals to humans and cause human diseases [2]. Human-to-human transmission is primarily through contact and droplet spread from sneezing or coughing. The clinical characteristics of COVID-19 are not distinct from other viral respiratory tract infections, and most individuals may have mild symptoms or be asymptomatic. However, severe cases may lead to acute respiratory failure and death. The World Health Organization (WHO) has identified fever, fatigue, and dry cough as common symptoms, but shortness of breath, myalgia, sore throat, and diarrhea have also been reported [3].

Previous research has shown that pandemics can cause significant trauma and increase anxiety levels in individuals [4-6]. Healthcare professionals on the front line of the COVID-19 pandemic and directly involved in diagnosing, treating, and caring for patients with COVID-19 are at higher risk of developing high-level stress and anxiety [7,8]. During the SARS pandemic in 2003, healthcare professionals reported symptoms of long-term and high-level stress, anxiety, and depression.

Support staff, such as administrative personnel, secretaries, and cleaning personnel, who work alongside healthcare professionals in hospital environments, may also experience stress during the pandemic, despite not being directly involved in patient follow-up and treatment. This study aims to identify the anxiety levels of healthcare professionals and support staff during the pandemic.

## Materials and methods

This descriptive study was conducted on healthcare professionals and support staff at Erzincan Mengücek Gazi Training and Research Hospital, with ethical approval granted by the clinical research ethics committee of Erzincan University (approval number: 05/24). We attempted to reach all personnel without setting a specific sample size, and participants were included in the study after providing informed consent. All participants completed a survey form that included demographic information and the State-Trait Anxiety Inventory (STAI).

The STAI is a self-evaluation questionnaire with 20 short phrases developed by Spielberger et al. [9] to assess an individual's current anxiety level. Respondents rate how they feel at a given time and under certain conditions using a scale of 1 (not at all) to 4 (very much so), with a total score range of 20 to 80. Higher scores indicate a higher level of anxiety [10]. The Turkish adaptation, validity, and reliability study of the STAI was conducted by Öner and Le Compte [11].

**Statistical analysis**

Data analysis was performed using the statistical software "SPSS for Windows 22.0.1 Standard Version". The chi-square test was used to compare sociodemographic characteristics among the groups, while T-tests, Pearson's correlation test, and One-way analysis of variance (ANOVA) were used to compare numeric data such as age and inventory results. All numerical values were reported as means (standard deviations). The significance level was set at $P<0.05$.

## Results

More than half (55.9%) of the participants in our study were female, with a mean age of 36.1 (8.0). Most (71.1%) were married, 72.5% were university graduates, 13.7% had a chronic disease, and 6.4% had a history of psychiatric diseases. Of the personnel included in our study, 45.1% were healthcare professionals, including 24% physicians and 21% nurses, while 54% were non-healthcare personnel, such as medical secretaries, cleaning services, technicians, civil servants, and security officers.

Of the personnel included in our study, 47% worked in patient wards and outpatient clinics during the COVID-19 pandemic, and 45.6% had reduced working hours during this period. It was reported that 79.9% of participants had encountered COVID-19 patients, 97% considered the likelihood of encountering patients to be medium-high, and 36.8% frequently feared being infected. While 52.5% of participants believed that training on COVID-19 infection and protection was sufficient, 55.4% felt that hospital personnel did not take adequate protection measures.

A mere 8.8% of the personnel in our study reported receiving psychological support during the pandemic. Sleeping patterns were also evaluated, and it was found that participants had difficulties initiating sleep (35.3%), maintaining sleep (38.2%), and waking up early (34.8%).

The mean State Anxiety Inventory score for our study group was 44.7 (10.3) (range: 20–71). Pearson's correlation test was used to compare age and mean state anxiety scores, but no correlation was found (r=0.00, $P=0.99$). There was also no significant difference in mean scores based on years of professional experience or the presence of chronic or psychiatric diseases ($P=0.60$; $P=0.70$, respectively).

Table 1 shows the mean state anxiety scores for various sociodemographic and work-related characteristics. Female staff had higher mean anxiety scores than male staff ($P=0.001$). Although the mean anxiety scores for single personnel with primary school education were not significantly different from those of other groups, they were slightly higher ($P=0.62$; $P=0.58$, respectively). Although healthcare professionals had a higher mean anxiety score than non-healthcare personnel, there was no statistically significant difference ($P=0.59$). Mean anxiety scores were higher in intensive care personnel than those working in administrative services and operating rooms ($P=0.006$). The mean anxiety score was lower in personnel who believed they had sufficient training on protection against COVID-19 infection compared to personnel who believed the training was insufficient or those who did not receive any training ($P<0.001$).

The mean scores were significantly higher in personnel receiving psychiatric support during the pandemic and those with a frequent or high-level fear of being infected ($P=0.004$ and $P<0.001$, respectively). Examining sleeping patterns during this period, mean anxiety scores were significantly lower in those with mild or no problems initiating sleep, maintaining sleep, or

waking up early than those with moderate or severe sleeping problems ($P$<0.001) (Table 2).

Table 1: Some characteristics of participants and mean state anxiety scores.

| | n | % | State anxiety score mean (SD) | *P*-value |
|---|---|---|---|---|
| **Age** | 36.1 (8.0) | | r=0.00 | 0.99 |
| **Gender** | | | | |
| Female | 114 | 55.9 | 46.9 (10.9) | 0.001 |
| Male | 90 | 44.1 | 41.8 ( 9.9) | |
| **Marital Status** | | | | |
| Married | 145 | 71.1 | 44.4 (10.5) | 0.62 |
| Single | 59 | 28.9 | 45.2 (10.0) | |
| **Education Level** | | | | |
| Primary School | 9 | 4.4 | 48.1 ( 9.8) | 0.58 |
| High School | 47 | 23.0 | 44.2 (10.8) | |
| University | 148 | 72.5 | 44.6 (10.3) | |
| **Position** | | | | |
| Healthcare professional | 92 | 45.1 | 45.1 (10.8) | 0.59 |
| Non-healthcare professional | 112 | 54.9 | 44.3 (10.0) | |
| **Change in working hours** | | | | |
| None | 75 | 36.8 | 43.4 (10) | 0.12 |
| Increasing | 36 | 17.6 | 47.7 (12.0) | |
| Decreasing | 93 | 45.6 | 44.5 (9.8) | |
| **Unit** | | | | |
| Emergency | 33 | 16.2 | 44.6 (8.5) | 0.006 |
| Operation room | 19 | 9.3 | 40.9 (10.9) | |
| Ward | 52 | 25.5 | 46.3 (10.7) | |
| Intensive care | 12 | 5.9 | 54.5 (8.5) | |
| Outpatient Clinic | 44 | 21.6 | 44.3 (10.3) | |
| Laboratory | 5 | 2.5 | 44.2 (4.4) | |
| Administrative services | 39 | 19.1 | 41.8 (10.3) | |
| **The state of training on infection** | | | | |
| No | 41 | 20.1 | 46.9 (9.9) | <0.001 |
| Yes, sufficient | 107 | 52.5 | 41.7 (10.1) | |
| Yes, insufficient | 56 | 27.5 | 48.6 (9.5) | |
| **Are protection measures sufficient?** | | | | |
| No | 113 | 55.4 | 45,8 ( 9,6) | 0.07 |
| Yes | 91 | 44.6 | 43,2 (11) | |

SD: Standard deviation

Table 2: Some characteristics of participants and mean state anxiety scores

| | n | % | State Anxiety Score mean (SD) | *P*-value |
|---|---|---|---|---|
| **Psychiatric support** | | | | |
| No | 186 | 91.2 | 44.0 (10) | 0.004 |
| Yes | 18 | 8.8 | 51.4 (11.9) | |
| **Fear of being infected** | | | | |
| Not at all | 5 | 2.5 | 30.6 (11.9) | <0.001 |
| Sometimes | 67 | 32.8 | 40.8 (9.1) | |
| Frequently | 75 | 36.8 | 44.4 (7.9) | |
| Very much so | 57 | 27.9 | 50.8 (11.1) | |
| **Sleeping problems** | | | | |
| **Difficulty in initiating sleep** | | | | |
| None | 56 | 27.5 | 39.3 (9.4) | <0.001 |
| Mild | 72 | 35.3 | 44.0 (9.9) | |
| Moderate | 61 | 29.9 | 48.8 (9.5) | |
| Severe | 15 | 7.4 | 51.0 (9.2) | |
| **Difficulty in maintaining sleep** | | | | |
| None | 61 | 29.9 | 41 (9.2) | <0.001 |
| Mild | 78 | 38.2 | 44.7 (9.5) | |
| Moderate | 53 | 26.0 | 46.9 (11.3) | |
| Severe | 12 | 5.9 | 53.2 (10.3) | |
| **Waking up early** | | | | |
| None | 71 | 34.8 | 41.1 (9.8) | <0.001 |
| Mild | 66 | 32.4 | 44 (9.4) | |
| Moderate | 52 | 25.5 | 48.5 (10.6) | |
| Severe | 15 | 7.4 | 51.2 (9) | |

SD: Standard deviation

Table 3 compares some characteristics of healthcare professionals and non-healthcare personnel working at our hospital during the COVID-19 pandemic. There was no significant difference between healthcare professionals and non-healthcare personnel regarding psychiatric support and fear of being infected ($P$=0.29 and $P$=0.48, respectively). While 62% of healthcare professionals believed that protection measures against the pandemic were insufficient, 50% of non-healthcare personnel thought the measures were sufficient. Regarding changes in working hours, healthcare professionals had fewer working hours, while non-healthcare personnel had no changes in working hours ($P$<0.001). Regarding sleeping problems, healthcare professionals had moderate to severe problems initiating and maintaining sleep compared to non-healthcare professionals and had no problems waking up early compared to non-healthcare personnel ($P$=0.005, $P$=0.01 and $P$=0.01, respectively).

Table 3: Comparing some of the characteristics in healthcare professionals and non-healthcare personnel

| | Healthcare professionals n (%) | Non-healthcare personnel n (%) | *P*-value |
|---|---|---|---|
| **Psychiatric support** | | | |
| No | 86 (93.5%) | 100 (89.3%) | 0.29 |
| Yes | 6 (6.5%) | 12 (10.7%) | |
| **The fear of being infected** | | | |
| Never / Sometimes | 29 (31.5%) | 43 (38.4%) | 0.48 |
| Frequently | 34 (37%) | 41 (36.6%) | |
| Very much so | 29 (31.5%) | 28 (25%) | |
| **Are protection measures enough?** | | | |
| No | 57 (62%) | 56 (50%) | 0.08 |
| Yes | 35 (38%) | 56 (50%) | |
| **Sleeping problems** | | | |
| **Difficulty in initiating sleep** | | | |
| None | 27 (29.3%) | 29 (25.9%) | 0.005 |
| Mild | 21 (22.8%) | 51 (45.5%) | |
| Moderate | 36 (39.1%) | 25 (22.3%) | |
| Severe | 8 (8.7%) | 7 (6.3%) | |
| **Difficulty in maintaining sleep** | | | |
| None | 31 (33.7%) | 30 (26.8%) | 0.01 |
| Mild | 27 (29.3%) | 51 (45.5%) | |
| Moderate | 24 (26.1%) | 29 (25.9%) | |
| Severe | 10 (10.9%) | 2 (1.8%) | |
| **Waking up early** | | | |
| None | 37 (40.2%) | 34 (30.4%) | 0.01 |
| Mild | 19 (20.7%) | 47 (42%) | |
| Moderate | 27 (29.3%) | 25 (48.1%) | |
| Severe | 9 (9.8%) | 6 (5.4%) | |
| **Changes in working hours** | | | |
| None | 13 (14.1%) | 62 (55.4%) | <0.001 |
| Increasing | 22 (23.9%) | 14 (12.5%) | |
| Decreasing | 57 (62%) | 36 (32.1%) | |

## Discussion

The COVID-19 pandemic caused by the novel coronavirus is a global public health emergency. As with any infectious disease, healthcare systems must respond rapidly to the pandemic, with healthcare professionals bearing the brunt of the burden in developing a response.

