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Research Article

Investigation of mid-term functional skills and psychological factors in female patients undergoing total knee arthroplasty

Functional skills after total knee arthroplasty

Ahmet Serhat Genç, Nizamettin Güzel, Mahmut Yaran, Anıl Agar, İsmail Eseoğlu, Berna Anıl, Esra Korkmaz, Enes Akdemir, Gözde Kesikbaş, Ali Kerim Yılmaz, Lokman Kehribar

524-530

PDF 69 68 Citations 0

The role of obesity on autologous bone marrow transplant and post-transplant outcomes

Outcomes of obesity on bone marrow transplantation

Sevil Sadri, Cem İdrisoğlu, Yasa Gul Mutlu , Aliihsan Gemici, Huseyin Saffet Bekoz, Omur Gokmen Sevindik, Fatma Deniz Sargin

531-535

PDF 40 32 Citations 0

Factors linked to Kawasaki disease and MIS-C in children with prolonged fever: A retrospective cohort study

Prolonged fever in children

Özlem Erdede, Kübra Alkan, Erdal Sarı, Serpil Değrmenci, Rabia Gönül Sezer Yamanel

536-541

PDF 25 23 Citations 0

Exploring risk factors and management strategies for endometrial premalignant/malignant lesions in women with abnormal uterine bleeding: A retrospective cohort study

Risk factors for endometrial neoplasms

Anil Erturk

542-546

PDF 15 15 Citations 0

The impact of the 2023 Kahramanmaras (Turkey) earthquake on clubfoot management: A retrospective, observational study

Impact of the Kahramanmaras earthquake on clubfoot management

Nevzat Gönder, Oguz Kaya, Ibrahim Halil Demir

547-550

PDF 12 20 Citations 0

Effect of waist circumference and body mass index on respiratory function

Waist circumference and respiratory function

Gökhan Çoraplı , Mahmut Çoraplı

551-554

PDF 13 14 Citations 0

Is the reduced risk of post-operative nausea and vomiting in low flow anesthesia applications associated with pre-operative neutrophil/lymphocyte ratio values?

PONV risk in low flow anesthesia applications

Sevgi Kutlusoy, Ahmet Aydın, Erdinç Koca

555-559

PDF 35 23 Citations 0

Evaluation of alanine aminotransferase responses in chronic hepatitis B patients using entecavir or tenofovir disoproxil fumarate

Alanine aminotransferase responses in hepatitis B patients

Ufuk Sonmez, Özge Kaya, Derya Çağlayan, Alpay Arı

560-563

PDF 17 22 Citations 0

Primary closure method after asymmetrical excision of a pilonidal sinus treatment: A retrospective cohort study

Primary closure method of a pilonidal sinus treatment

Tuba Atak
564-567

PDF 21 23 Citations 0

Monocyte to high-density lipoprotein ratio and neutrophil to lymphocyte ratio in trigeminal neuralgia patients: A retrospective cohort study

MHR and NLR in trigeminal neuralgia

Zeynep Tuncer , Nurcan Akbulut , Ural Can Ekmekçi , Gözde Gürsoy Çirkinoğlu, Vesile Öztürk , Yüksel Erkin
568-573

PDF 16 15 Citations 0

Musculoskeletal injuries profile of patients applying to a sports medicine outpatient clinic

Musculoskeleteal injuries in sports medicine

Merve Demir Benli
574-578

PDF 19 15 Citations 0

Fibrinogen to albumin and C-reactive protein to albumin ratio can play an important role in catheterization decisions in COVID-19 pneumonia patients: A retrospective cohort study

Catheterization decisions in COVID-19 pneumonia

Veysel Tosun, Ali Yaşar Kılınç
579-583

PDF 21 13 Citations 0

Volumetric apparent diffusion coefficient histogram analysis for determining the degree of differentiation of periampullary carcinomas

Volumetric ADC histogram analysis of periampullary carcinomas

Mustafa Orhan Nalbant, Ercan Inci
584-589

PDF 15 12 Citations 0

Value of ischemia-modified albumin in ankylosing spondylitis

Ischemia-modified albumin in ankylosing spondylitis

Nurdan Orucoglu Yildirim , Senay Balcı , Lulufer Tamer
590-594

PDF 10 7 Citations 0

Impact of COVID-19 pandemic on acute appendicitis: A retrospective cohort study

Impact of COVID-19 pandemic on acute appendicitis

Tuba Atak
595-597

PDF 19 12 Citations 0

Examination of the effect of bupivacaine on brain tissue in rats with induced experimental renal failure

Neurotoxicity of bupivacaine in renal failure

Nezir Yılmaz, Mehmet Tepe, Öznur Uludağ
598-601

PDF 14 13 Citations 0

Factors affecting the outcome of older adults followed in the intensive care unit according to age stages

Mortality in older adults in ICU

Mustafa Deniz, Pınar Ayvat

602-606

PDF 13 9 Citations 0

Demographic characteristics of patients with anosmia consulting to the COVID-19 outpatient clinic

Anosmia and COVID-19

Sibel Doğan Kaya, Suzan Şahin , Bülent Kaya, Gülfem Akengin Öcal, Sabahat Çağan Aktaş, Müge Tokatlı Çoban, Pınar Öngörü, Öznur Ak, Ayşe Batırel

607-609

PDF 17 14 Citations 0

The etiological, demographic, and seasonal characteristics of patients with dizziness and vertigo

Characteristics of patients with vertigo

Fatma Atalay, Ayhan Kars, Kubra Topal, Sezai Sacid Anbar, Zeynep Yavuz

610-613

PDF 17 25 Citations 0

Kite excision in complicated pilonidal sinuses: A retrospective cohort study of a tissue-sparing technique

Wide excision in complicated pilonidal sinuses

Zehra Ünal Özdemir

614-617

PDF 23 21 Citations ?

The effect of quercetin, a flavonoid, on lung injury caused by sepsis

Quercetin and sepsis-related lung injury

Murat Bıçakcıoğlu , Mevlüt Doğukan, Mehmet Duran, Zümrüt Doğan, Bilge Aydın Türk

618-622

PDF 12 11 Citations ?

The prevalence and impact of sarcopenia in myeloproliferative neoplasms

Sarcopenia in in myeloproliferative neoplasms

Yildiz Ipek, MüJgan Kaya Tuna

623-627

PDF 22 16 Citations ?

Renal implications of off-pump coronary artery bypass grafting: A retrospective cohort study analyzing postoperative creatinine levels

Acute kidney injury in off-pump coronary artery bypass grafting

Kamil Darcin, Muhammet Ahmet Karakaya

628-631

PDF 13 12 Citations ?

The protective effect of hydroxytyrosol on the heart in rats fed corn syrup: The role of spexin, pentraxin-3

The protective effect of hydroxytyrosol on heart

Elif Onat, Ahmet Türk

632-636

PDF 5 5 Citations ?

A retrospective cohort study of human papillomavirus (HPV) genotypes in women with abnormal Pap smear cytology in Turkey

Human papillomavirus (HPV) genotypes with abnormal Pap

Hayati Beka

637-640

PDF 0 0 Citations ?

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Research article

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Investigation of mid-term functional skills and psychological factors in female patients undergoing total knee arthroplasty

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Ethics Committee Approval
The study was approved by the Samsun University Clinical Research Ethics Committee (no: SÜKAEK 2022/5/14).
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: Previous studies have yielded conflicting clinical, psychological, and functional outcomes in patients undergoing total knee arthroplasty (TKA). This study aimed to more precisely evaluate the clinical outcomes, mid-term general physical and psychological health status, functional abilities, and improvements in patients' quality-of-life undergoing TKA.
Methods: This cross-sectional study included 25 female patients older than 55 years who underwent unilateral TKA due to osteoarthritis (OA). The Five Repetition Sit-to-Stand Test (5STS), Stair-Climbing Test (SCT), 6-Minute Walking Test (6MWT), Berg Balance Scale (BBS), Tampa Scale for Kinesiophobia (TSK), and Short Form Health Survey (SF-12) scores of the patients were evaluated using means. Meanwhile, the Lower Limb Length (LLL), Navicular Drop Test (NDT), Proprioception Assessment, Foot Posture Index (FPI-6), Foot Function Index (FFI), Lower Extremity Functional Scale (LEFS), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Oxford Knee Score (OKS) were evaluated by comparing the operated (OP) sides that underwent TKA with the non-operated (NONOP) sides diagnosed with OA.
Results: The study found that LLL (P=0.001), abduction/adduction forefoot on rearfoot (ABD) (P=0.017), and T.FPI-6 (P=0.014) in the FPI-6 parameters, as well as KOOS (P<0.001), OKS (P<0.001), LEFS (P<0.001), and FFI (P<0.001) results, were significantly in favor of the OP limb. Besides some parameters in FPI-6, no significant difference was found between the OP and NONOP extremities in terms of prone and supine proprioception values (P>0.05).
Conclusion: Overall, it was found that TKA plays a crucial role in recovery and regaining functional skills. Including preoperative evaluations with a control group and patients of both sexes in future studies and examining the relationships between the conducted tests and scales may contribute to better evaluating the results.

Keywords: total knee arthroplasty, functional skills, psychological factors, osteoarthritis

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Introduction

The knee joint is a polycentric joint that enables varus and valgus movements and flexion, extension, and rotational movements. Due to its inherent structural vulnerabilities, the knee joint is susceptible to instability. This instability is countered by the joint capsule, internal and external lateral ligaments, cruciate ligaments, and the surrounding muscle tissue [1].

Osteoarthritis (OA) is a degenerative disease that leads to imbalances and functional limitations. It manifests through pain, physical disabilities, restricted movement, bone misalignment, and impaired muscle performance in weight-bearing joints like the hips and knees. This condition significantly diminishes the quality-of-life, particularly among middle-aged and older individuals [2,3].

In cases where conservative treatments fall short, arthroplasty operations come into play. These surgeries aim to alleviate the persistent pain from chronic arthropathy and enhance the knee joint's functionality. The procedure involves the removal of diseased bone and cartilage tissues, replacing the diseased bone and cartilage with components that cover the joint surface [4].

The foot, positioned distally, serves several crucial roles. It provides a supportive surface against perturbations, absorbs and adjusts to abrupt body movements, and offers stabilization when needed to mitigate the adverse impacts of excessive mobility on the lower extremities and the body as a whole [5].

Research within the literature has demonstrated that excessive pronation and variations in foot posture contribute to issues such as postural instability, recurring injuries, lower extremity discomfort, Achilles tendinopathies, and patella-femoral joint pain [6,7]. The structural aberrations of the foot, such as pronation or supination misalignment, along with high or low arches, are believed to heighten the risk of biomechanical irregularities and subsequent injuries [8]. Although the association between foot morphology and lower extremity injuries remains somewhat elusive, existing studies reveal varying degrees of correlation between arch structure and biomechanical characteristics of the lower extremities [9].

Proprioception refers to the perception of joint and extremity positions facilitated by neural inputs generated through receptors found in the joints and surrounding tissues [10]. This proprioceptive sense holds significant importance in joint stabilization and its upkeep [11]. Proprioception is categorized into two types: static proprioception (pertaining to sensing position) and dynamic proprioception (related to perceiving movement) [12]. When proprioceptive deficits are present, it leads to a reduction in the dynamic activity of the muscles encompassing the knee joint and responsible for its movement [13,14].

Deformities in the joint capsule and ligament structures can lead to positioning, coordination, and balance issues in the extremities of individuals who have undergone total knee arthroplasty (TKA) surgery. Changes in muscle strength and gait patterns resulting from TKA and the loss of proprioception contribute to an amplified postural sway [15]. This situation not only hinders the performance of daily activities, particularly among elderly patients who have undergone TKA but also elevates the risk of falls. The alteration in physical function and quality-of-life underscores the significant psychological impact [16].

Knee arthroplasty surgeries, when executed with meticulous patient selection and appropriate surgical techniques, have demonstrated enhancements in joint mechanics, pain reduction, and an expanded range of motion. This improvement fosters patient contentment by enabling them to comfortably engage in functional activities [17]. Compared to the pre-surgery state, patients undergoing TKA experience improved functional performance and balance [18]. The traditional presentation of clinical outcomes in TKA relies on objective criteria encompassing implant survival, joint range of motion, joint balance, and radiological findings [19].

Considering this breadth of information, the present study aims to assess the clinical outcomes, medium-term overall physical and psychological health status, functional capabilities, and the augmented quality-of-life in patients who have undergone TKA.

Materials and methods

Twenty-five female patients, ranging in age from 56 to 75 years with a mean age of 65 years, who were admitted to the Samsun Training and Research Hospital Orthopaedics and Traumatology Outpatient Clinic with a diagnosis of osteoarthritis (OA) between January 2019 and March 2021, were assessed in this cross-sectional study. The study included female patients over 55 who underwent TKA using Pacific Medical Group (PMG) fix-mobile cruciate retaining femoral components for the first time due to OA and who underwent a single joint operation. The average follow-up period was 18.3 months, ranging from 12 to 36 months.

The study was conducted using a single-blind method; patients were not informed about the nature of the study. A priori test with the G*Power 3.1 program determined the required number of participants. Based on the sample study conducted for power analysis, it was determined that the study could be successfully carried out with 18 patients (Effect size: 0.80, Actual Power: 0.89).

This research received approval from the Samsun University Clinical Research Ethics Committee (Approval No: SÜKAEK 2022/5/14).