Insufficient knowledge about the new virus causing the disease, the rapidly increasing demand for healthcare services, and the lack of information on the disease have led to heightened psychological states such as anxiety, stress, and depression, which were already prevalent in the general population. Numerous studies have examined the psychological states of healthcare professionals during pandemics [12-15]. However, there is a lack of research on non-healthcare professionals working in administrative, cleaning, or secretarial positions who have direct contact with healthcare professionals as an essential component of the healthcare system.

The mean anxiety score of all personnel in our study was 44.7 (10.3), indicating moderate anxiety. Mean scores were similar in healthcare professionals and non-healthcare personnel. Several studies have reported high anxiety levels, particularly among healthcare professionals, during pandemics [12,13,16,17]. Factors such as increased workload, lack of protective equipment, and delayed implementation of measures may contribute to higher anxiety levels in healthcare professionals. The use of a different inventory in our study compared to other studies and the flexible working hours of healthcare professionals may account for the differences in mean anxiety scores found. Additionally, although not directly involved in patient care, the fact that non-healthcare personnel were affected

by the increased workload and provided services in a high-risk hospital environment may explain their similar levels of anxiety to healthcare professionals.

Our study found that female personnel and those working in intensive care had significantly higher mean anxiety scores than male personnel and those working in administrative units. Like our findings, Lai et al. reported that women and frontline workers in China during the COVID-19 pandemic had a higher risk of developing negative psychiatric outcomes [13]. Elbay et al. also found that women and personnel in direct contact with infected patients had high mean anxiety scores in a study conducted in Turkey, in line with our results [12]. Our study suggests that personnel who received sufficient training on protection against the COVID-19 pandemic had significantly lower mean anxiety scores than those who received insufficient training or thought the training was inadequate. Training is a critical step before or after the outbreak of communicable diseases. In particular, protection training has a positive impact on individuals' physical and mental health.

It was concluded that individuals who feared being infected had significantly higher mean anxiety scores. Like Zhu et al.'s study [18], it was demonstrated that the fear of being infected with the virus or by one of their family members was a risk factor for developing anxiety. The fear of infection was compared between healthcare professionals and non-healthcare personnel, and like Lu et al.'s study [17], no significant difference was found between the two groups. Several studies have strongly associated stress with sleep quality [19-21]. Increasing anxiety affects sleep quality, which can cause difficulty initiating sleep or frequent wake-ups during sleep [21]. In our study, we found that the anxiety level was higher in personnel with sleeping problems, and similarly, we concluded that healthcare professionals had more sleeping problems than non-healthcare personnel. Many studies conducted during the pandemic have reported that sleeping disorders pose a potential risk, especially for healthcare professionals under stress [5,13,14,22].

**Limitations**

Our study has several limitations. First, it is a cross-sectional study with a small sample size. The changing working conditions of hospital employees during the COVID-19 pandemic made it challenging to reach enough participants. Second, this study relied on subjective self-reported questionnaires to obtain data, which may have resulted in biases due to the excessive workload in the hospital. As a result, the statistical analyses may have been affected by these issues beyond our control. Therefore, future studies should include a larger sample cohort to investigate the effects of social support on the anxiety and sleep quality of healthcare professionals working with increased stress and workload.

**Conclusion**

In our study, we found that all personnel working at our hospital had moderate-level anxiety. Healthcare professionals and non-healthcare personnel showed similar anxiety levels during the COVID-19 pandemic. Working in the same environment may have contributed to increased anxiety levels, even for those who did not have direct contact with patients. While it is important to protect the physical health of healthcare professionals, it is equally important to protect the mental health of non-healthcare personnel who work alongside them in the hospital environment. This study highlights the need for interventions and support systems to address the mental health needs of all personnel working in healthcare settings during pandemics.

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Research article

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# Assessment of the risk for cholecystitis when performing laparoscopic cholecystectomy in a retrospective cohort study

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**Ethics Committee Approval**
The study was approved by the Ethics Committee of CHC Kosovska Mitrovica (5191/14.09.2022). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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## Abstract

**Background/Aim:** Acute cholecystitis most often occurs as an acute exacerbation of chronic cholecystitis. In over 90% of patients, the primary factor in the development of acute cholecystitis is the obstruction of the gallbladder or cystic duct with an impacted calculus. In less than 10% of patients, acute cholecystitis can be attributed to other causes: direct trauma to the biliary tract, torsion of the gallbladder, twisting of the vascular loop after surgical procedures on the abdominal organs, and *Salmonella typhi* infection. The aim of this study is to compare preoperative variables in patients with acute cholecystitis, which are not only important for diagnosis but also have significance in determining the severity of acute cholecystitis in the preoperative period.

**Methods:** This retrospective systematic research included all clinical cases diagnosed with acute cholecystitis from January 2019 to December 2019, totaling 56 patients at CHC Kosovska Mitrovica. For the study, data from medical records were used for statistical analysis.

**Results:** A total of 56 patients (mean age 53 years; 26 men and 30 women) were included in this study. Among them, 32 patients (57.15%) had characteristics of simple cholecystitis, while 24 patients (42.85%) had severe cholecystitis. The group with severe cholecystitis consisted of older patients, with equal representation of both sexes, and higher levels of WBC, NE%, PLT, ALT, GGT, total bilirubin, and CRP ($P<0.05$). Imaging studies showed that the group with severe cholecystitis exhibited significantly more wall distension, particularly in the stratified wall, compared to the group with simple cholecystitis ($P<0.05$). Severe cholecystitis was associated with statin use (79.2%) and triglyceride values of 1.55 (0.47); both variables showed a statistically significant association with severe cholecystitis ($P<0.05$).

**Conclusion:** It is extremely important to skillfully identify patients with simple or severe forms of acute cholecystitis. Possible solutions include organizing campaigns to raise public awareness for faster consultations in cases of acute abdominal pain, establishing universal health coverage (diet), and improving technical platforms.

**Keywords:** cholecystitis, acute, statins

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## Introduction

Acute cholecystitis is an inflammatory process characterized by gallbladder distension, wall thickening, exudate formation, and the presence of pericholecystic fluid [1]. This disease is one of the most common gastrointestinal diseases that requires hospitalization and surgical treatment [2]. The most common cause of cholelithiasis is the deposition of cholesterol, which later forms cholesterol stones [3]. Symptomatic cholelithiasis is manifested by biliary colic, which refers to acute severe pain attacks localized in the right upper quadrant or epigastrium, lasting 15 to 30 minutes or longer [4]. Early diagnosis and staging of acute cholecystitis enable rapid treatment and reduce mortality and morbidity [5]. C-reactive protein (CRP), white blood cell count (WBC), and platelet count (PLT) are well-known hematological and biochemical predictors of severe inflammation [2]. Acute cholecystitis is one of the most common complications associated with gallstones and exhibits varying degrees of severity, with early laparoscopic cholecystectomy being the currently recommended best treatment [1,6,7]. Only 5% of patients develop gallstone-related complications such as cholecystitis, cholangitis, or biliary pancreatitis, while the remaining 95% remain free of biliary complications [4]. Cholecystectomy is one of the most common surgical procedures with a low rate of complications. "Severe" complications occur in about 2% and 5% of laparoscopic and open surgeries, respectively [8]. Laparoscopic cholecystectomy for complicated cases of acute cholecystitis is associated with the risk of vasculobiliary injuries and requires good surgical skills [9]. The aim of this study is to compare preoperative variables in patients with acute cholecystitis, which are not only important for diagnosis but also have significance in determining the severity of acute cholecystitis in the preoperative period.

## Materials and methods

The retrospective systematic research included all clinical cases diagnosed with acute cholecystitis in the period from January 2019 to December 2019, totaling 56 patients at CHC Kosovska Mitrovica. The sample size of the study was determined based on the number of respondents within the specified period. For the research, data from medical records were used for statistical analysis. The data collected for the study included age, sex, medical history, laboratory analyses (WBC, NE%, PLT, ALT, GGT, CRP, total bilirubin), and medical diagnosis (ultrasound examination).

### Statistical analysis

The statistical data processing was performed using the software program SPSS Statistics 20 (SPSS INC, Chicago, IL, USA). All numerical values were reported as means (standard deviations), while categorical variables were presented as percentages. Statistical significance between frequencies was assessed using the chi-square test ($\chi 2$), with a criterion for statistical significance set at $P<0.05$.

## Results

In this study, a total of 56 patients (mean age 53 years; 26 men and 30 women) were included. Among them, 32 patients (57.15%) had characteristics indicative of simple cholecystitis, while 24 patients (42.85%) had severe cholecystitis. Table 1 presents the comparison of preoperative variables between patients with simple cholecystitis and severe cholecystitis. The analysis revealed statistically significant differences in several variables, including white blood cells (WBC), percentage of neutrophils (NE%), platelets (PLT), alanine transaminase (ALT), gamma glutamyl transaminase (GGT), total bilirubin, C-reactive protein (CRP), and ultrasound findings, with all *P*-values being less than 0.05. Specifically, the group with severe cholecystitis consisted of older patients, with both sexes being equally represented. Furthermore, this group exhibited higher levels of WBC count, NE%, PLT, ALT, GGT, total bilirubin, and CRP compared to the group with simple cholecystitis ($P<0.05$).

Table 1: Demographic and preoperative characteristics of patients who underwent laparoscopic cholecystectomy for cholecystitis

| | Total patients (n=56) | Simple cholecystitis (n=32) | Severe cholecystitis (n=24) | *P*-value |
|---|---|---|---|---|
| **Age** | | | | 0.187 |
| **Mean (SD)** | 51.57 (14.51) | 49.34 (12.67) | 54.54 (16.47) | |
| **Median** | 52 | 52 | 52 | |
| **Gender** | | | | 0.847 |
| **Male** | 26 (46.4%) | 14 (43.75%) | 12 (50%) | |
| **Female** | 30 (53.6%) | 18 (56.25%) | 12 (50%) | |
| **Comorbidity** | | | | 0.243 |
| **Yes** | 36 (64.3%) | 18 (56.25%) | 18 (75%) | |
| **No** | 20 (35.7%) | 14 (43.75%) | 6 (25%) | |
| **DSBO** | | | | 0.947 |
| **<a month** | 16 (28.6%) | 9 (28.1%) | 7 (29.2%) | |
| **>3 month to a year** | 20 (35.7%) | 11 (34.4%) | 9 (37.5%) | |
| **>a year** | 20 (35.7%) | 12 (37.5%) | 8 (33.3%) | |
| **WBC** | | | | 0.045 |
| **Mean (SD)** | 11.58 (5.05) | 7.93 (1.99) | 16.45 (3.50) | |
| **Median** | 10.76 | 7.67 | 15.94 | |
| **NE%** | | | | 0.038 |
| **Mean (SD)** | 74.01 (12.59) | 65.64 (10.20) | 85.17 (3.34) | |
| **Median** | 78 | 66.67 | 84.90 | |
| **PLT** | | | | 0.209 |
| **Mean (SD)** | 274.47 (60.22) | 265.64 (57.80) | 286.23 (62.59) | |
| **Median** | 266.10 | 264.80 | 268.05 | |
| **ALT** | | | | 0.041 |
| **Mean (SD)** | 56.94 (41.99) | 30.00 (24.69) | 94.91 (30.21) | |
| **Median** | 42 | 23 | 89.50 | |
| **GGT** | | | | 0.016 |
| **Mean (SD)** | 56.41 (41.89) | 36.23 (29.64) | 87.70 (39.18) | |
| **Median** | 44 | 27 | 84 | |
| **Total bilirubin** | | | | 0.031 |
| **Mean (SD)** | 13.92 (5.50) | 10.47 (3.40) | 19.19 (3.52) | |
| **Median** | 14.10 | 10.75 | 18.40 | |
| **CRP** | | | | 0.042 |
| **Mean (SD)** | 23.82 (24.13) | 7.80 (4.74) | 46.11 (22.47) | |
| **Median** | 13.60 | 7.40 | 42.30 | |
| **Ultrasound findings** | | | | 0.050 |
| **No changes** | 23 (41.1%) | 23 (71.9%) | 0 (0%) | |
| **Distension** | 18 (32.1%) | 6 (18.8%) | 12 (50%) | |
| **Layered wall** | 15 (26.8%) | 3 (9.4%) | 12 (50%) | |

DSBO: duration of symptoms before operations

Then, specific variables were compared between groups (Table 2). These two groups showed significant differences in the use of drugs from the group "statins" and triglyceride values. Severe cholecystitis was associated with statin use (79.2%) and triglyceride values 1.55 (0.47), both variables showed a statistically significant association with severe cholecystitis ($P<0.05$) (Table 2).