In the current study, the functional and clinical outcomes of patients who underwent TKA were compared between their operated (OP) extremities and their non-operated (NONOP) extremities. Both the OP and NONOP extremities were diagnosed with stage 3 or stage 4 osteoarthritis (OA). Patients attended the clinic for a total of three evaluation sessions. During the initial visit, patients were briefed about the testing protocols, underwent anthropometric measurements, and participated in preliminary assessments. In the subsequent visit, patients performed a battery of tests, including The Five Repetition Sit-to-Stand Test (5STS), Stair-Climbing Test (SCT), 6-Minute Walking Test (6MWT), Berg Balance Scale (BBS), Proprioception Assessment, Navicular Drop Test (NDT), and Foot Posture Index (FPI-6). The third visit encompassed

evaluations using the Foot Function Index (FFI), Lower Extremity Functional Scale (LEFS), Tampa Scale for Kinesiophobia (TSK), Knee Injury and Osteoarthritis Outcome Score (KOOS), Oxford Knee Score (OKS), and Short Form Health Survey (SF-12).

The Five Repetition Sit-to-Stand Test (5STS)

Patients were instructed to cross their arms over their chest and to execute a single practice iteration of sitting and rising from a chair. Following the trial run, they were directed to sit on the chair and rise swiftly and continuously without pauses. The elapsed time from completing the fifth repetition was then documented [20].

Stair-Climbing Test (SCT)

The SCT is an assessment tool for gauging functional performance following TKA [21]. Participants were tasked with ascending and descending ten steps as swiftly as possible while ensuring their safety (step height: 20 cm) [22]. Patients were permitted to grasp the handrails beside the staircase throughout the test. The duration taken to execute the maneuver was subsequently measured in seconds.

6-Minute Walking Test (6MWT)

The 6MWT is a dependable approach for assessing the functional capacity of patients post-knee arthroplasty surgery. Individuals were instructed to ambulate at their maximal pace while maintaining their safety along a 30-meter linear corridor for 6 min; they were permitted to halt and rest as needed but were prohibited from running [23]. Assistive devices commonly used by patients, such as walking sticks, were permissible during the test. Regular updates on the remaining time were provided at 60-s intervals, accompanied by verbal encouragement [24]. Upon completing the 6 min, the distance covered during walking was documented in meters.

Berg Balance Scale (BBS)

The BBS, designed to assess the susceptibility to falls and balance impairment in older patients, has been validated in clinical settings and research studies [25,26]. Each item is assigned a score ranging from 0 to 4 points, culminating in a maximum total score of 56. The point distribution is as follows: 0 to 20 points indicate a high risk of falling, 21 to 40 points denote a moderate risk of falling, and 41 to 56 points indicate a low risk of falling. The evaluation used standard equipment, including a chair, a step, a 15-meter-long corridor, and a stopwatch. The resultant total score was duly recorded.

Evaluation of proprioception

In the study, knee joint proprioception measurements were acquired from the participants using a digital goniometer (2176-300 Insize Digital Protractor) with a precision of one degree. The goniometer was affixed to the patients' knee joint utilizing electromyography (EMG) bandages. Three distinct target angles (15°, 30°, and 45°) were established for subsequent measurements. Initially, the procedure was conducted with patients lying face-down and their eyes closed. During this process, the patients' hips were maintained in a neutral position, the goniometer was calibrated to zero at the complete extension of both knees, and the intended target angle was communicated verbally to the patients. Participants were instructed to concentrate on this angle, maintaining the knee in that position for 5 s, ensuring a comprehensive perception of the target angle. Subsequently, patients were prompted to align their knees with the designated target angle. The measurements were repeated three times for each target angle, and the average angular deviation from each measurement was computed. The entire sequence of steps was replicated with patients lying on their backs, and the assessment was conducted for both knees.

Navicular Drop Test (NDT)

This assessment was employed to evaluate the medial longitudinal arch heights of the participants. For the measurement of navicular height, each patient was instructed to place full weight on their bare feet, and the measurement was taken as the distance between the tubercle of the navicular – the insertion point of the tibialis posterior muscle – and the ground in this stance [27]. Subsequently, participants were requested to sit, and the distance from the navicular tubercle to the ground was gauged in the subtalar neutral position without any weight on their feet [28]. The disparity between this latter measurement and the initial navicular height yielded the recorded value for navicular drop (mm).

Foot Posture Index (FPI-6)

The FPI-6 assesses the stance of both the rearfoot and forefoot across multiple planes. Its validity and reliability for assessing foot posture under consistent load have been substantiated in existing literature on adult and pediatric populations [29]. During the assessment, palpation and visual observations were conducted while maintaining a shoulder-width stance with an even distribution of weight on both feet. Six parameters were evaluated, encompassing the position of the talus's head, the supra/infra malleolar inclination, the frontal plane orientation of the calcaneus, the configuration of the medial folds of the talonavicular joint, the appearance of the medial arch, and the forefoot's adduction/abduction about the rearfoot. Each parameter was assigned a score ranging from -2 to +2, with a score of zero denoting a neutral foot posture.

Foot Function Index (FFI)

The FFI was employed to quantify the impact of foot pathology on functional aspects such as pain, disability, and limitations in activity. Comprising 23 items grouped into three subcategories – pain, disability, and activity limitation – the scale generates higher scores indicative of greater pain, disability, and activity constraints [30]. The Turkish version's validity and reliability were established by [31]. The aggregated score derived from summing the patients' scores is divided by the maximum possible cumulative score attainable from these questions. This yields an index total score, multiplying the resultant fraction by 100.

Tampa Scale for Kinesiophobia (TKS)

Seventeen questions about falling and movement apprehension were appraised using a scoring system ranging from 1 to 4. Questions 4, 8, 12, and 16 were reverse-scored. A heightened score (with a maximum potential of 68) signifies a notable fear of falling and movement within the patient [32].

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS assessment has been established as reliable and valid for evaluating knee-related functional status, pain, daily activities, and quality-of-life [33]. The patients were presented with questions and instructed to select the response

that best aligned with their experiences over the preceding week. In total, 42 questions were posed to the patients, each offering five response choices. Responses to each question were scored on a scale of 0 to 4. A score of 0 signifies a considerable knee issue, while a score of 100 indicates an absence of problems concerning the knee [34].

Oxford Knee Score (OKS)

Within the OKS form, individual questions hold point values ranging from 0 to 4. Based on the responses provided by patients using a 5-point Likert-type scale across 12 questions, a score within the range of 0 to 48 was computed. Because of knee pain and the impact of osteoarthritis, a score of 0 reflects the poorest outcome, while 48 points correspond to the most favorable result [35].

Short Form Health Survey (SF-12)

The SF-12, condensed from the SF-36 by selecting 12 distinct items spanning eight subcategories, comprises two distinct dimensions: the Physical Component Score (PCS) and the Mental Component Score (MCS). Scores for SF-12 PCS and SF-12 MCS encompass a spectrum of 0 to 100, with higher scores indicative of enhanced health status [36].

Statistical analysis

The study's statistical analysis was performed using the SPSS 22.0 software package. The data's normal distribution was assessed through the Shapiro-Wilk test, while the Levene test was employed to verify homogeneity assumptions. Descriptive statistics were presented as means and standard deviations. Paired sample t-tests were conducted to compare the OP and NONOP sides. Furthermore, effect sizes were computed using Cohen's d effect size formula ((M2 − M1) / SDpooled) for paired group comparisons. Following this formula, a d value of 0.8 was considered indicative of a substantial effect size. *P*-value less than 0.05 were considered significant.

Results

The mean values of patients in our study were as follows: age, 65 years; height, 154.52 cm; weight, 87.92 kg; BMI, 36.96 kg/m²; and follow-up duration, 18.3 months. A statistically significant difference was observed between the OP and NONOP sides (*P*=0.001, 95% CI: 0.39–1.25) during the evaluation of LLL. Among the patients in the study, 52% had their OP knee on the right side, while 48% had it on the left (Table 1).

Table 1: Descriptive data (n=25).

	Mean	SD	Min	Max
Age (year)	65.00	5.431	56	75
Height (cm)	154.52	7.506	145	170
Weight (kg)	87.92	15.319	61	127
BMI (kg/m²)	36.96	6.83	27.11	52.18
Follow-up (month)	18.3	7.62	12	36

	OP	NONOP	t	*P*-value	ES	95% CI	
	Mean (SD)	Mean (SD)				LB	UB
LLL (cm)	86.60 (3.76)	85.78 (3.77)	-3.94	0.001*	21.78	0.39	1.25

	R	L
Operated knee	52%	48%

SD: Standard deviation, Min: Minimum, Max: Maximum, BMI: Body mass index, R: Right, L: Left, OP: Operated, NONOP: Non-operated, CI: Confidence interval, LB: Lower bound, UB: Upper bound, ES: Effect size, LLL: Lower limb length

The mean time for the 5STS test was 22.43 s, while the mean SCT time was 16.87 s. The mean distance covered in the 6MWT was 319.36 meters (Table 2).

Regarding the assessment scores, the mean BBS score of our patients was 48.76, whereas the mean TKS score was 46.36. In our SF-12 evaluation, the mean scores were 42.74 for SF-12 PCS, 42.85 for SF-12 MCS, and 85.59 for SF-12 T (Table 3).

Table 2: Mean values of 5STS, SCT, and 6MWT.

	Mean	SD	Min	Max
5STS (sec)	22.43	6.24	11.04	38.23
SCT (sec)	16.87	8.93	7.29	44.03
6MWT (m)	319.36	90.15	139	449

SD: Standard deviation, Min: Minimum, Max: Maximum, 5STS: The five repetition sit-to-stand test, SCT: Stair-climbing test, 6MWT: 6-Minute walking test

Table 3: Mean scores of BBS, TKS, and SF-12.

	Mean	SD	Min	Max
BBS	48.76	6.57	36	55
TKS	46.36	7.68	26	59
SF-12 PCS	42.74	11.82	22.60	62.94
SF-12 MCS	42.85	11.92	24.29	63.18
SF-12 T	85.59	18.60	58.12	114.34

SD: Standard deviation, Min: Minimum, Max: Maximum, BBS: Berg balance scale, TKS: Tampa scale for kinesiophobia, PCS: Physical, MCS: Mental, T: Total

When comparing proprioception values on the OP and NONOP sides at 15, 30, 45, and 60 degrees in the prone position, no statistically significant differences were observed for any of the angles: 15º (*P*=0.203, 95% CI: -3.98–0.89), 30º (*P*=0.361, 95% CI: 3.47–1.31), 45º (*P*=0.609, 95% CI: -3.72–2.22), and 60º (*P*=-10.096, 95% CI: -2.65–0.81) (Table 4).

Similarly, when evaluating OP and NONOP side proprioception values at 15, 30, 45, and 60 degrees in the supine position, no statistically significant differences were found for the following angles: 15º (*P*=0.979, 95% CI: -3.10–3.18), 30º (*P*=0.600, 95% CI: -2.69–4.55), 45º (*P*=0.511, 95% CI: -2.09–4.09), and 60º (*P*=0.356, 95% CI: -0.97–2.60) (Table 4).

Table 4: Comparison of OP and NONOP proprioception values in prone and supine positions.

Variables	OP	NONOP	t	*P*-value	ES	95% CI	
	Mean (SD)	Mean (SD)				LB	UB
P 15º S	6.14 (3.78)	7.69 (4.80)	-1.308	0.203	0.36	-3.98	0.89
P 30º S	4.75 (2.50)	5.82 (4.91)	-0.931	0.361	0.27	-3.47	1.31
P 45º S	4.70 (3.14)	5.45 (6.17)	-0.518	0.609	0.15	-3.72	2.22
P 60º S	3.19 (3.51)	4.10 (2.75)	-1.096	0.284	0.28	-2.65	0.81
S 15º S	7.71 (6.98)	7.68 (5.19)	0.026	0.979	0.00	-3.10	3.18
S 30º S	7.70 (5.89)	6.77 (6.90)	0.531	0.600	0.14	-2.69	4.55
S 45º S	7.77 (6.28)	6.77 (6.25)	0.667	0.511	0.16	-2.09	4.09
S 60º S	6.69 (4.74)	5.88 (4.90)	0.941	0.356	0.17	-0.97	2.60

SD: Standard deviation, OP: Operated, NONOP: Non-operated, CI: Confidence interval, LB: Lower bound, UB: Upper bound, ES: Effect size, P: Prone, S: Supine

In assessing the foot posture index on the OP and NONOP sides, no significant differences were observed between T.H. (*P*=1.00, 95% CI: -0.12–0.12) and LAT. M. (*P*=0.504, 95% CI: -0.65–0.33), CALC. (*P*=0.382, 95% CI: -0.21–0.53), TNJ (*P*=0.574, 95% CI: -0.21–0.37), and MA (*P*=0.056, 95% CI: -0.01–0.49) values. However, statistically significant differences were found in ABD (*P*=0.017, 95% CI: 0.07–0.65) and T.FPI-6 (*P*=0.014, 95% CI: 0.25–1.99) values (Table 5).

Table 5: Comparison of OP and NONOP side values of FPI-6 parameters.

Variables	OP	NONOP	t	*P*-value	ES	95% CI	
	Mean (SD)	Mean (SD)				LB	UB
T.H.	1.24 (10.09)	1.24 (10.09)	0.000	1.00	0.00	-0.12	0.12
LAT. M.	0.44 (1.45)	0.60 (1.29)	-0.679	0.504	0.12	-0.65	0.33
CALC.	0.72 (1.17)	0.56 (1.12)	0.891	0.382	0.14	-0.21	0.53
TNJ	0.32 (1.38)	0.24 (1.33)	0.569	0.574	0.06	-0.21	0.37
MA.	0.64 (10.04)	0.40 (0.87)	2.01	0.056	0.25	-0.01	0.49
ABD	1.68 (0.56)	1.32 (0.69)	2.57	0.017*	0.57	0.07	0.65
T.FPI-6	5.08 (3.70)	3.96 (3.94)	2.66	0.014*	0.29	0.25	1.99

SD: Standard deviation, OP: Operated, NONOP: Non-operated, CI: Confidence interval, LB: Lower bound, UB: Upper bound, ES: Effect size, T.H.: Talar head palpation, LAT. M.: Curves above and below the lateral malleolus, CALC.: Inversion/eversion of the calcaneus, TNJ: Prominence in the region of the TNJ, MA: Congruence of the medial longitudinal arch, ABD: Abduction/adduction forefoot on rearfoot, T.FPI-6: Total foot posture index

Statistical significance was observed in the following parameters: KOOS (P<0.001, 95% CI: -38.20–28.60), OKS (P<0.001, 95% CI: 9.85–12.55), LEFS (P<0.001, 95% CI: 14.74–21.82), FFI P. (P<0.001, 95% CI: -17.02–12.62), FFI I. (P<0.001, 95% CI: -25.02–16.58), FFI L. (P<0.001, 95% CI: -11.17–7.95), and FFI T. (P<0.001, 95% CI: -51.39–39.97). However, no significance was observed in the NDT parameter (P=0.307, 95% CI: -0.26–0.09) (Table 6).

Table 6: Comparison of OP and NONOP side values of KOOS, OKS, LEFS, FFI and NDT.

Variables	OP	NONOP	t	*P*-value	ES	95% CI	
	Mean (SD)	Mean (SD)				LB	UB
KOOS	41.26 (19.04)	74.66 (19.07)	-14.35	<0.001*	1.75	-38.20	-28.60
OKS	30.80 (11.33)	19.60 (9.14)	17.08	<0.001*	1.09	9.85	12.55
LEFS	45.08 (20.42)	26.80 (14.80)	10.65	<0.001*	1.03	14.74	21.82
FFI P.	23.88 (17.60)	39.20 (15.80)	-18.59	<0.001*	0.92	-17.02	-13.62
FFI I.	33.52 (25.25)	54.32 (20.45)	-10.17	<0.001*	0.90	-25.02	-16.58
FFI L.	11.96 (12.60)	21.52 (14.57)	-12.24	<0.001*	0.70	-11.17	-7.95
FFI T.	69.36 (47.43)	115.04 (43.30)	-16.51	<0.001*	1.01	-51.39	-39.97
NDT (mm)	0.86 (0.42)	0.95 (0.45)	-1.04	0.307	0.20	-0.26	0.09

SD: Standard deviation, OP: Operated, NONOP: Non-operated, CI: Confidence interval, LB: Lower bound, UB: Upper bound, ES: Effect size, KOOS: Knee Injury and Osteoarthritis Outcome Score, OKS: Oxford Knee Score, LEFS: Lower extremity functional scale, FFI P.: Foot function index pain, FFI I.: Foot function index insufficiency, FFI L.: Foot function index activity limitation, FFI T.: Foot function index total, NDT: Navicular drop test

Discussion

The study aimed to compare the clinical and functional outcomes of patients who underwent unilateral TKA for stage 3 or stage 4 osteoarthritis (OA) between the operated (OP) extremity and the non-operated (NONOP) extremity. The study's results demonstrated significant differences favoring the OP limb in various parameters.

Among the parameters analyzed, including LLL, ABD, and T.FPI-6 in the FPI-6 assessment and KOOS, OKS, LEFS, and FFI scores, the OP limb consistently showed superior outcomes compared to the NONOP limb. While some parameters within the FPI-6 assessment indicated differences, no significant distinction was observed between the OP and NONOP limbs in terms of proprioception values measured in both prone and supine positions.

Numerous conducted studies have consistently reported an increase in leg length discrepancy (LLL) following TKA [37-39]. Our study's findings align with this prevailing perspective. However, it's noteworthy that differing threshold values, such as 10 mm and 15 mm, have been employed in other investigations examining LLL [37,40]. In contrast, our study did not rely on radiological outcomes for LLL assessment; measurements were taken in centimeters using a simple measuring tape.

In our study, the measurement of LLL revealed an 8.2 mm disparity between the OP and NONOP sides when mean values were compared. Although these outcomes may not yield a definitive radiological conclusion, they do distinctly indicate that a 10-15 mm variation exists when assessed with standard deviations. This observation implies that the outcomes for both the OP side after TKA application and the sides diagnosed with OA fall within the ranges stipulated in the existing literature.

The impact of foot stance on mechanical alignment and dynamic function of the lower extremities has long been acknowledged [41]. The medial section of the lower extremity bears a greater force during weight-bearing than the lateral section. This imbalance may lead to excessive pronation and a reduction in the medial longitudinal arch in the extremity with the OA-affected knee [42]. This phenomenon has received considerable attention in various studies utilizing techniques like NDT and FPI-6 [41,43-47].

While our study did not uncover a noteworthy difference in NDT scores, it did reveal significant findings in ABD within the FPI-6 scale. Additionally, outcomes approaching significance were observed in MA, further underlining the notable discrepancy in the FPI-6 score. As emphasized by previous researchers, these outcomes support our study's conclusion that a reduction in the medial longitudinal arch occurs in patients who have undergone TKA. This alteration likely contributes to the substantial difference between pronation and ABD outcomes, as the collected data indicates.

Assessing post-TKA balance and functional capabilities necessary for daily activities is crucial [48]. Schilke et al. [49] emphasized that roughly 97% of lower extremity muscle strength is required for rising from a chair. The evaluation of walking assumes significance as it is closely linked with an active and self-reliant lifestyle post-TKA [50].

Within our study, mean scores derived from tests such as the 5STS [51], SCT [22,36], 6MWT [23,36], and BBS [52], designed to appraise post-TKA balance and functional capacities, closely mirrored those reported in various existing literature. Our study found no significant disparity between the OP and NONOP sides in these metrics. Generally, research efforts have often focused on contrasting the pre- and post-TKA periods or comparing TKA recipients with control groups. In our study, a distinct approach was adopted, comparing knees with TKA to non-operated knees diagnosed with OA. This, however, introduces a noteworthy limitation when juxtaposed with other studies. The scoring discrepancy arises because the scores displayed positivity on the OP side and negativity on the OA-diagnosed side, stemming from the amalgamation of both OP and OA-diagnosed sides during walking, sit-up, and balance evaluations.

Patients frequently develop a fear of movement, potentially leading to kinesiophobia after undergoing TKA [53]. This apprehension could reasonably impact their functional abilities. In a study by Doury-Panchout et al. [54], a TSK score exceeding 40 indicated kinesiophobia. They reported that individuals with kinesiophobia covered a significantly shorter distance in the 6MWT than those without kinesiophobia. While we didn't apply a similar categorization based on TSK results in our study, opting instead to assess mean scores, our TSK mean score of 46.4 aligns with findings in the literature [53,55], clearly indicating the presence of kinesiophobia among patients.

Our study's notably elevated TSK score could be attributed to the unilateral TKA approach taken with patients, combined with the diagnosis of Stage 3 and 4 OA in the other knee. Future research endeavors should consider studying patients undergoing bilateral TKA or unilateral TKA with a healthy or Stage 1 and 2 OA-diagnosed counterpart for a more definitive understanding. Such investigations could provide clearer insights into the outcomes.

In today's context, patient expectations and satisfaction have become crucial benchmarks for evaluating TKA outcomes [56,57]. Consequently, researchers have increasingly turned to health-related quality-of-life scales to offer more comprehensive assessments of disease impacts and treatment effects [58]. Our

study's mean scores, akin to those documented in the literature, align across various scales, including SF-12 (PCS, MCS) [58-60], KOOS [61], OKS [62,63], and LEFS [64].

The positive outcomes post-TKA surgery, in terms of knee scores and quality-of-life, are evident. Indeed, given the assessment of functional issues and pain experienced by patients diagnosed with Stage 3 and 4 OA, the relief provided by TKA has anticipated psychological and functional benefits. Notably, within our current patient cohort, it's reasonable to anticipate that sides without TKA but diagnosed with Stage 3 and 4 OA would yield higher positive outcomes in knee scores and quality-of-life following surgery. This conjecture supports the noteworthy difference between the OP and NONOP sides in the FFI. The findings of our study robustly underscore an enhancement in patient satisfaction and functional advancement post-TKA, closely aligned with established trends in the literature.

Researchers have notably underscored the importance of assessing proprioception, particularly within patient cohorts like those with OA, given its strong correlation with knee functional performance [65]. Generally, a trend toward enhanced proprioception levels post-TKA is recognized [65,66]. Nevertheless, some studies report no significant difference in proprioception levels between the preoperative and post-operative phases [67,68].

In our study, the resemblance in proprioception results between the OP and NONOP sides prompts consideration. This likeness suggests that using a prosthesis that preserves the ligament structure without interrupting it, as seen in TKA, potentially yields comparable knee functions and proprioception outcomes. This notion aligns with findings indicating that structures like the anterior cruciate ligament play a substantial role in proprioception [68].

Limitations and Conclusion

In our study, TKA was assessed using a variety of tests and scales. As a general outcome, it was determined that TKA plays a crucial role in recovery and the regaining of functional skills. It is believed that several factors, such as age, length of follow-up period, and the severity of osteoarthritis (OA) in patients, might influence the evaluation of post-TKA processes. Furthermore, our study exhibits several noteworthy limitations. The absence of a healthy control group and the lack of data from the preoperative period, coupled with the absence of post-operative evaluations at various follow-up periods, impeded more profound and insightful assessments and comparisons following TKA.

Notwithstanding these limitations, our study revealed that TKA significantly impacts knee scores and functional tests, though it appears to not affect proprioception levels. This understanding aids in gaining a clearer insight into the effects of TKA on OA patients. For future investigations, incorporating preoperative assessments involving control groups and encompassing both genders, exploring the correlations between tests and scales, and conducting distinct comparisons at diverse follow-up periods could all contribute to a more comprehensive evaluation of the results.

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The role of obesity on autologous bone marrow transplant and post-transplant outcomes

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Ethics Committee Approval
The study was approved by the Medipol University Institutional Ethics Committee (E-10840098-772.02-6746, dated: December 29, 2021).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Autologous hematopoietic cell transplantation (AutoHCT), administered at high doses, has improved survival rates among patients with refractory or recurrent lymphoma and multiple myeloma (MM). However, inconsistencies in defining obesity, varying body weight ranges, and heterogeneous patient populations have been examined. Some researchers have hypothesized that significantly overweight patients face a higher risk of transplant-related complications. This study investigates the association between body mass index (BMI), obesity, and autologous peripheral stem cell mobilization.
Methods: A retrospective evaluation of data from 180 patients who underwent peripheral stem cell mobilization at our clinic between 2014 and 2020 was conducted. Excluding patients under 18 years of age, the primary objective was to assess how BMI influences autologous transplant outcomes and mortality. This retrospective cohort study aimed to determine whether obesity constitutes an independent risk factor for autologous bone marrow transplantation.
Results: Among the patients, the most prevalent diagnosis (47.2%) was MM, with notable differences in incidence rates across BMI categories (P=0.039). Obesity and overweight were associated with a higher incidence of MM (47.2%), whereas normal and underweight individuals had predominantly been diagnosed with DLBCL (44.2%). Significant differences in CD34 cell counts were observed among BMI groups (P=0.033). Overweight and obese individuals exhibited lower CD34 cell counts than underweight/normal groups (P=0.033). The treatment group showed significantly higher CD34 cell counts than the G-CSF alone group (P=0.046). Female gender (P=0.022), PLT engraftment (P=0.024), post-chemo-mobilization hospital-stay duration (P=0.019), and G-CSF count were identified as mortality risk factors (P=0.017).
Conclusions: This investigation found no adverse correlation between mortality and weight among patients with various hematological malignancies undergoing AutoHCT. Obesity alone should not be a contraindication for proceeding with AutoHCT in clinically warranted hematological malignancy treatment, as no significant survival differences were observed among overweight, obese, and normal-weight individuals.

Keywords: autologous bone marrow transplant, mobilization, obesity

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Introduction

The increasing global prevalence of overweight and obesity represents a significant public health concern impacting developed and developing nations [1,2].

The pharmacokinetics of high-dose chemotherapy in overweight patients remain poorly understood, with several studies expressing concerns about potential higher toxicity when dosage adjustments aren't made or the potential for increased relapse risk with modifications based on ideal body weight (IBW) [3]. In refractory or recurrent lymphoma, high-dose autologous hematopoietic cell transplantation (AutoHCT) has demonstrated superior long-term disease-free survival compared to standard-dose chemotherapy [4,5]. While new antimyeloma drugs have improved patient outcomes, the most substantial advancement was AutoHCT, a treatment that has significantly enhanced survival rates and remains the most prominent approach in antimyeloma therapy [6]. Risk factors, such as severe disease, advanced age, prior treatments, and biological characteristics, contribute to long-term outcomes following bone marrow transplantation for hematological malignancies. While some of these factors are widely acknowledged, others remain debated.

Obesity has emerged as a risk factor for diseases and premature mortality, as indicated by a wealth of research. Although obesity is recognized for elevating the risk of common medical conditions like cardiovascular disease [7,8], diabetes [9], cancer [10,11], and premature death [12], its role as a definitive risk factor in the context of transplantation initiation has yet to be established. Several studies have examined the effects of obesity, being underweight or overweight status in individuals undergoing hematopoietic stem cell transplantation [13,14]. However, the outcomes of these investigations on the influence of BMI on peripheral stem cell mobilization have shown significant variability and ambiguity. Consequently, our institution explored the relationship between body mass index (BMI) and autologous peripheral stem cell mobilization in obesity. The primary aim was to assess how obesity impacts transplant outcomes within our cohort of autologous transplant recipients, with potential implications for mobilization and cell dosage considerations.