Table 2: Correlation of preoperative characteristics of patients with calculous cholecystitis

| | Total patients (n=56) | Simple cholecystitis (n=32) | Severe cholecystitis (n=24) | *P*-value |
|---|---|---|---|---|
| **Statins preoperatively** | | | | 0.026 |
| **Yes** | 28 (50%) | 9 (28.1%) | 19 (79.2%) | |
| **No** | 28 (50%) | 23 (71.9%) | 5 (20.8%) | |
| **Smoking status** | | | | 0.286 |
| **Yes** | 34 (60.7%) | 17 (53.1%) | 17 (70.8%) | |
| **No** | 22 (39.3%) | 15 (46.9%) | 7 (29.2%) | |
| **Alcohol** | | | | 0.341 |
| **Don't use it** | 29 (51.8%) | 19 (59.4%) | 10 (41.7%) | |
| **≤ 2 cups** | 17 (30.4%) | 9 (28.1%) | 8 (33.3%) | |
| **> 2 cups** | 10 (17.8%) | 4 (12.5%) | 6 (25%) | |
| **Cholesterol** | | | | 0.370 |
| **Mean (SD)** | 4.94 (1.63) | 4.77 (1.68) | 5.17 (1.57) | |
| **Median** | 5.10 | 4.80 | 5.70 | |
| **Triglycerides** | | | | 0.013 |
| **Mean (SD)** | 1.37 (0.53) | 1.25 (0.54) | 1.55 (0.47) | |
| **Median** | 1.22 | 1.14 | 1.49 | |
| **$Ca^+$** | | | | 0.621 |
| **Mean (SD)** | 2.40 (1.66) | 2.41 (0.12) | 2.38 (0.22) | |
| **Median** | 2.41 | 2.42 | 2.35 | |

## Discussion

It is indeed crucial to develop proficient identification skills for distinguishing between patients with a simple or severe form of acute cholecystitis. Possible solutions to achieve this goal include organizing campaigns to raise public awareness about the importance of seeking prompt medical consultation in cases of acute abdominal pain, establishing universal health coverage (including dietary aspects), and improving technical platforms for accurate diagnosis and treatment. CRP, being an independent and non-specific systemic marker for inflammation, correlates with the severity of surgical trauma, infection, and inflammation. Significant differences exist in the initial levels of CRP, WBC, and percentage of neutrophils (Ne%) [2]. The complicated form of cholecystitis is characterized by older age, higher WBC count, elevated neutrophil count, increased CRP levels, and ultrasound findings indicative of gallbladder abnormalities [10]. Ultrasound variables such as gallbladder wall thickness and stratification are more commonly observed in severe cholecystitis cases that require conversion to open surgery [1]. The prevalence of gallstones is significantly higher in women compared to men [9]. In previous studies, the average age of patients was reported to be 45.1 (11.1) years, with a majority of female patients [11]. The average total bilirubin value was 1 mg/dl (55.6 µmol/L), which is considerably higher than the average in our study, and no correlation was found between total bilirubin and the severity of cholecystitis. The average WBC was 12.6, which is approximately similar to the values observed in our study. On admission, CRP levels were reported to be 88.4, which does not align with our findings [12]. It is important to acknowledge the limitations of this study, including the small number of subjects with acute cholecystitis. Subjects diagnosed with chronic cholecystitis or gallbladder polyposis were excluded from the study, which may impact the generalizability of the findings.

### Conclusion

Based on the analysis of anamnestic data, laboratory analyses, radiological diagnostics, and operative findings, a total of 56 patients were included in this study. Among them, 32 patients exhibited characteristics indicative of simple cholecystitis, while 24 patients had severe cholecystitis. The group with severe cholecystitis consisted of older patients, with both sexes being equally represented. Additionally, this group demonstrated higher levels of WBC, NE%, PLT, ALT, GGT, total bilirubin, and CRP. Imaging studies revealed significant distension, particularly in the gallbladder wall, in the group with severe cholecystitis. Furthermore, the use of statins and triglyceride levels of 1.55 (0.47) were significantly associated with severe cholecystitis. These variables can serve as risk factors for predicting severe cholecystitis with high accuracy in the preoperative period.

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# Differentiation of glioblastoma, brain metastases and central nervous system lymphomas using amount of vasogenic edema and diffusion MR imaging of tumor core and peritumoral zone- Searching for a practical approach

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**Ethics Committee Approval**
The study was approved by institutional review board of Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital (2022-04/75).
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.

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## Abstract

**Background/Aim:** The differential diagnosis of solitary brain tumors poses challenges for clinicians and radiologists, often leading to invasive biopsy procedures. Therefore, this study aimed to evaluate the variations in edema volume and diffusion characteristics between the tumor core and peritumoral zone in cases of glioblastoma, brain metastasis, and central nervous system lymphoma. The aim was to identify additional parameters for conventional magnetic resonance imaging (MRI) that could aid in the differential diagnosis.

**Methods:** A total of 39 patients (13 with central nervous system lymphoma, 13 with glioblastoma, and 13 with brain metastases) were included in this retrospective cohort study. Apparent diffusion coefficient (ADC) values were calculated from the ADC maps obtained from Brain MRI for both the lesion and peritumoral region. Additionally, the largest diameter of the vasogenic edema-mass complex was measured using T2 sequences. In the contrast-enhanced series, the largest diameter of the metastatic lesion was measured. The edema-mass ratio was determined by dividing the diameter of the edema-mass complex by the diameter of the mass.

**Results:** There was a statistically significant difference in the edema-mass ratio among the tumor types ($P$=0.008). Further analysis using Bonferroni correction revealed that this difference was primarily due to glioblastoma. Compared to patients with lymphoma and brain metastases, lesions diagnosed as glioblastoma exhibited a lower edema-mass ratio. Additionally, a statistically significant difference was observed in the ADC value measured from the lesion according to the tumor type ($P$=0.017). It was determined that lesions associated with central nervous system lymphoma had lower ADC values than those with glioblastoma.

**Conclusion:** Including lesional and perilesional ADC values obtained through diffusion-weighted examination and edema mass ratio measurements may enhance the accuracy of differential diagnosis. Utilizing these imaging characteristics in a multiparametric approach, as suggested by this research, can improve the accuracy of diagnosing malignant cancers, thereby enabling better patient management and treatment decisions.

**Keywords:** magnetic resonance imaging, brain edema, brain neoplasms, neuroimaging

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## Introduction

Pre-treatment characterization and differential diagnosis of malignant brain tumors remain problematic in daily clinical practice, particularly when distinguishing between glioblastoma, metastasis, and central nervous system lymphomas (CNSLs) in solitary brain lesions using conventional magnetic resonance imaging (MRI) [1].

Accurate initial diagnosis and appropriate subsequent treatment are crucial factors that significantly impact patient monitoring and management. The treatment choice can vary significantly depending on the type of brain lesion, emphasizing the importance of accurate differential diagnosis [1-3]. Currently, many patients undergo invasive biopsy procedures to aid in the differential diagnosis process.

Standard MR imaging offers valuable information for the differential diagnosis of solitary malignant brain tumors. For instance, CNSLs typically appear as homogeneously enhanced masses on contrast-enhanced T1-weighted sequences, particularly in immunosuppressed patients. In contrast, glioblastomas often exhibit ring-like lesions with central necrosis. However, it is important to note that solid-enhancing glioblastoma lesions lacking necrosis can resemble CNSLs, while atypical CNSLs with necrosis may mimic glioblastoma lesions [4,5]. Metastatic tumors, conversely, can present with a wide range of distinct imaging features.

Despite the availability of publications on advanced MR techniques, such as diffusion-weighted imaging (DWI), dynamic susceptibility-weighted contrast-enhanced perfusion-weighted imaging (DSC-PWI), and susceptibility-weighted imaging, the accurate characterization and differential diagnosis of malignant brain tumors remain a significant challenge in current radiology practice [6-8].

By quantifying physiological differences in water diffusion, DWI assists in detecting microscopic structural changes that may not be apparent in conventional MR examination. The apparent diffusion coefficient (ADC) provides a quantitative measure of diffusion characteristics. Tumors with high cellularity often exhibit restricted diffusion and consequently have low ADC values. As a result, ADC is considered a valuable marker for tumor cellularity [9,10].

Primary or secondary malignant brain tumors are often accompanied by perilesional vasogenic edema. While the precise pathophysiology of peritumoral edema remains unclear, it is recognized that the extent of peritumoral edema can vary depending on the histopathological and clinical characteristics of the tumor [11].

Our objective was to assess the disparities in edema volume and diffusion characteristics between the tumor core and peritumoral zone among cases of glioblastoma, brain metastasis, and central nervous system lymphoma. This evaluation aimed to identify supplementary parameters for conventional MR examination that could aid in the differential diagnosis.

## Materials and methods

Our institutional review board, at the Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital, has approved this retrospective study (2022-04/75). Prior to contrast-enhanced imaging, informed consent was obtained from the patients.

We retrospectively evaluated patients who underwent brain MRI at our radiology clinic between January 2019 and January 2022. The inclusion criteria for this evaluation were patients diagnosed with a supratentorial solitary brain tumor, whose diagnosis was pathologically confirmed, and who underwent follow-up.

Patients meeting the following criteria were excluded from the study: those who did not undergo brain MRI prior to surgery or radiation therapy, those for whom clinical information could not be obtained, those without a definitive diagnosis, and those diagnosed with a neurodegenerative disease.

Consequently, the study included a total of 39 patients, consisting of 13 cases of CNSL, 13 cases of glioblastoma, and 13 cases of brain metastases. All the identified lesions were located in the supratentorial region and were accompanied by perilesional edema.

**MRI Examination and Post-processing**

All imaging procedures were conducted using a 1.5 T MR scanner (Signa Exp, GE Medical Systems) equipped with a 16-channel HNS (head-neck-spine) coil. A standard MR examination was performed prior to contrast administration, which included axial T1-weighted images, axial, coronal, and sagittal T2-weighted images, and axial FLAIR images. Additionally, as per the standard protocol, a post-contrast 3D T1W sequence was acquired. Throughout the entire MR examination, patients were instructed to keep their eyes closed, and no sedation or anesthesia was administered to any of the patients.