Materials and methods

Patients who underwent peripheral stem cell mobilization at our clinic between 2014 and 2020 were subjected to a retrospective study. The study encompassed parameters such as patients' age, gender, diagnosis, the count of administered chemotherapies, the extent of radiation exposure, and the mobilization strategies employed (including isolated GCF and chemoembolization), all meticulously documented. The registration data comprehensively incorporates disease type, patient age, gender, pretransplantation performance status, disease stage, responsiveness to chemotherapy, date of initial diagnosis, specifics regarding the donor and graft type (derived from either bone marrow or blood stem cells), details about the high-dose conditioning regimen, post-transplantation engraftment, instances of disease recurrence and survival rates, instances of new malignancy development, and the causes of death.

Inclusion criteria encompassed patients falling within the age bracket of greater than 18 years and less than 65 years. The study's evaluated endpoints included relapse rates, overall survival, disease-free survival (LFS), and transplantation-related mortality (TRM). Specifically, TRM was characterized as any mortality occurring within the initial 28 days post-transplantation or at any point during a continuous state of complete remission. Relapse was delineated as the duration prior to a clinical recurrence, progression of the illness, or persistence of the illness. For patients afflicted with chronic disease, events at day 28 were considered relevant for the relapse assessment.

Obesity was characterized by BMI at the time of transplantation, calculated as weight (kg)/height $(m^2)^2$. BMI classifications were based on World Health Organization (WHO) definitions: A BMI of 18 or less indicated underweight, >18–25 was considered normal, >25–30 was categorized as overweight, and a BMI exceeding 30 was classified as obese. In the present study, participants mobilized solely with G-CSF received a daily dose of 5 µg/kg G-CSF administered twice daily for 5 days. In contrast, patients who received G-CSF following chemotherapy were administered cyclophosphamide at 2 g/m^2 for multiple myeloma (MM) patients and 4 g/m^2 for lymphoma patients, followed by G-CSF initiation on day 5. Mobilization failure was defined as the inability to achieve a CD34+ cell count of 2×10^6 cells/kg after G-CSF administration or after a chemotherapy regimen followed by G-CSF.

The study population was divided into three groups based on BMI: underweight and normal, overweight and obese. Various factors, including the number of days of growth factor (G-CSF) administration, CD34+ cell count on the collection day, duration until platelet and neutrophil engraftment, and post-chemoembolization hospital stay length, were assessed for comparison among these groups. The primary focus of the study was to elucidate the impact of BMI on autologous transplant outcomes and adult patient mortality. The objective was to understand how obesity influences post-transplant results, to guide treatment choices and to lay the groundwork for future investigations. Ethical approval for the study was obtained from the Medipol University Institutional Ethics Committee (E-10840098-772.02-6746, dated: December 29, 2021).

Statistical analysis

Patients were stratified into three distinct BMI groups: underweight (BMI <18) and normal (18–24.9), overweight (25.0–29.9), and obese (≥30.0), based on their body mass index. In this investigation, the effect size was calculated through an assessment of the CD34 cell count parameter (in millions/kg) using 20 observations from each BMI group (underweight/normal, overweight, and obese) conducted by the researcher prior to conducting the power analysis. The effect size, denoted as f=0.235 (medium), was computed for this purpose. With a targeted statistical power of 80%, a significance level of 0.05, and employing a two-tailed hypothesis, the subsequent analysis indicated that a total of 180 observations were required, distributed across the three independent groups, with a minimum of 60 observations per group. The analytical procedures were conducted utilizing the G*Power 3.1 software.

Categorical characteristics across the BMI groups were compared using either the Exact or Pearson chi-square test, while continuous variables were assessed through the Mann-Whitney U or Kruskal-Wallis test. Regarding mortality, the initial analysis involved univariate logistic regression (LR) to evaluate its association. Subsequently, a stepwise LR analysis was conducted for variables that displayed significance in the initial univariate analysis. The Spearman correlation coefficient was employed to explore the relationship between two quantitative variables. Quantitative variables were presented as median and interquartile range (IQR), representing the difference between the 75th and 25th percentiles (P75-P25), while qualitative variables were presented in terms of counts and percentages. Statistical significance was considered at a *P*-value of <0.05. For analysis of the clinical data, IBM SPSS version 23.0 was employed.

Results

Table 1 presents the distribution of general patient characteristics among BMI groups. The median age of the 180 cases was 53 years (IQR: 22), and there was a significant difference in the age distribution among BMI categories. Underweight/normal-weight patients were younger than those in the other groups. With a median BMI of 28 and an IQR of 6.7, 37.8% of the patient population was classified as obese. The most prevalent diagnosis among the cases was MM (47.2%), followed by DLBCL (40.6%). The incidence rate in the BMI groups showed a significant difference (*P*=0.039). In obese and overweight cases, MM (47.2% and 44.9%, respectively) was the most frequently observed diagnosis, while in normal and underweight individuals, DLBCL (44.2%) was the predominant one.

Regarding the CD34 cell count on the first collection day, there were noteworthy variations across BMI groups (*P*=0.033). All patients received their initial transplant. The cell count was significantly lower in the overweight and obese categories compared to the underweight/normal groups, as indicated by the post hoc analysis.

Table 2 evaluates demographic variables concerning CD34+ cell count. The median CD34 cell count was 7.4, with an interquartile range of 4.25. The cell count was markedly lower in the obese and overweight categories than in the underweight/normal groups (*P*=0.033). Cases in the treatment group exhibited significantly higher CD34 cell counts than those in the G-CSF alone group (*P*=0.046). No meaningful association was observed between other features and CD34+ cell count.

To identify significant predictors of death, univariate and stepwise multivariate LR models were employed (Table 3). Female gender (*P*=0.022), PLT engraftment (*P*=0.024), hospital stay after chemo-mobilization (*P*=0.019), and G-CSF count were identified as risk factors for mortality (*P*=0.017). The Univariate LR analysis revealed female gender as a statistically significant risk factor (Odds Ratio = 2.80; 95% CI 1.16-6.75, [*P*=0.022]). Individuals with DLBCL faced a significantly higher mortality risk than those with MM (Odds Ratio = 4.84; 95% CI 1.89-12.39, [*P*=0.017]). The individual risk factors for mortality included hospitalization following chemo-mobilization for PLT

Table 1: Baseline characteristics of cancer patient.

	Underweight/normal (n=43)	**Overweight (n=69)**	**Obese (n=68)**	***P*-value**
	n (%)	**n (%)**	**n (%)**	
Gender				
Female	13 (30.2)	24 (34.8)	32 (47.1)	0.153
Male	30 (69.8)	45 (65.2)	36 (52.9)	
Age Median (IQR)	43 (31)	51 (14)	54 (13.5)	0.016
Chemotherapy serial				
1-2	38 (90.5)	54 (85.7)	56 (93.3)	0.374
3-4	4 (9.5)	9 (14.3)	4 (6.7)	
Diagnosis				
HL	8 (18.6)	7 (10.1)	3 (4.5)	0.039
DLBCL	19 (44.2)	30 (43.5)	24 (35.8)	
M. Myeloma	14 (32.6)	31 (44.9)	40 (59.7)	
Other	2 (4.7)	1 (1.4)	0 (0)	
Pre-collection RT				
Yes	8 (19.5)	6 (9.5)	9 (14.3)	0.348
No	33 (80.5)	57 (90.5)	54 (85.7)	
Chemo-mobilization				
G-CSF alone	3 (7.1)	9 (13.8)	7 (10.6)	0.552
Chemotherapy	39 (92.9)	56 (86.2)	59 (89.4)	
CD 34 cell count (million/kg)	8.35 (3.80)	7.40 (5.70)	7.10 (3.80)	0.033
PLT engraftment >20,000 (days)	13 (3)	12 (3)	14 (4)	0.649
PLT engraftment >50,000 (days)	17 (5.5)	13 (5)	16 (3)	0.323
Neutrophil engraftment >500(days)	11 (2)	10 (2)	11 (2)	0.215
Neutrophil engraftment >1000(days)	12 (2)	11 (1)	12 (3)	0.387
G-CSF, days	7 (3)	5 (3)	5 (2)	0.064
Stay in hospital after chemo-mobilization (days)	17 (5)	16 (6)	16 (5)	0.406
Febrile neutropenia in mobilization				
Yes	22 (51.2)	40 (59.7)	37 (55.2)	0.671
No	21 (48.8)	27 (40.3)	30 (44.8)	
Mortality				
Alive	25 (65.8)	44 (81.5)	45 (83.3)	0.101
Dead	13 (34.2)	10 (18.5)	9 (16.7)	
Outcome				
Failure	3 (8.6)	6 (11.5)	2 (4.1)	0.386
Successful	32 (91.4)	46 (88.5)	47 (95.9)	
Poor mobilization with Chemo+G-CSF				
Yes	4 (9.3)	11 (16.4)	7 (10.4)	0.448
No	39 (90.7)	56 (83.6)	60 (89.6)	
3rd-month assessment				
CR	10 (58.8)	15 (60)	19 (65.5)	0.421
PR	3 (17.6)	8 (32)	8 (27.6)	
Progression	4 (23.5)	2 (8)	2 (6.9)	

Descriptive statistics for quantitative variables were given using the median (IQR: percentile 75-percentile 25).

engraftment and mobilization, along with increased G-CSF days. In cases where variables were found together (P>0.05), no statistically significant risk factor was established, according to the stepwise multivariate LR analysis results.

Table 2: Comparison between patient characteristics and CD34+ cell count.

		CD 34 (UL)	
	n	Median (IQR)	*P*-value
Gender			
Female	69	7.1 (4.3)	0.244
Male	111	8 (4)	
Age			
<45	56	7.9 (3.8)	0.336
45-54	51	7.75 (5.6)	
55-59	26	7.5 (4.9)	
60 +	47	7.1 (3.5)	
Chemotherapy serial			
1-2	148	7.7 (4)	0.514
3-4	17	7.15 (2.9)	
Pre-collection RT			
Yes	23	8 (5)	0.848
No	144	7.2 (4.5)	
Diagnosis			
HL	18	7.3 (3.8)	0.089
DLBCL	73	7 (4.2)	
M. Myeloma	85	10 (3.3)	
Other	3	8.15 (5.5)	
BMI			
Underweight/Normal	43	8.38 (3.8)	0.033
Overweight	69	7.4 (5.7)	
Obese	69	7.1 (3.8)	
Chemo-mobilization			
G-CSF alone	19	7 (3.5)	0.046
Chemotherapy	154	7.8 (4.5)	
Disease status			
CR	44	7.4 (5)	0.882
PR	19	7.1 (4.3)	
Progression	8	9.25 (3.35)	

Descriptive statistics for quantitative variables were given using the median (IQR: percentile 75-percentile 25).

Discussion

The present study examined various aspects of obesity and its impact on autologous stem cell transplantation. Obesity stimulates the production of pro-inflammatory cytokines, which subsequently encourage tumor growth [15,16]. Within the adipose compartment, hematopoietic stem cells, lymphocytes, and other hematopoietic cells reside, potentially playing a crucial role in transplant biology and kinetics [15-17]. Several investigations have demonstrated a connection between obesity and unfavorable cancer outcomes [18,19]. Prior studies have identified factors such as age (>60 years), history of radiation exposure, multiple chemotherapy regimens, and previous lenalidomide administration as contributors to poor mobilization [20,21]. While CD34 cell counts declined in groups with risk factors like age and multiple therapies outlined in this study, statistical significance was not established. Moreover, overweight and obese patients displayed reduced CD34+ cell counts. Notably, the association of radiation exposure with outcome aggregation was limited, possibly due to the small proportion of irradiated patients and the diversity of the patient sample. As Moreb et al. [22] indicated, insufficient mobilization risk is notably higher in male MM patients who have undergone multiple chemotherapies and possess a higher optimal body weight. Although gender was identified as a factor influencing mortality, no statistically significant disparity between genders was detected.

The overweight and obese categories had significantly lower cell counts than the underweight/normal groups. Patients with DLBCL faced substantially higher mortality risks than those with MM. Noteworthy mortality risk factors encompassed PLT engraftment values exceeding 50,000 and extended G-CSF administration. A prior single-center study unveiled distinct disadvantages for overweight and obese patients. In the research conducted by Tarella et al. [23], among 121 NHL patients, 28 exhibited a BMI exceeding 28 kg/m^2, with merely five undergoing autologous transplantation. Among the remaining 23 patients, six encountered unspecified dose reductions, shown to impact OS and PFS durations. However, no statistically significant differences in BMI's impact on mortality or disease-free survival were observed. Risk factors for mortality were gender, diagnosis, PLT engraftment values surpassing 50,000, post-chemo-mobilization hospital stays, and G-CSF counts.

Contrastingly, Flegal et al. [24] scrutinized mortality rates related to overweight and obesity in the US population, concluding no escalated mortality rates. Our investigation echoed this pattern, at least in part. Similarly, Wuchter et al. [25] examined a patient cohort mobilized solely through chemotherapy and G-CSF, finding no correlation between body weight and mobilization efficacy. The diversity within patient populations complicates the attainment of definitive conclusions. In contrast, the present study predominantly encompassed

Table 3: Univariate and stepwise multivariate LR analysis of factors for mortality.