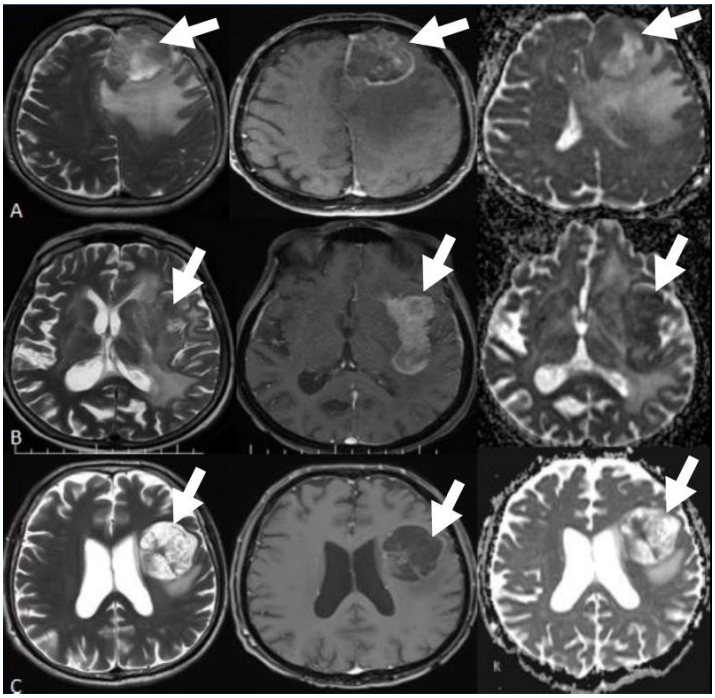
DWI was conducted using a transverse single-shot echo-planar sequence with the following parameters: TE (Echo Time) of 89.9 ms, TR (Repetition Time) of 8000 ms, a slice thickness of 5 mm, FOV (Field of View) of 26 cm, matrix size of 128 × 128, NEX (Number of Excitations) of 1, and diffusion-sensitive gradients with b-values of 1000 s/mm$^2$ in three orthogonal directions.

Two experienced radiologists, each with over ten years of Brain MRI expertise, assessed the MRI images. ADC values were derived from the central and peritumoral regions of the lesions, specifically within a 1 cm distance from the lesion border, using the ADC maps of the patients. Calculations were made using a similar and small ROI (5 mm$^2$).

When necrosis was present, measurements were conducted excluding the necrotic area. The smallest ADC value was determined based on three measurements for each lesion, and the corresponding peritumoral region was documented.

Furthermore, the T2 sequences were utilized to measure the largest diameter of the vasogenic edema-mass complex. In the contrast-enhanced series, the largest diameter of the metastatic lesion was measured. Lastly, the edema-mass ratio (EMR) was determined by dividing the diameter of the edema-mass complex by the diameter of the mass. The case samples were presented in Figure 1.

Figure 1: T2, contrast–enhanced T1 and ADC maps of supratentorial, solitary brain tumors (arrows); (A): Glioblastoma, (B): CNSL, (C): Solitary metastasis.




CNSL: central nervous system lymphoma

### Statistical analysis

For the statistical analysis of the study findings, the Statistical Package for the Social Sciences version 25.0 (IBM Corp., Armonk, NY, USA) software was utilized. Descriptive, graphical, and statistical methods were employed to assess the distribution of scores obtained from each continuous variable. The Shapiro-Wilk test assessed the normality of scores derived from continuous variables. Descriptive statistical methods, such as numbers, percentages, means, medians, standard deviations, were employed to evaluate the research data. Additionally, for comparisons involving more than two groups in quantitative data with a normal distribution, ANOVA (variance) analysis was performed. Data that did not exhibit a normal distribution were analyzed using the Kruskal-Wallis test.

The Bonferroni test was employed to identify the specific groups from which the differences originated. Pearson's chi-square tests were conducted for qualitative group comparisons. ROC (Receiver Operating Characteristic) analysis was utilized to determine the most suitable edema mass ratio and lesion ADC for differentiation in the presence of a glial brain tumor. The significance level was set at a 95% confidence interval with a threshold of $P$ <0.05.

## Results

The mean age of the 39 patients included in the study was 58.00 (13.41) years, ranging from 24 to 80 years. Of the participants, 64.1% were male. No statistically significant difference was observed in age distribution and gender representation across different tumor types ($P$=0.705 for age, $P$=0.120 for gender).

A statistically significant difference in EMR was found among different tumor types ($P$=0.008). Further analysis using the Bonferroni method revealed that this difference was primarily driven by glioblastoma. Patients diagnosed with glioblastoma exhibited lower EMR than those with lymphoma and brain metastases.

A statistically significant difference was observed in the ADC value measured from the lesion based on tumor type ($P$=0.017). The Bonferroni analysis indicated that this difference specifically existed between patients with glioblastoma and lymphoma. Consequently, it was determined that lesions associated with CNSL exhibited lower ADC values than those with glioblastoma. There was no significant difference in peritumoral ADC values according to tumor type ($P$=0.098). Patient and lesion characteristics according to tumor types are summarized in Table 1.

Table 1: Distribution of Patient Characteristics by Tumor Type (n=39)

| | **All (n=39)** | **Glioblastoma[1] (n=13)** | **CNSL[2] (n=13)** | **Metastasis[3] (n=13)** | | | |
|---|---|---|---|---|---|---|---|
| **Variables** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | $\chi 2/F/K\text{-}W_{\chi 2}$ | ***P*-value** | **dif** |
| **Gender** | | | | | $\chi^2$=4.234 | 0.120 | |
| Female | 14(35.9) | 2(15.4) | 7(53.8) | 5(38.5) | | | |
| Male | 25(64.1) | 11(84.6) | 6(46.2) | 8(61.5) | | | |
| | **Mean(SD)** | **Mean(SD)** | **Mean(SD)** | **Mean(SD)** | | | |
| **Age** | 58.00(13.41) | 60.08(13.49) | 55.62(16.00) | 58.31(10.98) | $F$=0.352 | 0.705 | |
| **EMR** | 2.24(0.75) | 1.73(0.46) | 2.46(0.79) | 2.53(0.72) | $K\text{-}W_{\chi 2}$=9.633 | 0.008* | 1<2,3 |
| **Lesion ADC** | 0.74(0.21) | 0.85(0.18) | 0.62(0.16) | 0.77(0.22) | $F$=4.569 | 0.017* | 1>2 |
| **Perilesional ADC** | 1.36(0.25) | 1.47(0.23) | 1.26(0.23) | 1.34(0.25) | $F$=2.478 | 0.098 | |

*$P$<0.05, CNSL: central nervous system lymphoma, EMR: edema-mass ratio, *F:* One-Way ANOVA (analysis of variance); $\chi 2$*:* Chi-Square Test; $K\text{-}W_{\chi 2}$: Kruskal-Wallis-H Test, SD: Standard deviation, dif: difference

The results of the ROC analysis revealed that the area under the curve (AUC) for EMR in determining the presence of glioblastoma was 0.81 (95% CI: 0.66-0.95). This indicates a statistically significant diagnostic value of EMR in identifying the presence of glioblastoma ($P$=0.002).

Following the ROC analysis, the optimal EMR value for glioblastoma was determined to be 1.82. At this cutoff value, the sensitivity was 69.2%, specificity was 84.6%, positive predictive value (PPV) was 69.2%, negative predictive value (NPV) was 84.6%, and overall accuracy was 79.5%.

Furthermore, the AUC for the lesion ADC value in diagnosing glioblastoma was determined to be 0.71 (95% CI: 0.54–0.88). Consequently, the lesion ADC value exhibited statistical significance in its ability to diagnose glioblastoma ($P$=0.037).

Following the ROC analysis, the optimal ADC value for glioblastoma was determined to be 0.83. At this cutoff value, the

sensitivity was 53.8%, specificity was 84.6%, PPV was 63.6%, NPV was 78.6%, and overall accuracy was 74.4% (Table 2).

Table 2: Optimal Cut off Value for EMR and Lesion ADC min Value in Determining the Presence of GBM (ROC Analysis Results)

| | | Glioblastoma | | Glioblastoma |
|---|---|---|---|---|
| EMR | Cutoff value | ↓1.82 | Lesion ADC Value | ↑0.83 |
| | AUC(%95 CI) | 0.805(0.660-0.950) | | 0.707(0.536-0.878) |
| | *P*-value | 0.002 | | 0.037 |
| | Sensitivity | 69.2%(9/13) | | 53.8%(7/13) |
| | Specificity | 84.6%(22/26) | | 84.6%(4/26) |
| | PPV | 69.2%(9/13) | | 63.6%(7/11) |
| | NPV | 84.6%(22/26) | | 78.6%(22/28) |
| | Accuracy | 79.5%(31/39) | | 74.4%(29/39) |

GBM: glioblastoma

## Discussion

Our study unveils that the diffusion characteristics and the extent of edema might offer certain advantages in the differential diagnosis of solitary malignant brain tumors with perilesional edema, a task that proves challenging using standard conventional MR examination. Consequently, our study evaluated the diffusion characteristics of the lesion, the perilesional region, and the extent of edema, aiming to determine their diagnostic value.

In the present study, we identified a statistically significant distinction in the measured ADC values from the lesion based on the tumor type, specifically between lymphoma and glioblastoma. Notably, lymphoma patients exhibited significantly lower ADC values. Previous studies in the literature have predominantly focused on evaluating ADC values for the differential diagnosis of glioblastoma (GBM) and metastasis. While some studies have reported significant differences in ADC values [10,12], others have found no substantial variance [13]. Furthermore, literature reports indicate lower ADC values in lymphoma cases than other malignant tumors attributed to the tumor's histology. Lymphomas are characterized by giant cells and a reduced extravascular space, which has been postulated as the underlying reason for restricted diffusion and lower ADC values [3].

Glioblastoma, known for its high aggressiveness and extensive infiltration, is recognized to exhibit infiltration in both the perilesional area and the contrasting tumor cortex. On the other hand, in metastasis cases, perilesional edema is typically attributed to pure vasogenic edema resulting from compression of the surrounding tissue. Previous studies have consistently demonstrated that the perilesional area in glioblastoma cases is associated with low ADC values, whereas metastases tend to display higher ADC values [14-17].

The study involved 74 cases of solitary malignant brain tumors, consisting of 27 glioblastomas, 30 metastases, and 17 CNSLs. The findings revealed a notable disparity in the ADC values measured from the perilesional area between metastasis and glioblastoma cases, indicating a significant difference. Conversely, no significant distinction was observed in CNSLs.

In contrast to the existing literature, our study did not identify a statistically significant difference in ADC values within the perilesional region among these three tumor types.

In contrast to the previous studies in the literature that examined perilesional edema regardless of lesion size, our study focused on assessing the significance of the EMR in the context of the differential diagnosis. By comparing the extent of perilesional edema, we observed that lesions diagnosed with glioblastoma exhibited lower EMR values than patients with lymphoma and brain metastases.

To our knowledge, no other publication in the English literature has compared cases of GBM, metastasis, and lymphoma based on the extent of perilesional edema.

### Limitations

Despite the encouraging results, the research has several restrictions. First, the study's sample size was relatively small, restricting the data's capacity to be generalized. Second, the analysis only included individuals with glioblastoma, brain metastases, and CNSLs as their sole histologically confirmed diagnoses; this may not accurately reflect the complete range of brain malignancies seen in clinical practice. Third, since the research was retrospective, it had biases and limitations. Fourth, the study did not assess the diagnostic efficacy of other imaging modalities, which may be complementary in the differential diagnosis of these malignancies, such as perfusion-weighted imaging or magnetic resonance spectroscopy.

To confirm the results of this investigation and provide more precise diagnosis algorithms for these brain tumors, more extensive prospective trials that include a wider variety of imaging modalities are required.

### Conclusion

In conclusion, our study demonstrates that the combination of lesional and perilesional ADC values measured by diffusion-weighted examination and edema mass ratio measurements can potentially increase the accuracy of differential diagnosis between glioblastoma, brain metastases, and central nervous lymphoma. Furthermore, the study suggests that a multiparametric approach utilizing these imaging parameters may improve the diagnostic accuracy of these malignancies, enabling better patient management and treatment decisions.