	Univariate LR		Stepwise Multivariate LR	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Male vs. Female	2.80 (1.16 6.75)	0.022	1.53 (0.50 4.73)	0.458
Per 10-year increase age	1.01 (0.98 1.03)	0.892		
KT Series 3-4 vs. 1-2	3.39 (0.42 27.41)	0.252		
BMI				
Underweight/Normal	1			
Overweight	0.44 (0.17 1.14)	0.091		
Obese	0.39 (0.14 1.03)	0.056		
Diagnosis				
M. Myeloma	1			
HL	1.22 (0.23 6.54)	0.813	1.15 (0.05 7.61)	0.695
DLBCL	4.84 (1.89 12.39)	0.001	2.20 (0.23 20.66)	0.491
Other	1.38 (0.10 15.18)	0.985	1.43 (0.16 12.87)	0.752
Pre-collection RT	2.54 (0.89 7.26)	0.081		
G-CSF alone and Chemotherapy	0.89 (0.23 3.47)	0.886		
CD 34 (UL) Cell Count	0.93 (0.84 1.04)	0.214		
Stay in hospital after chemo-mobilization (days)	1.08 (1.01 1.15)	0.019	1.00 (0.89 1.12)	0.999
PLT engraftment >20,000 (days)	1.06 (0.98 1.15)	0.153		
PLT engraftment >50,000 (days)	1.07 (1.01 1.14)	0.024	1.06 (0.99 1.13)	0.092
Neutrophil engraftment >500(days)	1.09 (0.90 1.31)	0.370		
Neutrophil engraftment >1000(days)	0.99 (0.95 1.04)	0.795		
G-CSF, days	1.19 (1.03 1.36)	0.017	1.06 (0.85 1.32)	0.614
Febrile neutropenia in mobilization	1.54 (0.67 3.56)	0.309		
Poor mobilization with chemo+G-CSF	0.94 (0.29 3.07)	0.922		
Outcome (Success vs. Failure)	0.46 (0.11 1.93)	0.289		

LR logistic regression, Bold text indicates a statistically significant difference with a *P*-value less than 0.05.

patients mobilized via chemotherapy and G-CSF, wherein CD34 cell counts in the chemotherapy group notably exceeded those in the G-CSF-only group. Additionally, cell counts significantly dwindled within the overweight and obese categories compared to the underweight/normal groups. Evidently, the influence of body weight on mobilization exhibited only partial effectiveness.

Two significant studies conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) yielded congruent findings when investigating autologous outcomes within extensive cohorts of lymphoma and myeloma patients [26,27]. In examining a substantial myeloma cohort, Vogl et al. [26] revealed no discernible distinctions in transplant outcomes between obese and non-obese individuals. Similarly, Navarro et al. [27] ascertained that higher BMI does not impact transplant-related mortality in a comprehensive analysis of autologous lymphoma patients. Additionally, the study reported an elevated overall survival rate among obese patients. Comparing the age distribution, underweight/normal-weight patients displayed lower ages compared to the other groups within the present study. Notably, MM emerged as the predominant diagnosis, followed by DLBCL. Interestingly, MM constituted the prevailing diagnosis among obese and overweight patients, whereas DLBCL held prevalence among individuals with normal and underweight statuses.

Despite the statistically significant disparity in CD34 cell counts between the overweight/obese and underweight/normal groups, it's worth noting that the studies mentioned above collectively indicate that this discrepancy doesn't influence transplant-related mortality. The present study identified several risk factors for mortality, including a PLT engraftment value exceeding 50,000, prolonged hospital stays following chemo-mobilization, and an extended duration of G-CSF administration. Intriguingly, univariate and stepwise multivariate LR models failed to reveal any mortality and survival rate divergence between obese and non-obese patients.

Limitation

The present study has certain limitations, primarily stemming from its retrospective cohort design and the inclusion of diverse disease categories, predominantly lymphoma and myeloma, and the utilization of various mobilization strategies involving G-CSF alone or in conjunction with chemotherapy. Nonetheless, in order to validate and contextualize these findings within contemporary circumstances, additional research efforts are warranted.

Conclusion

The present study uncovered no adverse correlation between obesity and mortality or engraftment among patients with diverse hematological malignancies undergoing AutoHCT. Furthermore, BMI exhibited no impact on neutrophil and platelet engraftment speed. It's worth noting that prior research highlighting negative biases held by physicians toward overweight individuals suggests the potential existence of biases in treatment decisions and processes. The current study dispels the misconception that overweight or obese patients might receive less efficient or safe treatment than their normal-weight counterparts, provided they possess the necessary fitness and qualifications. The study achieves this by demonstrating that diminished CD34+ cell counts do not negatively affect mortality or engraftment. A meticulously designed prospective trial is essential to lend robustness to these findings, ideally through collaborative efforts across multiple centers. Therefore, in clinical scenarios where therapeutic necessity is evident, obesity alone should not deter pursuing AutoHCT for hematological malignancies. This conclusion stems from our inability to discern survival disparities among individuals of varying weight categories: overweight, obese, and normal.

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Factors linked to Kawasaki disease and MIS-C in children with prolonged fever: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the ethics committee of the Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital (protocol number: 120, dated May 11, 2022). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Prolonged fever in children presents a diagnostic challenge due to its diverse underlying causes. While infectious diseases historically played a primary role, recent shifts in disease patterns and the emergence of conditions such as multisystem inflammatory syndrome in children (MIS-C) have added complexity. Understanding factors contributing to prolonged fever, particularly the rise in MIS-C and Kawasaki Disease (KD), is vital for accurate diagnosis and timely intervention. This study aimed to identify the etiologies causing prolonged fever in children with temperatures exceeding 38°C for a minimum of 5 days and to examine its relationship with conditions like MIS-C and KD following the coronavirus disease 2019 (COVID-19) pandemic.

Methods: We conducted a retrospective cohort study at a pediatric hospital in Istanbul, Turkey, involving 243 children aged 3 months to 17 years with prolonged fever (>38°C for ≥5 days) between April 2020 and October 2022. We collected data on patient demographics, clinical characteristics, laboratory results, and final diagnoses. The study categorized patients into Group 1 (KD and MIS-C) and Group 2 (other causes). We performed logistic regression analysis to identify factors associated with KD and MIS-C, using hospitalization days and levels of C-reactive protein (CRP), ferritin, and D-dimer. We calculated sensitivity, specificity, and likelihood ratio values and generated ROC (Receiver operating characteristic) curves. The threshold for statistical significance was set at $P<0.05$.

Results: This study encompassed 243 patients with prolonged fever. The primary causes of admission included infection-related illnesses (60.91%, n=148), MIS-C (18.52%, n=45), and KD (10.70%, n=26). Significant differences were observed in lymphocyte count ($P<0.001$), CRP level ($P<0.001$), ferritin level ($P<0.001$), D-dimer level ($P<0.001$), hospitalization days ($P<0.001$), and echocardiographic findings ($P<0.001$) between the groups. Logistic regression analysis revealed noteworthy associations between the presence of KD and MIS-C and hospitalization days ($P=0.001$), elevated CRP levels ($P=0.018$), elevated ferritin levels ($P=0.009$), and elevated D-dimer levels ($P=0.001$). Ferritin exhibited an AUC (Area under curve) of 0.737 ($P<0.001$), and D-dimer demonstrated an AUC of 0.782 ($P<0.001$) in differentiating between the presence of KD and MIS-C.

Conclusion: The prevalence of infectious and inflammatory conditions remains high in cases of prolonged fever, with a noticeable increase in the occurrence of KD and MIS-C since the onset of the COVID-19 pandemic. Notably, ferritin, CRP, and D-dimer levels are valuable indicators for identifying children at elevated risk of developing KD and MIS-C. While data were collected during the epidemic, additional data collection beyond this period would be necessary.

Keywords: prolonged fever, Kawasaki disease, child, multisystem inflammatory syndrome in children

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Introduction

Over four decades ago, initial investigations were undertaken into the underlying causes of persistent fever in children. Various medical conditions, including infections, specific inflammatory disorders, neoplastic diseases, and rheumatological conditions, can manifest with shared fever symptoms [1]. Typically, fever caused by viral infections often affects children without a discernible cause [2]. In developing nations, fever frequently becomes a reason for hospital admissions. Its prevalence ranges from 0.5 to 3% of all pediatric hospitalizations, with the primary challenge linked to prolonged fever being identifying its underlying source [3]. While most fever instances stem from self-limiting viral infections that resolve naturally, the diagnostic approach differs based on the risk associated with distinct age groups [4]. Cases of prolonged fever with uncertain origins present difficulties for medical professionals and patients, often resulting in extended hospital stays [5]. Fever accounts for roughly 30% of visits to primary care facilities and emergency departments for children [6]. Repeated trips to the emergency room correlate with prolonged durations of children's fevers [7]. Parents may experience significant concerns regarding the potential adverse effects of fever, known as "fever phobia" [8].

Kawasaki disease (KD) represents a medium-vessel vasculitis characterized by an unknown origin and is frequently encountered in children less than 5 years old. The primary hallmark of KD is the onset of an acute, prolonged, and persistent fever [9]. As reported by Verdoni et al. [10] in April 2020, instances of KD in Bergamo, Italy, have escalated by a factor of 30 since the inception of the coronavirus disease 2019 (COVID-19) pandemic. Additionally, there has been a rise in conditions resembling KD in connection with COVID-19 [11]. This specific presentation is acknowledged as multisystem inflammatory syndrome in children (MIS-C) by the United States Centers for Disease Control and Prevention (CDC) [12]. The origin of the pediatric hyperinflammatory condition known as MIS-C can be attributed to the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). While sharing certain similarities with KD, MIS-C is a recently recognized disorder lacking definitive diagnostic tests [13]. The diagnosis of MIS-C necessitates the observation of either a recent COVID-19 infection, direct contact with a confirmed COVID-19 case, or positive outcomes from polymerase chain reaction, serology, or antigen tests [14]. Swift identification and appropriate treatment hold paramount importance for both these conditions.

The evolving nature of prolonged fever in children has spurred the necessity for an exhaustive investigation into its underlying determinants. We postulated that persistent fever in children, characterized by temperatures surpassing 38°C for a minimum of 5 days, exhibits links to diverse underlying causes, with infectious diseases traditionally holding the predominant role. Moreover, considering the shifts in disease patterns and the emergence of conditions like multisystem inflammatory syndrome in children (MIS-C) and KD, we foresee heightened intricacy in the etiological landscape of prolonged fever. Our study aimed to pinpoint the contributing factors to prolonged fever in children and to delve into the relationship between this phenomenon and conditions such as MIS-C and KD, particularly in light of the COVID-19 pandemic. Additionally, this study sought to identify the risk factors associated with both KD and MIS-C.

Materials and methods

Study design and participants

This study employed a retrospective cohort design to investigate potential factors contributing to outcomes that manifested spontaneously throughout the study without deliberate interventions. The primary focus of this study was prolonged fever as the outcome of interest, involving an examination of its potential underlying causes within the study's timeframe.

The research took place at a maternal and children's hospital in Istanbul, Turkey, from 10 April 2020 to 31 October 2022. Our well-established training and research hospital, with a legacy spanning 160 years, serves a diverse patient population ranging from 0 to 18 years of age and provides complimentary medical services. Two-hundred-fifty patients, aged between 3 months and 17 years, who had been admitted to the hospital due to prolonged fever exceeding 38°C (lasting for more than 5 days) [15,16] were assessed. After excluding patients with incomplete data, the analysis was conducted on a cohort of 243 individuals.

Data collection and inclusion criteria

Information was extracted from the hospital's electronic health record system, encompassing patient age, gender, clinical attributes, initial laboratory findings, associated symptoms, clinical indications, ultimate discharge diagnosis, and duration of hospitalization. Two researchers independently reviewed and validated the collected data. Fever was defined as an axillary temperature of ≥38°C upon admission. In our classification, fever was denoted by at least one axillary temperature reading ≥38°C upon admission, meticulously documented using a calibrated thermometer.

Episodes of fever led patients to the emergency unit through three distinct pathways: (i) referrals from other medical facilities, (ii) referrals from outpatient cases exhibiting febrile symptoms, and (iii) referrals from other emergency departments. The duration of the hospital stay was calculated from the admission date to the discharge date.

The hospital stay was calculated from the day of admission to the discharge date. Chest radiographs, blood tests assessing C-reactive protein (CRP) levels, total and differential white blood cell counts (WBC), Ferritin, D-dimer, sedimentation rates, urinalysis, blood and stool cultures, as well as cerebrospinal fluid cultures, were requested based on clinical judgment by the pediatrician.

Cardiac assessments were conducted using echocardiographic data, evaluating various outcomes such as irregularities in coronary arteries, valve regurgitation, pericardial effusion, and ventricular configuration and performance. Utilizing the Z-score categorization method detailed in the revised 2017 American Heart Association guidelines, coronary artery anomalies were categorized according to Z-scores for one or more branches, following established criteria [17].

The inclusion criteria encompassed febrile patients of all ages and genders, identified through triage and documented by the attending physician, supported by diagnostic records, clinical

indicators, and symptoms. Records lacking laboratory test results or inadequate patient demographic and clinical details were excluded.

The study's etiologies were classified into distinct categories: infectious diseases, KD, MIS-C, acute undetermined febrile illnesses, malignancy, and a miscellaneous category. The "others" category combined various etiologies due to their limited case numbers. Patients were segregated into specific groups (KD and MIS-C) based on diagnostic criteria delineated by the American Heart Association [17] and the Centers for Disease Control and Prevention (CDC) [18].

Group classification

Patients were divided into two distinct groups. Group 1 encompassed patients diagnosed with classical KD, atypical KD, and multisystem inflammatory syndrome in children (MIS-C), adhering to well-defined diagnostic criteria. On the other hand, Group 2 consisted of patients afflicted by other origins of prolonged fever, including infectious diseases, acute undetermined febrile illnesses, malignancy, and miscellaneous factors. The primary goal of this comparison was to delineate the unique attributes, laboratory indicators, and outcomes linked to these two groups. Ethical approval was secured from the ethics committee of the Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital (protocol number: 120, dated May 11, 2022). Written informed consent was acquired from all patients or their legal guardians while hospitalized. The study adhered to the principles outlined in the Declaration of Helsinki.

Statistical analysis

In this study, statistical analyses were carried out employing the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA). Alongside descriptive statistical methods (mean, standard deviation, median, and interquartile range), the data assessment involved scrutinizing variable distributions using the Shapiro-Wilk normality test. For comparisons between normally distributed variables, an independent t-test was utilized, while the Mann-Whitney U test was applied for comparisons involving qualitative data.

Logistic Regression analysis was conducted to identify factors influencing the presence of KD +MIS-C. Additionally, Areas under the ROC curve were computed to aid in the differential diagnosis of KD +MIS-C presence. The variables' sensitivity, specificity, positive predictive value, negative predictive value, LR (+) values, and cut-off values were determined. Results were evaluated with a significance level of $P<0.05$.

The sample size was calculated using G*Power 3.1, a software application developed by Franz Faul at the University of Kiel, Germany. Setting the Type I error rate to 0.05 and a confidence level of 90%, the analysis determined that a minimum total sample size of 172 was required.

Results

A total of 322 patients were admitted to our hospital due to a fever lasting longer than 5 days, with 250 patients being hospitalized and 243 included in the study. Table 1 presents the baseline characteristics and laboratory results of the participants. All patients were included in the study. Among them were 126 boys (51.85%), with a median age of 39 months (IQR, 19–58 months).

The mean lymphocyte count in Group 1 was statistically significantly lower than in Group 2 ($P<0.001$). Additionally, CRP, Ferritin, and D-dimer levels were significantly higher in Group 1 compared to Group 2 ($P<0.001$, $P<0.001$, $P<0.001$, respectively). Furthermore, the mean hospitalization days in Group 1 were significantly greater than those in Group 2 ($P<0.001$), and the distribution of echocardiographic findings in Group 1 was notably higher than that in Group 2 ($P<0.001$).

The most prevalent cause of fever was infectious respiratory disease (60.91%), predominantly linked to upper (54.61%) and lower (14.18%) respiratory tract infections, as well as acute otitis media (13.48%). Other common reasons for admission included MIS-C (18.52%) and KD (10.70%) (Table 2). Three patients had positive urine culture test results, while only one exhibited positive blood culture results. Cerebrospinal fluid cultures were sterile among the seven patients who underwent

Table 1: Baseline characteristics and laboratory findings.

		All patients		Group 1 n=72		Group 2 n=171		*P*-value
Age (month)	Mean(SD)	42.71 (28.16)		42.79 (29.56)		42.68 (27.66)		0.821‡
	Median (IQR)	39 (19-58)		34 (20-58)		40 (19-59.5)		
Sex	Female	117	48.15%	40	56.34%	77	44.77%	0.101+
	Male	126	51.85%	31	43.66%	95	55.23%	
Hospitalization (days)	Mean(SD)	6.42 (4.58)		9.39 (4.46)		5.2 (4.05)		<0.001‡
	Median (IQR)	5 (3-8)		9 (7-10)		4 (3-6)		
WBC(10^9/L)	Mean(SD)	13.8 (7)		14.24 (7.96)		13.61 (6.57)		0.526*
Neutrophil(10^9/L)	Median (IQR)	8.76 (6.38)		9.56 (6.79)		8.43 (6.19)		0.288‡
	Mean(SD)	7.5 (4.27-12.26)		7.42 (4.64-12.79)		7.55 (3.83-11.84)		
Lymphocyte (10^9/L)	Median (IQR)	3.73 (2.69)		3.45 (2.42)		3.85 (2.79)		<0.001‡
	Mean(SD)	3.05 (2.04-4.74)		2.84 (1.75-4.6)		3.1 (2.24-4.77)		
Platelet(10^9/L)	Mean(SD)	319.17 (141.07)		327 (185.07)		315.94 (118.76)		0.579*
CRP(mg/L)	Median (IQR)	94.32 (77.51)		128.5 (79.73)		80.22 (72.21)		<0.001‡
	Mean(SD)	76.92 (32.8-137)		117.4 (66.7-177.97)		63.98 (23.47-126.52)		
Ferritin(mcg/L)	Median (IQR)	217.98 (313.59)		390.25 (497.23)		137.52 (97.43)		<0.001‡
	Mean(SD)	134.1 (79.85-240)		230.2 (129.3-325)		117.8 (68.97-180.5)		
D-dimer (µg/mL)	Median (IQR)	1.78 (2.5)		3.24 (3.76)		1.08 (0.99)		<0.001‡
	Mean(SD)	1.05 (0.63-1.96)		2.07 (1.06-3.86)		0.8 (0.52-1.2)		
Sedimentation	Median (IQR)	70.96 (34.65)		88.54 (28.25)		60.89 (34.05)		<0.001‡
	Mean(SD)	77 (42.25-98.75)		98 (81-110)		64 (34.5-85)		
Fever (day)	Median (IQR)	7.7 (2.64)		7.62 (1.69)		7.73 (2.94)		0.361‡
	Mean(SD)	7 (6-9)		7 (7-8)		7 (6-9)		
Cardiac involvement	Absent	198	89.59%	52	73.24%	146	97.33%	<0.001+
	Present	23	10.41%	19	26.76%	4	2.67%	
Comorbidities	Absent	239	98.35%	70	98.59%	169	98.26%	0.852+
	Present	4	1.65%	1	1.41%	3	1.74%	

* Independent t-test, ‡ Mann-Whitney U test, + Chi-square test, CRP: C-reactive protein, MPV: mean platelet volume

lumbar puncture. Cardiac involvement was detected in 23 patients (10.41%) through echocardiography. In the MIS-C and KD groups, 26.72% of patients exhibited cardiac involvement. In this subset, seven patients displayed coronary artery abnormalities, six had myocardial dysfunction, twelve had valvular regurgitation, and two exhibited pericardial effusion. In the other group, 2.67% of patients showed cardiac involvement, with two having minimal mitral regurgitation and two having minimal pericardial effusion. Among all patients, 41.6% reported no additional symptoms. The most common additional complaint was cough (11.52%), followed by rashes (8.64%) (Table 3).

Table 2: The final diagnosis of the patients.

		n	%
Final Diagnosis	Kawasaki Disease	26	10.70
	MIS-C	45	18.52
	Infectious Diseases	148	60.91
	Unidentified febrile illness	21	8.64
	Malignancy	2	0.82
	Others	1	0.41
Infectious Diseases	Acute gastroenteritis	5	3.55
	Acute lower respiratory system infectious diseases	20	14.18
	Encephalitis	1	0.71
	Urinary tract infection	6	4.26
	Lymphadenopathy	10	7.09
	Myositis	2	1.42
	Acute otitis media	19	13.48
	Sepsis	1	0.71
	Acute upper respiratory system infectious diseases	77	54.61

Table 3: Additional symptoms on fever of the patients.

		All patients		Group 1 n=72		Group 2 n=171	
Additional symptoms	Abdominal pain	15	6.17%	11	15.49%	4	2.33%
	Coughing	28	11.52%	0	0.00%	28	16.28%
	Sore throat	16	6.58%	4	5.63%	12	6.98%
	Headache	1	0.41%	0	0.00%	1	0.58%
	Skin rash	21	8.64%	13	18.31%	8	4.65%
	Diarrhea	18	7.41%	6	8.45%	12	6.98%
	Joint pain	5	2.06%	1	1.41%	4	2.33%
	Lymphadenopathy	6	2.47%	0	0.00%	6	3.49%
	Eye slip	2	0.82%	1	1.41%	1	0.58%
	Aphthous lesions	6	2.47%	1	1.41%	5	2.91%
	Febrile seizure	2	0.82%	0	0.00%	2	1.16%
	Conjunctivitis	13	5.35%	5	7.04%	8	4.65%
	Joint swelling	1	0.41%	0	0.00%	1	0.58%
	Ragat	1	0.41%	1	1.41%	0	0.00%
	Vomiting	1	0.41%	0	0.00%	1	0.58%
	Myalgia	3	1.23%	0	0.00%	3	1.74%
	Earache, discharge	3	1.23%	0	0.00%	3	1.74%
	No additional symptom	101	41.56%	28	39.44%	73	42.44%

Logistic regression analysis was conducted using variables such as days of hospitalization, lymphocyte count, CRP level, ferritin level, and D-dimer level to identify factors influencing the presence of KD + MIS-C. Hospitalization days (P=0.001), elevated CRP (P=0.018), elevated ferritin (P=0.009), and elevated D-dimer (P=0.001) were statistically significant (P=0.001) (Table 4). In the differential diagnosis of KD + MIS-C, Ferritin and D-dimer levels exceeded the desired threshold (0.700). The AUC values were 0.737 [0.672–0.795] and 0.782 [0.720–0.836] respectively (Table 5, Figure 1). The cut-off values for sensitivity, specificity, positive and negative predictive values and likelihood ratios of laboratory parameters are presented in Table 6.

Table 4: Logistic regression analysis to search factors affecting the presence of KD+MIS-C.

	OR (%95 Cl)	*P*-value
Hospitalization (days)	1.23 (1.11–1.37)	0.001
Lymphocyte (10^9/L)	1.03 (0.88–1.20)	0.752
CRP(mg/L)	1.04 (1.01–1.09)	0.018
Ferritin(mcg/L)	1.05 (1.02–1.06)	0.009
D-dimer (µg/mL)	2.04 (1.47–2.84)	0.001

CRP: C-reactive protein, OR: odds ratio, Cl: confidence interval

Table 5: Receiver operating characteristic curve analysis.

	AUC	SE	95% CI	*P*-value
Lymphocyte	0.564	0.041	0.495–0.632	0.098
CRP	0.680	0.040	0.612–0.742	0.001
Ferritin	0.737	0.038	0.672–0.795	<0.001
D-dimer	0.782	0.036	0.720–0.836	<0.001

CRP: C-reactive protein

Figure 1: Receiver operating characteristic curves and related areas under the curve for determining KD and MIS-C among patients with long fever.

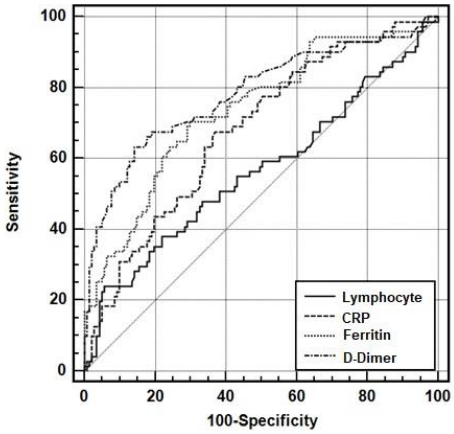

Table 6: The sensitivity, specificity, positive predictive value, and negative predictive value of the parameters.

	Cut-off	Sensitivity	Specificity	PPV	NPV		LR (+)
Lymphocyte	≤1.51	23.94	94.19	63.0	75.0		1.12
CRP	>85.86	67.61	63.95	43.6	82.7		1.88
Ferritin	>154	70.42	70.39	52.6	83.6		2.38
D-dimer	>1.6	63.38	85.71	68.2	82.9		4.44

CRP: C-reactive protein, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio

Discussion

Our research has uncovered that the primary cause of extended fever leading to hospitalization is infectious disease, primarily associated with respiratory tract infections. However, it is important to note that reporting respiratory tract infections has declined at our hospital, a trend attributed to the COVID-19 restrictions implemented [19]. Pediatricians have observed a significant reduction in respiratory viral infections and various infection-related conditions during the COVID-19 pandemic [20].

There has been an increased frequency of cases involving MIS-C and KD after infectious diseases. A study demonstrated that children experiencing febrile illnesses lasting beyond seven days exhibited compromised health-related quality of life [21]. Numerous studies have been published on the origins and evaluation of prolonged fever in children. The predominant cause of fever episodes is non-threatening viral infections that resolve independently without treatment. However, the approach to diagnosis varies depending on the level of risk associated with the child's age [4]. Research indicates that infectious diseases are the leading cause of fever [22,23]. However, there is currently no firmly established predictive significance concerning severe bacterial infection solely based on the prolonged duration of fever before seeking medical care [24,25].

Children often experience fever due to viral infections, even when the precise cause is not readily identifiable [26]. In our investigation, 41.6% of patients displayed no accompanying symptoms. The most prevalent supplementary issue among those who did was coughing, followed by rashes. Mar et al. [27] also noted that an extended fever duration consistently correlated with a sore throat. According to alternate research findings,

approximately 60% of individuals with a sore throat continue to exhibit symptoms beyond the third day [28].

In the study conducted by Klein-Kremer et al. [7], an analysis of fever-related concerns within the participant group revealed that out of 219 individuals (45%), coughing was reported, 148 individuals (30%) experienced vomiting, and 74 individuals (15%) complained of a "runny nose". Following infectious diseases, the prominent causal factors were MIS-C and KD. An entirely novel condition, MIS-C, emerged during the COVID-19 pandemic. This ailment typically manifests after COVID-19 infection and exhibits clinical features, symptomatology, and laboratory characteristics similar to KD. However, it is worth noting that while the two conditions share similarities, they possess distinct diagnostic criteria due to the absence of a singular diagnostic test [14].