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# A retrospective cohort study investigating the etiology of primary spontaneous pneumothorax in children: Radiological and genetic analysis

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**Ethics Committee Approval**
The necessary permissions were obtained from the families and the institution for the study. The study was approved by the Balikesir University Faculty of Medicine Clinical Research Ethics Committee (2021/259). 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.

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## Abstract

**Background/Aim:** Spontaneous pneumothorax is a serious health concern due to its life-threatening nature. It occurs when air sacs in the lungs rupture, causing air to accumulate in the chest cavity and making normal breathing difficult. Primary spontaneous pneumothorax (PSP) refers to the accumulation of air in the pleural space without any traumatic or iatrogenic cause. The objectives of our study are to identify the predisposing factors in PSP patients, determine which patients should undergo genetic analysis, and present the results of a new treatment algorithm.

**Methods:** This study is a retrospective cohort analysis of children diagnosed with PSP and admitted to the emergency department or pediatric surgery clinic. The study evaluates demographic data, radiological findings, and molecular genetic analyses of these patients. Treatment planning was conducted using thoracic computed tomography (CT) or high-resolution computed tomography (HRCT) after the acute phase, and eligible patients were selected for genetic analysis based on syndromes commonly associated with PSP.

**Results:** The study included 14 patients, 10 boys and four girls, with an average age of 16.14 (0.95) years. PSP was detected on the right side in nine male patients and on the left side in one male patient, while in girls, it was detected on the right side in two patients and on the left side in two patients. Radiological findings included air cysts, fibrotic changes, and pleural thickening. Folliculin (FLCN) mutation was detected in two patients after genetic analysis.

**Conclusion:** In the stratified treatment protocol, radiological findings were used as a guide, and the detection of possible syndromic mutations by genetic analysis was deemed important for future management.

**Keywords:** primary spontaneous pneumothorax, video-assisted thoracic surgery, child, lung

## Introduction

Pneumothorax is a condition where air accumulates in the pleural cavity, causing partial or complete lung collapse. Spontaneous pneumothorax is a serious health concern due to its life-threatening nature. It occurs when air sacs in the lungs rupture, causing air to accumulate in the chest cavity and making normal breathing difficult. This condition is a medical emergency because increasing air pressure in the chest can hinder the functioning of the heart, major blood vessels, and other organs, potentially leading to death if left untreated. Additionally, spontaneous pneumothorax is a recurring problem with a high risk of recurrence, requiring continued monitoring and further treatment if necessary. Primary spontaneous pneumothorax (PSP) refers to the accumulation of air in the pleural space without any traumatic or iatrogenic cause [1]. The incidence rate of PSP is approximately 18-28/100,000 per year for men and 1.2-6/100,000 per year for women [2]. The most common cause of PSP is the rupture of apical subpleural blebs, and it mainly affects young, tall, and thin men [3]. The treatment of PSP varies significantly, resulting in significant heterogeneity in treatment approaches [4]. The objectives of our study are to identify the predisposing factors in PSP patients, determine which patients should undergo genetic analysis, and present the results of a new treatment algorithm.

## Materials and methods

The study is a retrospective cohort study in which the potential causes of a spontaneously occurring outcome are examined during the study period without any intervention. In this particular study, the outcome under investigation is PSP, and its possible causes were explored during the study period. The study sample comprises cases of primary spontaneous pneumothorax who sought medical attention at the emergency department between January 2019 and December 2021 and were subsequently admitted to the pediatric surgery clinic. The participants were requested to return to the hospital for the study, and their demographic data, radiological findings, and molecular genetic analyses were conducted to determine the causes of PSP.

Upon admission to the emergency department, chest X-rays were obtained in all cases following initial medical history and examinations. In appropriate cases, thorax computed tomography (CT) was also performed. Once pneumothorax was diagnosed, follow-up or intervention decisions were made based on the extent of lung atelectasis. Treatment planning was subsequently carried out with thorax CT or high-resolution computed tomography (HRCT) after the acute phase. The clinical protocol utilized in the treatment of the cases is outlined below.

1. If the distance between the lung and chest wall is less than 1 cm (in the form of a collapse) and there is no respiratory distress, only serial chest X-rays and/or thorax CT/HRCT are performed, and the patient is followed up in the service or intensive care unit.
2. If the distance is between 1-2 cm, needle aspiration under ultrasound guidance is performed, and the patient is followed up in the intensive care unit with serial chest X-rays and CT/HRCT.
3. If the distance is larger than 2 cm, sedation is applied, and tube thoracostomy (TT) is performed under surgical conditions, and the patient is followed up with serial chest X-rays and CT/HRCT, and intensive care unit monitoring is performed for air leakage- oscillation.
4. Autologous blood patch application in cases where air leakage continues (repeated twice if necessary).
5. Segmentectomy and pleurodesis with video-assisted thoracoscopic surgery (VATS) in cases where air leakage continues.
6. Segmentectomy and pleurodesis with thoracotomy in cases where air leakage continues.

Participants who were discharged after successful treatment were invited for a follow-up examination during the study period, and their demographic characteristics were documented. In addition, genetic analysis was requested from the participants to assess the presence of syndromes commonly associated with PSP. Fourteen patients were invited for a follow-up examination, but three of them declined to undergo genetic testing. The remaining 11 patients underwent genetic analysis.

**Radiological assessment:** The initial evaluation was performed by the surgeon, who subsequently made necessary treatment and follow-up decisions. An anteroposterior chest X-ray obtained upon admission to the hospital was sufficient to determine whether follow-up or TT was required. Thorax CT or high-resolution thorax CT (HRCT) was used to identify lesions and plan possible interventions once respiratory distress and lung expansion had subsided. A single radiologist evaluated chest radiographs, CT, and/or HRCT images of all patients under elective conditions. The primary pathological findings observed included air cysts (blebs), pleural thickening, and fibrotic changes. The thorax CT slices were 1 cm, and the HRCT slices were 2 mm (with 0.8 mm spacing).

**Genetic analysis:** Genetic analysis was requested from patients on a voluntary basis to identify possible gene mutations and syndromes. Eleven patients agreed to the genetic analysis request.

**DNA isolation:** 200 µl of peripheral venous blood sample collected in an EDTA tube was taken from all patients included in this study. DNA isolations from peripheral blood were performed according to the standard procedure of the High Pure PCR Template Preparation Kit (Roche, Germany). DNA concentrations were measured using Qubit 3.0 (Invitrogen dsDNA HS Assay Kit).

Permissions were obtained from the participating families and institution for this study, and approval was granted by the Balikesir University Faculty of Medicine Clinical Research Ethics Committee (2021/259). Traumatic and iatrogenic pneumothorax cases were excluded from the study.

**Statistical analysis**

Statistical analyses were performed using MedCalc for Windows, version 19.1 (MedCalc Software). A normal distribution of the data was verified using the Kolmogorov-Smirnov test. The homogeneity of variance was determined using the Levene test. The level of statistical significance was set at *P*-value less than 0.05.

## Results

Between January 2019 and December 2021, 14 patients were treated for PSP. Ten of the patients were male, and four were female. The average age of the patients was 16.14 (0.95) years. PSP was detected on the right side in nine male patients and on the left side in one male patient, while in females, it was detected on the right side in two patients and on the left side in another two patients.

The complaints that brought the patients to the emergency room were difficulty breathing and back pain. Five male patients presented to the emergency room with symptoms that had started more than 6 hours prior, while the others presented within 1 hour.

Out of the 14 patients in our cohort, only one recovered with follow-up alone (protocol 1). TT was applied to the remaining 13 patients (protocol 3). All but three of them (patients 11, 13, and 14) were successfully treated. One of the remaining three patients (patient 11) received an autologous blood patch (protocol 4), but despite it being repeated twice, the air leak did not close. Consequently, segmentectomy with VATS (protocol 5) was performed on all three patients.

The mean tube withdrawal time was 3.2 (0.35) days, and the mean body mass index (BMI) of all patients was 20.7. The mean BMI was 20.53 in the patients who underwent protocol 3, while it was 21.03 in those who underwent protocol 5, but the difference was not statistically significant.

Radiological pathology was detected in three of the patients who underwent protocol 3 and in all three patients who underwent protocol 5.

Genetic analysis was performed on 11 of the 14 patients, and the results are shown in Table 1. Among these patients, Folliculin (FLCN) mutation was detected in two individuals (patients 11 and 12), but no similarities were observed in terms of BMI, radiological pathology, or treatment protocol.

Table 1: Patient information

| No | Gender | Side | BMI | Radiologic findings | Genetic analysis | Treatment steps |
|---|---|---|---|---|---|---|
| **1** | M | R | 21.4 | Normal | NA | 1 |
| **2** | M | R | 20.9 | **Air cysts** | NA | 3 |
| **3** | M | R | 22.7 | Normal | NA | 3 |
| **4** | F | L | 19.8 | Normal | Normal | 3 |
| **5** | M | R | 21.6 | **Air cysts** | Normal | 3 |
| **6** | M | R | 20.4 | Normal | Normal | 3 |
| **7** | M | R | 19.6 | Normal | Normal | 3 |
| **8** | F | R | 19.4 | **Pleural thickening** | Normal | 3 |
| **9** | F | L | 19.5 | Normal | Normal | 3 |
| **10** | M | L | 23.1 | **Air cysts** | Normal | 3 |
| **11** | M | R | 20.4 | **Air cysts, Pleural thickening** | Mutation + | 3-4-5 |
| **12** | M | R | 18.3 | Normal | Mutation + | 3 |
| **13** | F | R | 19.2 | **Air cysts, Fibrotic changes** | Normal | 3-5 |
| **14** | M | R | 23.5 | **Air cysts, Fibrotic changes** | Normal | 3-5 |
| **Total** | 4 F<br>10 M | 11 R<br>3 L | 20.7 | 7 Normal<br>7 Pathologic | 2 Abnormal | |

M: Male, F: Female, R: Right, L: Left, BMI: Body Mass Index, NA: Not applicable

## Discussion

Pneumothorax is a condition characterized by the entry of air between the two layers of the pleura. It can develop due to various causes, such as trauma, infection, iatrogenic factors, or idiopathic-spontaneous reasons. The most common symptom of pneumothorax is respiratory distress. Spontaneous pneumothorax is often observed in adolescent boys, typically on the right side of the thorax.

The guidelines for treating PSP prepared by the British and American Thoracic Societies are designed for adults. According to these guidelines, if the distance between the thoracic wall and the lung tissue is between 2 and 3 cm, the condition is considered serious, and intervention is recommended. However, there are differences in the thorax structure between adults and children, as well as in how the severity of pneumothorax presents clinically in these populations. As a result, the use of these guidelines is limited in pediatric cases. For this reason, our clinic has developed a partially different treatment algorithm [5]. This algorithm suggests that needle aspiration may be the first treatment option if the pneumothorax is below 20% of the thoracic surface area. For patients with a higher percentage of pneumothorax, the application of a chest tube may be sufficient. If neither treatment is successful, further surgical intervention should be considered [6].

High-resolution computed tomography (HRCT) has been described as an excellent technique for studying lung diseases in children. It can be very helpful in confirming the presence and extent of lung disease. When combined with clinical findings, HRCT can suggest an accurate clinical diagnosis and eliminate the need for biopsy [5,7]. It is particularly useful in children with diffuse airways and interstitial lung disease [8,9]. In our series of patients with PSP, air cysts (blebs), pleural thickening, and fibrotic changes are often observed during radiological evaluation. It is important to note that air cysts smaller than 1 cm can be easily detected by taking a 2 mm cross-sectional slice with HRCT. However, cysts smaller than 1 cm (2 mm cross-section - 8 mm gap) that do not enter the cross-sectional area may be overlooked.