As reported by Kim et al. [29], even though there was an increase in the proportion of infants under 1 year of age hospitalized for KD, the prevalence of refractory KD and challenging cases did not significantly increase during social distancing. While MIS-C and KD exhibit marked inflammation and inflammatory vasculopathy, further research is essential to ascertain whether these conditions represent distinct immunopathogenic disorders [30].

Prompt diagnosis and treatment are paramount for both MIS-C and KD. Patients afflicted with both conditions tend to display elevated levels of inflammatory markers [31]. In the acute phase of KD, laboratory indicators such as elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and WBC count will be observed [32]. Leukopenia, rather than an increase in WBC count, is predicted during the acute phase of MIS-C, along with higher CRP and ESR. Troponin, D-dimer, and brain natriuretic peptide levels are frequently elevated. While fibrinogen and ferritin levels are elevated, MIS-C is characterized by more typical increases in D-dimer and ferritin levels [33].

Our study identified statistically significant CRP, ferritin, and D-dimer levels elevations in the MIS-C and KD groups compared to the other groups.

Limitations

Certain limitations of this study must be acknowledged, particularly concerning potential biases that could impact the validity and generalizability of our findings. Firstly, since this study was retrospective and conducted at a single center, it is important to consider the inherent limitations of such a design and the limited external applicability of the results. The study's findings might not offer a fully comprehensive representation of the broader population due to the specific patient pool associated with a single institution.

Secondly, using electronic health records for data collection introduces the potential for information bias. Despite efforts to ensure data accuracy, the study's retrospective nature limits control over data collection, which may lead to potential misclassification of variables.

Furthermore, an inherent limitation of our study design is the absence of a control group. Establishing direct causal relationships between prolonged fever and specific conditions, such as MIS-C and KD, becomes challenging without a comparative group. This limitation restricts our ability to draw definitive conclusions regarding the factors causing these conditions.

Additionally, the study's timeframe during the COVID-19 pandemic might have influenced the results due to changing medical practices. Despite these limitations, this study offers valuable insights into the landscape of prolonged fever in children, illuminating the prevalent causes and associations, particularly in emerging conditions like MIS-C and KD.

In the future, research involving larger multicenter cohorts and longitudinal designs could offer more robust evidence and help address some of the limitations above.

Strengths

This study focused on investigating prolonged fever in a pediatric population, contributing valuable insights into this significant health concern among children. The research involved an in-depth analysis of data from a substantial number of patients, bolstering the statistical robustness and reliability of the findings. The study delved into clinically pertinent outcomes, such as cardiac involvement and diagnostic markers, which are pivotal in making well-informed medical decisions.

Advanced statistical techniques, including logistic regression and ROC curve analysis, were employed to probe the factors influencing the presence of particular conditions. Patients from a maternal and children's hospital with diverse socioeconomic backgrounds were encompassed in this study, amplifying the potential applicability of the discoveries to comparable healthcare settings. By investigating the correlation between prolonged fever and specific conditions, this research addresses gaps in the existing literature, thereby providing valuable insights for clinical practice.

Conclusion

This study imparts valuable insights into the multifaceted nature of prolonged fever in pediatric patients, shedding light on various contributing factors. The prevalence of infectious diseases, KD, and multisystem inflammatory syndrome in children (MIS-C) underscores the evolving landscape of fever etiologies, which the COVID-19 pandemic has further influenced. The study's findings underscore the importance of swift diagnosis and timely intervention, as evidenced by the correlation between elevated inflammatory markers and MIS-C and KD. The distinct immunopathogenesis of MIS-C and KD necessitates ongoing exploration to unravel their nuanced differences.

Looking ahead, collaborative endeavors across various research centers offer the potential to validate and expand upon these revelations, ultimately refining clinical approaches and enhancing patient outcomes. The impact of the pandemic on epidemiology, clinical presentation, and outcomes raises pertinent questions. While data were collected during the epidemic, a need for additional data post-pandemic becomes apparent to comprehensively address these aspects.

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Exploring risk factors and management strategies for endometrial premalignant/malignant lesions in women with abnormal uterine bleeding: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Approval No: 2011-KAEK-25 2023/08-14).
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: Abnormal uterine bleeding (AUB) in women can often be attributed to a range of underlying factors, including endometrial premalignant and malignant lesions. However, despite the prevalence and potential severity of these lesions, the specific risk factors contributing to their development have not been fully explained. This study aims to explore the risk factors linked to these lesions and to elucidate the corresponding management strategies, filling a crucial gap in our understanding of the underlying causes of AUB.

Methods: This retrospective cohort study was conducted among women presenting with AUB and undergoing endometrial biopsy at a gynecology clinic between July 2018 and January 2022. We recorded patients' demographic and clinical characteristics, ultrasonographic findings, and histopathological results of endometrial biopsies. Excluded from the study were patients under 30 years old, pregnant women, those with biopsy results from another center, individuals diagnosed with cancers other than endometrial cancer, cases of insufficient endometrial biopsies, and patients with missing data. The included patients were categorized into two groups: benign and premalignant/malignant, based on histopathological results, and subsequently compared using clinicodemographic findings. Logistic regression analysis was conducted to identify significant risk factors for premalignant/malignant endometrial lesions. We assessed the predictive capacity of endometrial thickness (ET) for premalignant/malignant lesions through receiver operating characteristic (ROC) analysis.

Results: A total of 391 patients were analyzed, with a mean age of 50.9 (7.7) years. Among these patients, 89.3% (n=349) were classified as benign, while 10.7% (n=42) exhibited premalignant/malignant lesions. The premalignant/malignant group displayed higher age and BMI compared to the benign group (55.83 [10.55] vs 50.3 [7.6], P<0.001 and 29.17 [3.40] vs 27.73 [3.67], P=0.018, respectively). Logistic regression analysis identified age, BMI, and ET as significant risk factors associated with premalignant/malignant endometrial lesions. ROC analysis for predicting premalignant/malignant lesions using ET yielded cut-off values of 10.5 mm for premenopausal women (sensitivity 62.5%, specificity 58.7%, AUC [95% CI]: 0.688 [0.56-0.80], P =0.012) and 8.5 mm for postmenopausal women (sensitivity 88.5%, specificity 70.2%, AUC [95% CI]: 0.854 [0.78-0.92]; P<0.001).

Conclusion: In summary, our findings shed light on the pivotal role of age, BMI, ET, and menopausal status in tailoring management strategies for patients with AUB, underscoring the importance of individualized approaches in enhancing patient care. However, definitive conclusions warrant multi-center prospective investigations to validate these findings in a larger population.

Keywords: uterine bleeding, endometrial carcinoma, endometrial hyperplasia, postmenopausal period, pre-menopause

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Introduction

Endometrial cancer (EC) is an increasingly prevalent gynecological malignancy worldwide [1]. While its incidence rates peak in the 60s, it can also manifest before the age of 40 [2]. The primary symptom of EC is abnormal uterine bleeding (AUB), prompting approximately 90% of cases to seek medical attention [3]. Abnormal bleeding patterns associated with EC include intermenstrual bleeding, heavy bleeding, frequent menstruation, and postmenopausal bleeding [3,4]. However, similar bleeding patterns can arise from benign conditions. In cases of AUB, differential diagnosis between cancer and benign causes necessitates histopathological confirmation via endometrial biopsy, curettage, or hysterectomy specimens. Consequently, many women are subjected to unnecessary invasive diagnostic procedures due to cancer risk concerns. Thus, predicting malignancy risk has gained paramount importance in endometrial assessments. Despite ongoing research on markers and diagnostic tools for high-risk prediction, a global consensus on the optimal clinical management of endometrial evaluations remains elusive [5-7].

This retrospective study aims to evaluate risk-based approaches for diagnosing premalignant or malignant endometrial lesions in women presenting with abnormal uterine bleeding. By assessing the efficacy of these approaches, this study seeks to enhance diagnostic accuracy, minimize unnecessary procedures, and contribute to a more informed consensus on managing endometrial assessments in clinical practice.

Materials and methods

This retrospective cohort study was conducted at the Bursa Gemlik State Hospital's Obstetrics and Gynecology Clinic. It involved patients who presented to the gynecology and obstetrics outpatient department between July 2018 and January 2022 and had undergone endometrial biopsy. Ethical approval was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (Approval No: 2011-KAEK-25 2023/08-14). Throughout the study, adherence to the principles of the Helsinki Declaration was ensured.

A total of 427 patients who were over 30 years of age with complaints of AUB and who had undergone endometrial biopsy were reviewed for the study. Demographic data, including age, height, weight, pregnancy history, medical history, physical examination findings, pre-biopsy ultrasound results, and laboratory findings were extracted from electronic medical records. Patients with AUB and documented endometrial biopsy histopathology results were included, while those under 30 years of age, pregnant women, patients with biopsy results reported from another center, individuals diagnosed with cancers other than endometrial cancer, and cases of insufficient endometrial biopsies were excluded. Additionally, patients for whom data retrieval was challenging were excluded from the study to mitigate potential information bias.

In this retrospective study, the sample size was determined based on the available data from the study period. The study aimed to include all eligible cases within the specified timeframe to maximize the available information. While a predetermined sample size calculation was not feasible due to the retrospective nature of the study, efforts were made to include a comprehensive dataset of patients meeting the inclusion criteria. The study size was determined by the number of eligible cases that met the criteria for data availability, enabling us to conduct a meaningful analysis of the research objectives.

Included patients (n=391) were categorized based on histopathological results and divided into two groups: benign and premalignant/malignant. The premalignant/malignant group comprised cases with hyperplasia with or without atypia, endometrial intraepithelial neoplasia (EIN), and endometrial carcinoma. The benign group included cases with findings, such as endometrial fragments, proliferative endometrium, secretory endometrium, endometrial polyps, endometritis, atrophy, and metaplasia. Gynecologic pathologists made the histopathological diagnoses.

Transvaginal ultrasonography (TVUS) was performed before the procedure to measure endometrial thickness (ET) in all patients. Endometrial biopsy samples were obtained using a No. 4 Karman cannula via therapeutic curettage in an outpatient setting. Patients who had not experienced menstruation for over a year were classified as postmenopausal. AUB patterns were classified according to the International Federation of Gynecology and Obstetrics (FIGO) [8]. Bleeding occurring during the regular menstrual cycle was referred to as intermenstrual bleeding, while bleeding that significantly affected the quality of life was categorized as heavy menstrual bleeding. Irregular bleeding that was not cyclic or consistent, but had a normal amount, was defined as irregular bleeding. Bleeding patterns were categorized as postmenopausal bleeding, intermenstrual bleeding, heavy menstrual bleeding and irregular bleeding.

The primary outcome was the incidence of premalignant/malignant lesions. The secondary outcome involved assessing the relationship between endometrial premalignant/malignant lesions and the variables under consideration.

Statistical analysis

Statistical analysis was performed using SPSS statistics for Windows version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Normally distributed continuous variables were presented as mean (standard deviation), while non-normally distributed or continuous non-normally distributed variables were expressed as median (minimum: maximum). Categorical variables were displayed as percentages (%). The normality of data was evaluated using the Kolmogorov-Smirnov test. Non-normally distributed variables were compared using the Mann-Whitney U or Kruskal-Wallis test, while those that were normally distributed were assessed using the Student's t-test or ANOVA. Categorical variable comparisons were conducted using the chi-square or Fisher's exact test. Logistic regression analysis was employed to identify risk factors. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 391 patients were included in the analysis. The mean age was 50.9 (7.7) years, ranging from 36 to 88 years.

The mean BMI was 27.8 (3.6), with values spanning from 17.9 to 38.8 kg/m^2. Among the participants, 241 (61.6%) were premenopausal, while 150 (38.4%) were postmenopausal. The histopathological examination revealed that 349 (89.3%) had benign results, while 42 (10.7%) were classified as having premalignant or malignant conditions. The distribution of histopathological results among the patients is presented in Table 1.

Table 1: Histopathology results of the patients.

	n (%)
Secretory/proliferative endometrium	174 (44.5)
Atrophic endometrium/metaplasia/endometritis	66 (16.8)
Benign endometrial fragments	14 (3.5)
Endometrial polyp	95 (24.2)
Endometrial hyperplasia (atypical /non-atypical)	22 (5.6)
Endometrial intraepithelial neoplasia	13 (3.3)
Endometrial cancer	7 (1.7)

Upon analyzing the patients' clinical and demographic characteristics, it was observed that the mean age in the benign group was significantly lower than that in the malignant group (50.30 [7.16] vs. 55.83 [10.55], *P*<0.001). Furthermore, the proportion of patients over age 60 years was notably higher in the malignant group (Table 2). The groups also exhibited dissimilarities in terms of BMI, with a majority of patients in the malignant group having a BMI >25 kg/m2 (Table 2). Regarding gravidity, parity, systemic diseases, and smoking habits, no substantial differences were noted between the two groups. Notably, the proportion of menopausal patients was significantly higher in the malignant group, and a higher frequency of postmenopausal bleeding complaints was observed within this group (35.5% vs. 61.9%, *P*<0.001). Among premenopausal patients, there were no significant variations in bleeding patterns between the two groups (Table 2).

Table 2: Clinicodemographic characteristics of patients according to groups.