Thorax CT involves taking 1 cm sections, which allows for the detection of all lesions in that range but with low resolution. Following CT scans, 3D studies are performed to increase the probability of detecting lesions with sagittal and coronal sections. In our series, no significant superiority was found between thorax CT and HRCT due to these factors.

The stepped treatment protocol was found to make decision-making and planning easier based on the clinical conditions and radiological variables of the patients. Patients 11, 13, and 14 were considered to have advanced-stage PSP due to recurrent complaints and/or continued air leakage. It is unclear whether the radiological findings of fibrotic changes and pleural thickening were due to a previous infection. Based on anamnesis and background information, these patients were diagnosed with PSP since no infection was detected prior to admission. It was observed that the patients had a low BMI and asthenic body structure, leading to the consideration of examining the development of PSP in tall and thin children in terms of a potential syndromic problem.

Pneumothorax can sometimes be a symptom of a multisystem genetic syndrome, which can be divided into three classes: 1) those caused by mutations in tumor suppressor genes, 2) connective tissue disorders, and 3) syndromes in which the normal lung architecture is deleted [1,10]. Studies have found that mutations in the FLCN gene can cause pneumothorax in

children, resulting in either a single event or recurrent attacks [9]. To detect possible genetic causes of pneumothorax, thoracic CT and genetic testing are recommended [1,9]. Although the function of the FLCN gene is not yet known, studies in mice have demonstrated that it regulates the mammalian target of Rapamycin (mTOR) pathway [1]. In Birt-Hogg-Dubé syndrome (BHD), which is characterized by skin fibrofolliculomas, multiple lung cysts, spontaneous pneumothorax, and kidney cancer, mutations in the FLCN gene have been detected. FLCN is located on chromosome 17p11.2 and contains 14 exons that encode folliculin, an evolutionarily conserved protein consisting of 579 amino acids with no significant homology to any other human protein [8]. In BHD, the incidence of PSP is high, and the risk of kidney cancer is seven times higher [8,9]. The European BHD consortium has reported that patients with PSP and FLCN mutations have a high risk of renal malignancy, regardless of familial phenotype [7].

**Limitations**

The severity of complaints in PSP cases may differ when radiological and genetic results are evaluated together. Radiological pathology may not be revealed in every patient, and the probability of detecting a genetic abnormality is uncertain. Although our series had a limited number of patients, genetic mutations were not found to be significant in children with PSP. While providing genetic counseling to these children and their families to detect syndromic problems is important, genetic analysis cannot be recommended for all PSP cases based on our current knowledge.

**Conclusions**

It should be noted that PSP may develop in cases with low BMI values and FLCN mutations detected for another reason. Since classical treatment protocols are insufficient in children, the stratified treatment protocol is guided by radiological findings. The creation of prospective series will shed light on the future of PSP treatment in children.

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Research article

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# A new obesity treatment method that does not require restriction in food intake and organ resection

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**Ethics Committee Approval**
The study was approved by the Experimental Animals Local Ethics Committee of Bezmialem Vakif University (April 2021/no: 21-046).

**Conflict of Interest**
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## Abstract

**Background/Aim:** There are numerous treatment methods available for obesity, with bariatric surgery being the most effective. However, these techniques come with the risk of serious complications. This study presents a novel obesity treatment device that can shorten the length of the small intestine without the need for surgical intervention.

**Methods:** Our new device comprises three main components: a 25 cm long rope, with one end attached to a 1 cm diameter plastic ring and the other end attached to a 2 mm diameter, 5 g sphere. Twenty-one male Wistar albino rats (6 months old, mean weight 400 g, outbred) were divided into three equal groups. Laparotomy and gastrotomy were performed on the subjects in Group 1, and all three parts of the device were placed into the gastrointestinal tract. In Group 2, only the plastic ring was placed in the stomach, and in Group 3, only a gastrotomy was performed. All subjects were followed for 3 months, during which their body weight, serum ghrelin, leptin, and nesfatin-1 levels were recorded, and the amount of food they consumed was measured. After sacrificing the animals, the stomach, proximal, and distal intestines were resected for histopathological evaluation.

**Results:** The subjects in Group 1 experienced weight loss, whereas those in Groups 2 and 3 showed statistically significant weight gain ($P$<0.001 and $P$=0.022, respectively). Serum ghrelin levels were significantly increased in Groups 1 and 3 ($P$=0.015 and 0.031, respectively), while serum leptin levels were significantly decreased in Group 1 ($P$=0.015). Plasma nesfatin-1 levels were significantly higher in Group 1 compared to the other groups ($P$=0.014). There was no statistically significant difference in feed consumption between the groups. Histopathological examination revealed significantly higher fibrosis and inflammation scores in the proximal small intestine of Group 1 compared to the other groups ($P$=0.008 and $P$=0.005, respectively).

**Conclusions:** This new device facilitates rapid and effective weight loss without the need for restricting oral food intake or organ resection. Changes in serum ghrelin, leptin, and nesfatin-1 levels did not affect these results. We hypothesize that the effective weight loss is linked to the shortening of the small intestine length. Our future plans involve modifying the device for endoscopic application in humans.

**Keywords:** obesity, treatment, new, medical device, endoscopy, bariatric

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## Introduction

According to data from the World Health Organization (WHO) [1], obesity is recognized as the most serious health problem affecting humanity. It is a critical risk factor for cardiovascular diseases, diabetes, and cancer. Additionally, obesity reduces life expectancy by 5–20 years [2]. Various treatment options exist for combating obesity, ranging from dietary interventions to radical organ resections [3]. The primary approach to obesity treatment involves limiting calorie intake orally. A weight loss of 5–10% achieved through diet has been shown to reduce disease risk and have positive effects on health for individuals who are overweight or obese [4,5]. However, many individuals struggle to adhere to diets due to individual, medical, or psychological factors. In such cases, endoscopic or surgical interventions have been employed [6]. Surgical techniques can be classified as restrictive, malabsorptive, or a combination of both [7-9].

Due to its ability to deliver faster results compared to other treatment options, obesity surgery has become the method of choice in contemporary practice [1,10]. However, like any surgical procedure, it carries inherent risks of complications, some of which can be life-threatening. Additionally, obesity surgery is a costly treatment option [10]. This study introduces a novel obesity treatment approach that has not been previously described in the literature. Notably, this treatment can be administered endoscopically without the need for surgical intervention when applied to human subjects.

## Materials and methods

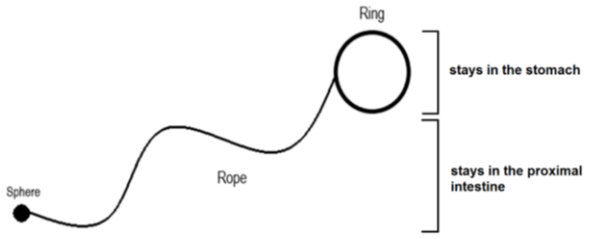
Consent was obtained from the Experimental Animals Local Ethics Committee of Bezmialem Vakif University (April 2021, no: 21-046). For the power analysis, we determined a sample size of 21 male Wistar albino rats (mean weight: 400 g), which were randomly assigned to three equal groups (n = 7). This allocation ensured a 95% confidence interval and a significance level of $P<0.05$. The rats were fed a standard pellet feed specifically designed for small experimental animals and were housed in cages made of plastic with stainless steel wire ceilings. The cages were layered with wood shavings and maintained on a 12-h light-dark cycle. Prior to surgery, all subjects underwent an overnight fasting period and were weighed. Additionally, 2 ml of blood was collected from each rat to measure serum levels of ghrelin, leptin, and nesfatin-1.

A new medical device (Figure 1) was utilized in this study, which was designed and patented by our team (Turkish Patent Institute Application No: 2019/00613). Our device comprises three main components: a 25 cm long rope, with one end connected to a plastic ring measuring 1 cm in diameter, and the other end attached to a 5 g sphere with a diameter of 2 mm.

The device structure consists of three main parts:

- **The stomach ring:** This ring is made of biologically inert plastic, measuring 2 mm in thickness and 10 mm in diameter. Its thinness ensures it does not impede the passage of food from the stomach to the duodenum, while its diameter is sufficiently large to prevent it from passing through the pylorus. The ring is connected to the rope, which in turn is attached to the sphere located in the small intestine.
- **The connecting rope:** A 25 cm long surgical rope, 3/0 in thickness, made of polypropylene, serves as the connection between the ring and the sphere. One end of the rope is connected to the ring inside the stomach, and the other end is attached to the sphere in the small intestine.
- **The small intestine sphere:** Constructed from stainless steel, this sphere has a diameter of 2 mm and weighs 5 g. It features a central hole for attaching the rope. The sphere is designed with a small diameter and a smooth surface to prevent the passage of food through the small intestine and to minimize any potential damage to the mucosa.

Figure 1: Graphical view of the device




All rats in the study underwent a midline abdominal incision while under general anesthesia. A 10 mm incision was made on the anterior surface of the stomach (gastrotomy). In Group 1 (n = 7), the ring, sphere, and rope were inserted into the stomach through this incision. The sphere was then carefully guided through the pylorus into the second part of the duodenum using forceps. Subsequently, the gastrotomy incision was sutured using 3/0 vicryl, and the abdominal incision was closed with 3/0 polypropylene. In Group 2 (n = 7), the same procedures were performed, but only the ring was placed into the stomach. In Group 3 (n = 7), only the gastrotomy procedure was carried out, with nothing inserted into the stomach.

Following the surgery, the subjects were provided with standard pellet food, and their daily food intake was measured. Weekly weight measurements were taken for all subjects. After a three-month follow-up period, the subjects were euthanized, and their stomachs and small intestines were excised for histopathological examinations. Blood samples were collected from all subjects on both day 0 (before surgical operations) and day 90 (after euthanization) to measure serum ghrelin, leptin, and nesfatin-1 levels.

**Statistical analysis**

The parameters of the rats included in the study were reported as mean (SD), and statistical analyses were conducted using GraphPad Prism 8.0 statistical software. Non-parametric evaluations between groups were performed using the Kruskal-Wallis test, and for determining statistical significance, Dunn's multiple comparison tests were applied. In-group statistical analysis of non-normally distributed groups was carried out using the Wilcoxon signed-rank test. For comparisons of data with normal distribution between the groups, the One-Way analysis of variance (ANOVA) test was utilized, and Tukey's post-hoc test was applied to determine statistical significance. The paired t-test was used for the statistical analysis of groups with a normal distribution. Histopathological examinations involved comparisons between groups using the Kruskal-Wallis test, and subgroup analyses were performed using the Mann-Whitney test to assess differences between the groups.

## Results

Weights increased in Groups 2 and 3 but decreased in Group 1 (Table 1). The differentiation between Group 1 and Group 3 was statistically significant ($P$<0.001). Food consumption was not statistically different among all groups during the 3-month follow-up period: Group 1 consumed 59.02 g/day, Group 2 consumed 63.81 g/day, and Group 3 consumed 69.03 g/day.

Table 1: In-group and intergroup weight changes in the preoperative and postoperative periods. (SD: Standard derivation, *: <0.05).

| | Group 1 | Group 2 | Group 3 | *P*-value (0ne way ANOVA) |
|---|---|---|---|---|
| **Preoperative weight mean (SD)** | 427.70 (49.75) | 387.40 (54.16) | 389.00 (56.83) | 0.305 |
| **Postoperative weight mean (SD)** | 366.40 (71.34) | 408.70 (70.39) | 413.30 (49.32) | 0.347 |
| **Weight differences (%)** | -14.3% | +5.4% | +6.1% | |
| ***P*-value (paired T-Test)** | <0.001* | 0.079 | 0.022* | |

Postoperative ghrelin values significantly increased in both Group 1 and Group 3 compared to their respective preoperative values (Table 2). A significant difference in plasma leptin levels was observed during the preoperative period ($P$=0.010). Subgroup analysis revealed that this difference was primarily attributed to variations between Group 2 and Group 3 ($P$=0.008). Only Group 1 exhibited a significant decrease in postoperative plasma leptin levels ($P$=0.015) (Table 3). Plasma nesfatin-1 levels were significantly higher in Group 1 compared to the other groups ($P$=0.014). In the group analysis, no changes were observed between the preoperative and postoperative periods in any of the groups (Table 4).

Table 2: Preoperative and postoperative in-group and intergroup plasma ghrelin changes. (SD: Standard derivation, *: <0.05).

| | Group 1 | Group 2 | Group 3 | *P*-value (Kruskal-Wallis) |
|---|---|---|---|---|
| **Preoperative ghrelin mean (SD)** | 11.27 (2.35) | 22.74 (18.63) | 10.62 (5.81) | 0.524 |
| **Postoperative Ghrelin mean (SD)** | 44.17 (22.66) | 31.18 (25.21) | 23.30 (10.94) | 0.202 |
| ***P*-value (Wilcoxon)** | 0.015* | 0.937 | 0.031* | |

Table 3: Preoperative and postoperative in-group and intergroup plasma leptin changes. (SD: Standard derivation, *: <0.05).

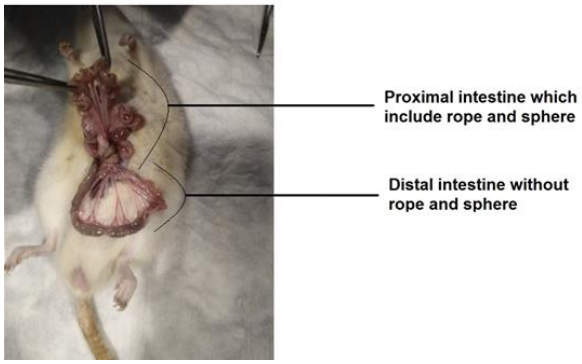
| | Group 1 | Group 2 | Group 3 | *P*-value (Kruskal-Wallis) |
|---|---|---|---|---|
| **Preoperative Leptin mean (SD)** | 3.07 (1.08) | 4.12 (1.06) | 2.19 (0.87) | 0.010* |
| **Postoperative Leptin mean (SD)** | 1.48 (0.76) | 2.97 (1.61) | 1.62 (0.85) | 0.129 |
| ***P*-value (Wilcoxon)** | 0.015* | 0.296 | 0.375 | |

Table 4: Preoperative and postoperative in-group and intergroup plasma nesfatin changes (SD: Standard derivation, *: <0.05).

| | Group 1 | Group 2 | Group 3 | *P*-value (Kruskal-Wallis) |
|---|---|---|---|---|
| **Preoperative Nesfatin mean (SD)** | 204.70 (60.46) | 259.10 (101.50) | 178.70 (34.20) | 0.277 |
| **Postoperative Nesfatin mean (SD)** | 259.3 (94.78) | 156.50 (63.40) | 107.6 (86.39) | 0.014* |
| ***P*-value (Wilcoxon)** | 0.296 | 0.078 | 0.156 | |

Macroscopic examination showed that the small intestines in Group 1 exhibited folding and shortening, while no changes were observed in the other groups (Figure 2). None of the subjects displayed signs of intestinal obstruction, such as kinking, dilatation, or peritoneal adhesion.

Figure 2: Laparotomy image of any Group 1 animal. The upper part of the image belongs to proximal and the lower part of the image belongs to the distal small intestine. It is obvious that the proximal small intestine is shortened and folded like an accordion over the intraluminal.




Histopathological evaluation of the stomach, proximal, and distal small intestines was conducted to assess fibrosis (Table 5) and inflammation (Table 6). The histopathological examination of gastric and distal small intestine specimens across all subjects revealed no significant differences in fibrosis and inflammation scores ($P$=0.061 and $P$=0.183, respectively, for fibrosis; $P$=0.424 and $P$=0.165, respectively, for inflammation). However, a significant difference was observed between the groups regarding fibrosis and inflammation in the proximal small intestine ($P$=0.001 and $P$=0.002, respectively). Subgroup analyses indicated that Group 1 had significantly higher fibrosis and inflammation scores than the other groups ($P$=0.008 and $P$=0.005, respectively).

Table 5: Classification of fibrosis histopathologically

| | |
|---|---|
| **Grade 0** | No fibrosis (no fibroblast and / or collagen fibers) |
| **Grade 1** | Minor fibrosis (few fibroblasts and / or collagen fibers) |
| **Grade 2** | Moderate fibrosis (more fibroblast and / or collagen fibers) |
| **Grade 3** | Advanced fibrosis (many fibroblasts and / or collagen fibers present) |

Table 6: Classification of inflammation histopathologically

| | |
|---|---|
| **Grade 0** | A few lymphocytes and plasmacytic cell in the mucosa |
| **Grade 1** | Increased number of mononuclear inflammatory cell infiltrations in the submucosa and lamina propria as a fallout |
| **Grade 2** | Increased number of mononuclear inflammatory cell infiltrates in the submucosa, lamina propria, and superficial muscular tissue, with partially aggregate-forming |
| **Grade 3** | Intense mononuclear inflammatory cell infiltration in all transmural layers |

## Discussion

Lifestyle regulation, diet, exercise, drug treatment, psychological, familial, and social support, as well as surgical interventions, are utilized in the current treatment of obesity [11]. Typically, obese patients can lose a significant amount of weight with an energy-restricted diet; however, they struggle to maintain this success in the long term [12,13]. Research shows that obese patients who lose weight through dieting tend to regain approximately 70% of the lost weight within 2 years [6,14]. Consequently, surgical treatment has become a frequently chosen option. Various techniques, such as organ resections, diversions, or bypass procedures, are employed in obesity surgery. However, these procedures come with serious complications and risks, including gastrointestinal tract disruption, anastomosis leakage, hemorrhage, pulmonary emboli, stenosis, infection, and sepsis, as well as bowel, liver, or major vessel injuries [15-20].

In this study, we evaluated a new patented medical device developed by our team, which primarily functions through the malabsorptive mechanism but possesses distinct characteristics. It is well-known that various types of food, particularly those high in sugar, are absorbed in the proximal small intestine. The extent of the small intestine's surface area

directly affects food absorption. Previous research has demonstrated that patients who undergo small bowel resection experience increased weight loss in relation to the length of the resected segment [21,22]. In this project, we aimed to decrease the surface area of the proximal small intestine without resorting to surgical intervention. We hypothesized that peristaltic movements would attempt to propel the sphere distally. However, the sphere is tethered to the ring by a rope, preventing the ring from passing through the pylorus. Consequently, tension arises between the ring and the sphere, causing the proximal small intestines to fold in a manner resembling an accordion around the intraluminal rope (see Figure 2). As a result, the absorptive area of the proximal small intestine is significantly reduced, even though oral food intake continues, leading to weight loss.

According to our hypothesis, we observed a statistically significant increase in weight among participants in Groups 2 and 3, whereas Group 1 showed a significant decrease in weight. It is important to note that food consumption among the study participants remained similar across all groups.

We assessed the changes in serum levels of three hormones (ghrelin, leptin, and nesfatin-1) associated with obesity before and after the intervention. Ghrelin is a hormone that typically rises during fasting, suppressing the postprandial period, and is considered a target in obesity treatment [23,24]. Increased basal ghrelin levels have been linked to increased eating behavior [25]. In this study, we observed elevated serum ghrelin levels in Groups 1 and 3. Consequently, despite participants in Group 3 gaining weight due to increased food intake, those in Group 1 experienced weight loss despite consuming comparable amounts of food. This finding aligns with the expected effects of elevated ghrelin levels.

Leptin is a hormone that typically suppresses appetite and food intake in individuals with normal weight, but in overweight and obese individuals, it can actually stimulate an increase in oral food intake [26-28]. Nesfatin-1, on the other hand, is an anorexigenic hormone that has been shown to reduce oral food intake by interacting with dopaminergic neurons [29,30]. Nesfatin-1 plays a role in maintaining body weight balance by reducing both oral food intake and gastrointestinal peristalsis [31]. In our study, we observed a decrease in serum leptin levels in Group 1, while Nesfatin-1 levels remained similar across all groups. However, when we analyzed the hormonal changes collectively among all subjects, we found that these hormonal changes did not significantly contribute to the mechanisms of weight loss.

In our view, the main mechanism behind the observed weight loss in this study is the reduction in the length of the proximal intestine, which leads to a decreased absorption area in the proximal small intestine. Our opinion is further supported by the results of the histopathological evaluation, which revealed significantly higher scores for fibrosis and inflammation in the proximal small intestine of Group 1.

The technique employed in this study offers a notable advantage in terms of its reversibility without the need for surgical intervention. If required, the rope can be cut endoscopically, allowing the rope and sphere to pass through the anus, while the ring can be removed endoscopically through the mouth. Furthermore, the amount of weight loss can be individually adjusted by modifying the length of the rope.

A significant limitation of this study was that due to the small size of the rats, we could not perform the procedures endoscopically and instead had to resort to laparotomy and gastrotomy. This limitation arises from the fact that our study subjects were small animals, and if larger animals were available for endoscopic procedures, it would have allowed for more precise interpretations regarding the applicability of our findings to humans.

Another limitation of this study is that we could not observe the potential diarrhea-inducing effect of the device in rats, as their defecation is continuous. However, it is important to note that the application of this device in humans may lead to diarrhea due to the shortened length of the small intestine.

The future research proposal for this study entails the development of biocompatible materials specifically designed for human anatomy, allowing for their endoscopic application. Once these materials are successfully produced, a phase 1 study can be initiated involving a limited number of morbidly obese patients, following the approval of the human ethics committee.

**Conclusion**

In conclusion, we have demonstrated the effectiveness of a novel obesity treatment technique that eliminates the need for surgical intervention, does not compromise gastrointestinal integrity, and does not impose restrictions on oral food intake. Our hypothesis regarding the weight loss outcomes being associated with the shortening of the small intestine length is supported by these promising results. However, to advance this device toward clinical applicability in humans, further development is required to create an endoscopically suitable form. Subsequently, small-scale studies should be conducted to evaluate its efficacy and safety in human subjects.

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Case report

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# Sealing of esophageal perforation with a fully covered biliary stent in a pediatric patient

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**Abstract**

Conservative treatment for esophageal perforations can cause problems related to both nutrition and wound healing in pediatric patients due to its long duration. This case report presents a 14-month-old female patient who underwent endoscopic balloon dilatation for esophageal stricture. The patient had been operated on for esophageal atresia in the neonatal period. Eight hours after discharge, the patient was hospitalized again due to esophageal perforation. Although conservative treatment lasting three weeks was the preferred method, it was unsuccessful. Therefore, a fully covered biliary stent was used instead of an esophageal stent, as the appropriate size stent could not be found. The stent sealed the perforation, and the patient started to be fed orally on the third day. The esophageal stent was removed on the 17th day, and no leakage was observed on the esophagogram. Although conservative methods are the first-line treatment for esophageal perforations in children, their long duration and the inability to feed for a long time are significant disadvantages. Fully covered self-expandable esophageal stents may be a reliable alternative for sealing esophageal perforations in pediatric patients, as they are in adults.

**Keywords:** esophageal perforation, conservative treatment, esophageal stent, fully covered self-expandable metallic stents, biliary stents, pediatrics

## Introduction

Iatrogenic esophageal perforation is a rare but serious complication that pediatric surgeons hope to avoid. It is mainly caused by therapeutic procedures performed endoscopically. Esophageal perforation can lead to various consequences, including localized para-esophageal abscess, diffuse mediastinitis, empyema, and even death [1]. As such, early diagnosis and treatment are vital.

Conservative methods are typically the preferred treatments for early-diagnosed and hemodynamically stable patients with esophageal perforations [2]. However, self-expandable esophageal stents and esophageal vacuum treatments are also effective methods [3,4]. If minimally invasive treatments fail or esophageal damage is severe, surgical treatment should always be considered a viable alternative [5].

In this case report, we describe the treatment of a 14-month-old girl who developed esophageal perforation after balloon dilatation. Despite an early diagnosis, conservative treatment lasting three weeks was unsuccessful. However, effective results were achieved within two weeks using a fully covered self-expandable biliary stent as an esophageal stent.

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**Informed Consent**
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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

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## Case presentation

A 14-month-old female patient who underwent esophageal atresia surgery during the neonatal period and had an anastomotic stricture underwent esophageal balloon dilatation. The patient was discharged on the same day after feeding without any problems. However, eight hours after discharge, the patient was brought to the emergency department complaining of inability to swallow and vomiting. No pathology was observed on the chest X-ray. The patient was hospitalized, and oral intake was stopped while intravenous fluid and electrolyte therapy were initiated.

The following morning, the patient developed significant respiratory distress, and an esophagogram (Figure 1) revealed esophageal perforation and right pneumothorax. The patient was taken to the operating room, and under general anesthesia, a chest tube, central venous catheter, and nasogastric tube were inserted. We decided not to perform surgical intervention for the primary repair of the esophageal perforation and instead opted for conservative management. The patient was started on broad-spectrum antibiotics and total parenteral nutrition.

On the fourth day, the patient removed the nasogastric tube. We decided not to reinsert it because the tube had been passing directly from the perforation site in the esophagus to the right thoracic cavity. Although the thoracic tube drainage did not decrease during the first week of follow-up, there was no significant change in the patient's general condition. Therefore, we decided to continue with the same treatment.

The patient's general condition was more stable in the second week than in the first. However, esophageal leakage was still present on the esophagogram at the end of the second week. Therefore, we decided to perform an esophagoscopy and insert a nasoduodenal tube. During the rigid esophagoscopy, we observed that the perforation was located just at the upper edge of the stricture and was approximately 5–7 mm in diameter. The relatively small size of the perforation led us to continue with conservative treatment. Although we attempted to feed the patient nasoduodenally, we could not pass the tube to the duodenum. This was a disappointment at the end of the third week.

We decided to place a stent in the esophagus. As no suitable fully covered self-expandable esophageal stent was available, we opted to use a fully covered nitinol biliary stent designed for adults as an esophageal stent. The stent we used was 8 cm in length, with a trunk section diameter of 10 mm and end diameters of 13 mm (Figure 2). A 6-cm stent may have been more suitable, but one was unavailable. To prevent stent migration, we tied it with a string and secured it on the nose side.

The first day after placing the stent was marked by restlessness and retching, leading us to consider removing the stent. However, the patient's symptoms subsided and stabilized on the following day. Chest tube drainage decreased from the first day, and we began feeding the patient orally on the third day after confirming no leakage on an esophagogram. On the seventh day, we removed the chest tube. We removed the esophageal stent on the 17th day, and an esophagogram showed no leakage (Figure 3). The patient continued with oral nutrition and was discharged on the 44th day with full recovery. Despite receiving total parenteral nutrition, the patient experienced significant weight loss of approximately 4–4.5 kg. She had no hemodynamically significant problems, but we had to transfuse her with red blood cell suspension twice. After six months, she was doing well with no complaints.

Figure 1: Esophageal leakage (black arrow) and right pneumothorax (white arrow: border of the collapsed lung).

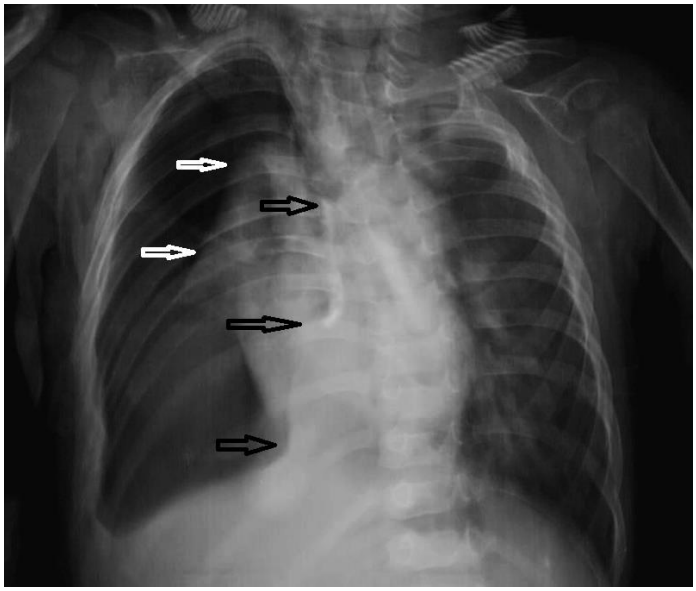


Figure 2: Fully covered self-expanded nitinol biliary stent in the esophagus (black arrow).

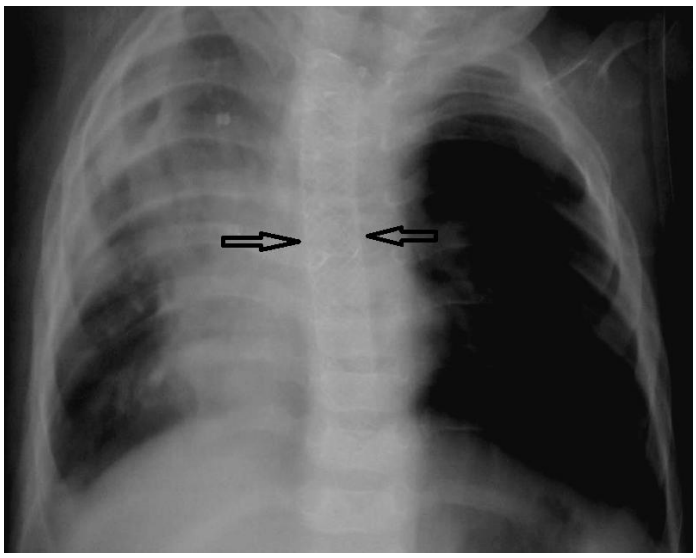
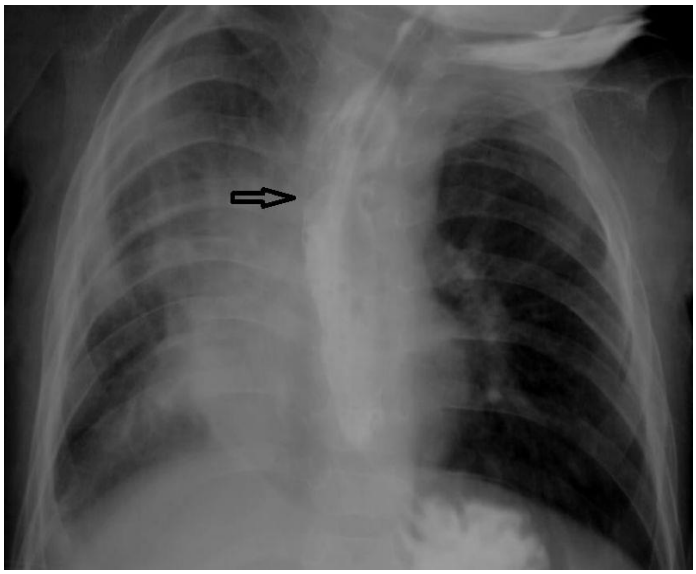


Figure 3: There was no leakage after the stent removal (black arrow: previous leakage site).



## Discussion

Esophageal perforation in children can be caused by blunt injury to the chest or neck, nasogastric tube placement, endotracheal intubation, caustic ingestion, foreign body ingestion, and endoscopic procedures [6]. Iatrogenic causes account for 77% of esophageal perforations, with an incidence rate of approximately 0.6% [7]. Although endoscopy is frequently used for diagnostic and therapeutic purposes in children, esophageal perforation is an extremely rare complication. The most common cause of esophageal perforation is stricture dilatation using the balloon or bougie method, as in the presented case [1].

While the mortality rate for esophageal perforations is around 28%, delayed diagnosis significantly increases morbidity and mortality [1,8]. Therefore, early diagnosis is a crucial factor for successful treatment. Any child who develops symptoms following an endoscopic esophageal procedure should be evaluated for the presence of esophageal perforation [9]. However, not all patients experience respiratory distress, tachycardia, and tachypnea during the early period. In our patient's case, no symptoms were observed during the early period, and she was discharged after normal oral feeding. The chest X-ray taken after the procedure was deemed normal, as was the second chest X-ray taken when she was admitted to the emergency department. In cases of uncertainty, it is essential not to rely solely on a simple chest X-ray, and it should be kept in mind that even an esophagogram may not reveal pathology in 10% of patients [1]. If necessary, tomography and esophagoscopy should also be performed for diagnosis.

The basis of conservative treatment for esophageal perforation includes discontinuing oral intake, administering total parenteral nutrition, initiating broad-spectrum antibiotics, and draining with a chest tube, if necessary. If the patient is hemodynamically stable and without sepsis or esophageal necrosis, aggressive conservative treatment has reportedly resulted in a 100% success rate within a reasonable timeframe [2]. Although the goal of conservative treatment is to preserve the patient's natural esophagus, in life-threatening situations, diversion or esophageal replacement surgeries can be considered [5]. However, what should be done if the patient is hemodynamically stable, and conservative treatment fails to produce results? Should we continue to wait? In the presented case, the patient's clinical condition did not significantly improve during the 3-week conservative treatment period, and nasoduodenal feeding was not feasible. Although nasogastric tube feeding was a possibility, the potential consequences of gastroesophageal reflux were concerning. As a result, the patient developed protein-energy malnutrition and impaired wound healing despite total parenteral nutrition.

Fully covered self-expandable esophageal stents may not be effective in treating stricture dilatations due to their high recurrence rates [10]. However, they have proven effective in treating esophageal perforations [3,11]. Although the recommended treatment time for esophageal stents is 6–8 weeks [12], this period can be shortened for perforation sealing. During this period, the patient can be fed orally with liquid food. While pain and retching are often temporary issues, stent migration may require repositioning, which occurs in 29% of patients [13]. In our case, we did not encounter any issues with stent migration, and we initiated oral feeding on the third day following esophageal stent placement. It should be noted that while the esophageal stent prevents the passage of saliva to the perforation site and allows for oral feeding, there is a risk of esophageal erosion and pressure on the fragile, traumatized esophageal wall. Therefore, choosing the correct diameter and size for the stent is essential.

Endoscopic vacuum therapy is a promising treatment method for esophageal perforations, with successful results. Studies conducted with children and adults have reported success rates of around 83–88% [4,14]. The median duration of endoscopic vacuum therapy in pediatric patients is 8 days [4], significantly shorter than esophageal stent therapy and conservative therapy.

### Conclusion

Although conservative treatment is still the preferred method for esophageal perforations in hemodynamically stable children, the length of treatment, hospital stay, and nutritional problems are significant disadvantages. Current approaches, such as self-expandable esophageal stents, could be a good alternative in cases where conservative treatment fails to achieve the desired result. In appropriate pediatric cases, fully covered self-expandable biliary stents could be used successfully if necessary.

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**ERRATUM**

The date of Previous Presentation on page 606 of the related article has been corrected by the author as follows:

April 17-19, 2021.

These errors only appear in the printed version of the article. The online version has already been corrected.

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