	Benign group (n=349)	Premalignant/ malignant group (n=42)	*P*-value
Age, years	50.30 (7.16)	55.83 (10.55)	<0.001
Age groups, n (%)			
<45 years	82 (23.5)	5 (11.9)	0.002*
45-60 years	240 (68.8)	27 (64.3)	
>60 years	27 (7.7)	10 (23.8)	
BMI, kg/m^2	27.73 (3.67)	29.17 (3.40)	0.018
BMI groups, n (%)			
<25 kg/m^2	76 (21.8)	3 (7.1)	0.007*
25-30 kg/m^2	186 (53.3)	20 (47.6)	
>30 kg/m^2	87 (24.9)	19 (45.2)	
Gravida	2 (0-12)	3 (0-8)	0.445
Parity	2 (0-9)	2 (0-7)	0.599
Any systemic disease, n (%)			
Yes	23 (6.6)	5 (11.9)	0.207*
No	326 (93.4)	37 (88.1)	
Smoking, n (%)	159 (45.6)	20 (47.6)	0.968*
Menopause, n (%)			
No	225 (64.5)	16 (38.1)	0.001*
Yes	124 (35.5)	26 (61.9)	
Premenopausal bleeding pattern, n (%)			
Intermenstrual	72 (31.9)	4 (25.0)	0.601*
Irregular	117 (51.8)	8 (50.0)	
Heavy bleeding	26 (11.5)	2 (12.5)	
Other	11 (4.9)	2 (12.5)	
Postmenopausal bleeding, n (%)	124 (35.5)	26 (61.9)	0.001*
Endometrial thickness, mm	9.41 (2.98)	12.09 (3.59)	<0.001
Premenopausal	10.56 (2.56)	12.56 (3.16)	0.011
Postmenopausal	7.32 (2.52)	11.80 (3.86)	<0.001

BMI: body mass index. Values are given mean (SD) and median (min-max). Mann Whitney-U test was performed. *Chi square test was performed.

In assessing ET through TVUS during the patients' initial presentation, it was evident that the mean thickness was significantly greater in the malignant group compared to the benign group, for both premenopausal and postmenopausal patients (Table 2).

In the logistic regression model applied to identify factors influencing the risk of premalignant/malignant histopathological outcomes, age, the presence of menopause, and ET were found to be significant independent factors (Table 3).

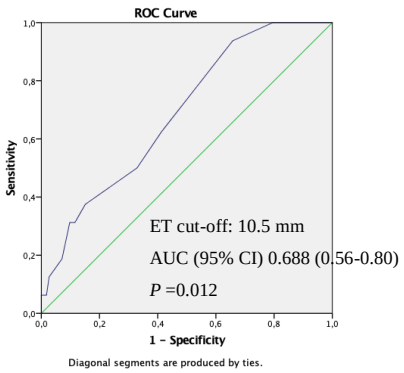
Table 3: Logistic regression analysis for independent factors on premalign/malign histopathology results.

	B	OR (95% CI)	*P*-value
Age, years	0.055	1.05 (1.00-1.11)	0.045
BMI, kg/m^2	0.067	1.06 (0.96-1.18)	0.200
Parity	0.176	1.19 (0.93-1.51)	0.149
Presence of menopause	1.351	3.86 (1.33-11.20)	0.013
ET, mm	0.345	1.41 (1.25-1.59)	<0.001

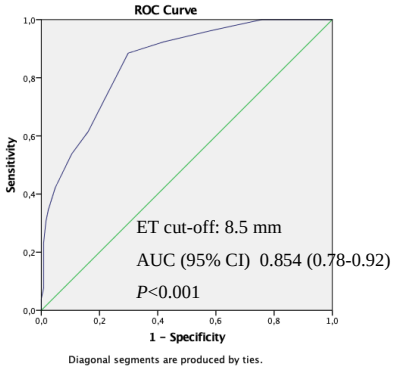
R^2 =0.293, *P*<0.001, BMI: Body mass index, ET: Endometrial thickness

When conducting ROC analysis to determine the optimal ET threshold for malignancy in both premenopausal and postmenopausal patients, the calculated cut-off value for ET was 10.5 mm for premenopausal patients and 8.5 mm for postmenopausal patients (*P*=0.012 and *P*<0.001, respectively) (Figure 1A-B). In premenopausal patients, a threshold of 10.5 mm yielded a sensitivity of 62.5% and a specificity of 58.7% in predicting malignancy (Figure 1A). In postmenopausal patients, a threshold of 8.5 mm demonstrated a sensitivity of 88.5% and a specificity of 70.2% in predicting malignancy (Figure 1B).

Figure 1: ROC analysis for determining the thresholds of endometrial thicknesses for malignancy in premenopausal and postmenopausal patients.



A: ROC analysis for premenopausal patients. The threshold for endometrial thickness (ET) was 10.5 mm with a sensitivity of 62.5%, specificity of 58.7%. AUC: Area under curve, CI: Confidence interval



B: ROC analysis for postmenopausal patients. The threshold for endometrial thickness (ET) was 8.5 mm with a sensitivity of 88.5%, and a specificity of 70.2%. AUC: Area under curve, CI: Confidence interval

Discussion

In individuals with AUB, we conducted a retrospective investigation to identify risk factors associated with the presence of endometrial premalignant and malignant lesions based on patients' demographic information and clinical findings. We found that patients with benign histopathology results tended to be younger and have a lower BMI. Notably, individuals aged 45 years and older with a BMI exceeding 25 kg/m^2 showed a higher frequency of reported premalignant/malignant outcomes.

Regression analysis further confirmed that age, menopause status, and ET were significant predictors for premalignant/malignant endometrial lesions. Upon segmenting patients based on menopause status and examining them in terms of ET, we calculated the ET threshold for premalignant/malignant lesions as 8.5 mm specifically for the postmenopausal group.

Various etiologies contribute to AUB in women during their reproductive years, classified under the FIGO acronym PALM-COEIN [8]. In women with AUB complaints, when suspicion arises following clinical evaluation, endometrial sampling is performed to exclude malignancy. In these cases, age can be considered an important variable in the decision to proceed with biopsy. While there is no globally defined age limit for endometrial biopsy, different guidelines provide divergent recommendations. For instance, Canadian guidelines suggest performing endometrial biopsy in women over the age of 40, whereas the American College of Obstetrics and Gynecology (ACOG) sets the age cut-off at 45 [9,10]. Conversely, studies have reported a lack of correlation between age and endometrial cancer (EC) during the premenopausal period [11]. In our study, we found an increased prevalence of premalignant/malignant endometrial lesions in the presence of AUB among women aged 45 and above, highlighting age as an independent variable for malignancy.

Among the risk factors for endometrial hyperplasia (EH) and endometrial carcinoma, chronic exposure to high estrogen levels or activity was recognized [12]. Obese patients experienced elevated endogenous estrogen levels due to the conversion of androstenedione to estrone and the aromatization of androgens to estradiol, processes occurring primarily in peripheral adipose tissue [13]. In a retrospective study encompassing approximately 900 premenopausal patients with AUB, Wise et al. [11] found that patients with a BMI ≥30 kg/m2 were four times more likely to develop endometrial hyperplasia or carcinoma compared to others. In the current study, although we observed that the majority of patients in the premalignant/malignant group had a BMI above 25, we could not establish this as a significant risk factor. This could be attributed to the smaller number of premenopausal patients in the premalignant/malignant group in our study compared to the study by Wise et al. [11] (16 vs. 41), potentially influencing the statistical power.

Assessment of AUB often begins with imaging methods to identify structural causes, with TVUS being the most commonly utilized technique [14]. Additionally, TVUS is used to assess ET. However, in premenopausal patients, ET can vary due to menstrual cycle fluctuations, limiting its utility in evaluating the presence of endometrial neoplasia. Moreover, consensus is lacking on the cut-off value for ET to detect any abnormality. Furthermore, there are no established screening guidelines for endometrial pathology in premenopausal women with AUB.

Nonetheless, a retrospective study involving premenopausal patients (n=1,084) reported a strong association between ET >13 mm and EH/EC [15]. Our study calculated a premenopausal ET threshold of 10.5 mm with approximately 60% sensitivity and specificity, suggesting its potential association with malignancy. Heremans et al. [16] reported a mean ET of 12.5 mm (95% CI: 10.4-14.6) in the premenopausal group with identified premalignant/malignant conditions and noted that this value could be even thinner in the presence of AUB complaints.

In the case of postmenopausal patients, TVUS can be helpful for endometrial assessment regarding the presence of premalignant/malignant lesions. According to a meta-analysis of around 6,000 postmenopausal patients from 35 prospective studies, when TVUS indicated an ET <5 mm, the probability of endometrial carcinoma was 1% [17]. However, subsequent meta-analyses have suggested that in symptomatic postmenopausal patients, further invasive diagnostic testing should be considered for all patients with a "thin" endometrial thickness [18,19]. A study that included asymptomatic postmenopausal women, reported an ET cut-off value of 6.75 mm with a sensitivity of 84.3% and a specificity of 89.9% for detecting malignancy [20]. In our study, all postmenopausal patients were symptomatic, and we calculated the cut-off value as 8.5 mm. We found that the presence of menopause was a significant determinant for endometrial premalignant/malignant lesions.

In our study focusing on risk factors and management strategies for endometrial premalignant/malignant lesions in women with AUB, several strengths deserve attention. These include the evaluation of each patient by a single physician, consistent application of biopsies and TVUS by the same clinician, inclusion of both premenopausal and postmenopausal patient groups, and the meticulous exclusion of other malignancies and adnexal masses.

Limitations

However, this study has certain limitations that should be acknowledge. The single-center nature, retrospective data collection, absence of additional interventions for advanced endometrial evaluation, inclusion of only symptomatic patients, and the lack of histopathological data from patients who had undergone hysterectomy should be noted as limitations. Future prospective studies could be structured by assessing the data of each patient presenting with AUB, taking into account their hysterectomy outcomes.

Conclusion

In conclusion, our study underscores the significance of a personalized approach in managing patients with AUB, considering essential factors such as age, BMI, ET, and menopausal status. This approach offers a valuable means to circumvent unnecessary interventions and ensures that high-risk patients are directed toward specialized assessment when warranted. However, to refine our understanding and establish well-defined risk factor thresholds, the need for multicenter, high-volume prospective studies becomes evident. By embracing this pursuit, we can pave the way for more precise clinical guidelines and improved patient care in the realm of abnormal uterine bleeding.

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The impact of the 2023 Kahramanmaras (Turkey) earthquake on clubfoot management: A retrospective, observational study

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Ethics Committee Approval
The study was approved by the Gaziantep Islam Science and Technology University non-interventional clinical research ethics committee (approval date: 20.07.2023, protocol No: 2023/280, decision No: 280.27.11).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Clubfoot is the most common congenital foot deformity. Although the etiology and pathoanatomy of clubfoot are not fully understood, dysplasia is present in all musculoskeletal structures below the knee at varying rates. The aim of any treatment regimen is to obtain a pain-free, properly positioned foot that has functional use. The objective of this investigation was to evaluate difficulties in the follow-up and treatment of patients with clubfoot treated in our clinic after the 2023 Kahramanmaras earthquake.

Methods: Data from patients with clubfoot treated with the Ponseti method at the Orthopedics and Traumatology Outpatient Clinic of Gaziantep Metropolitan Municipality Inayet Topcuoglu Hospital in Turkey between December 2022 and July 2023 were obtained from the hospital's electronic registry system. Patient demographics, the number of plaster casts made before the earthquake, the total number of plaster casts made, time delays in treatment due to the earthquake, and costs were all analyzed. The Dimeglio score was used for the morphological classification of clubfoot. We analyzed patient data from three time periods: the time of the initial treatment, the period before the earthquake, and the period after the earthquake.

Results: The study included 31 feet (16 left and 15 right) of 20 patients (11 males, 9 females). The mean age of the cohort was 3.5 months (standard deviation: 1.6 months). The median and minimum/maximum Dimeglio scores were 11 (9, 13), 6 (4, 8), and 9 (7, 11) at first admission, before the earthquake, and after the earthquake, respectively (P<0.001). The number of casts before the earthquake was 4.32 (0.32), and the total number of casts was 9.39 (1.38). The average time delay until retreatment after the earthquake was 12 weeks (range: 8–15 weeks). There was a significant positive correlation between the duration of the delay and the Dimeglio score measured after the earthquake (r=0.392, P=0.029). The additional cost per patient due to the delay was calculated to be 8290.8 ± 5033.761 TRY (308.78 ± 187.43 USD).

Conclusion: The 2023 Kahramanmaras earthquake had a significant impact on the management of clubfoot and other elective procedures. Dealing with the consequences of an unprecedented natural disaster is certainly challenging. However, by adopting carefully designed protocols and therapeutic approaches that are based on the unique characteristics of an illness, we can successfully alleviate the repercussions of such events.

Keywords: clubfoot, earthquake, casting, Ponseti method

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Introduction

Clubfoot is one of the most common congenital orthopedic abnormalities; it occurs in 1–2 cases per 1000 live births worldwide [1]. Clubfoot is approximately twice as common in males than in females [2]. There are varying degrees of pathology in almost all muscle and bone tissues below the knee [1,2]. Clubfoot is a complex pathology, not just a deformity of the foot, that should be treated immediately after birth and monitored regularly. Clubfoot can be accompanied by many deformities; however, the most common type is idiopathic clubfoot (ICF). Diagnosis, follow-up, and treatment are all important because there is a race against time to obtain a fully grounded, pain-free, and functional foot before a child reaches walking age. It is very difficult to obtain a foot with a normal morphology even if there are no disruptions in the treatment process. Any disruptions can manifest as recurrent cases, which will cause additional treatment burdens and negative consequences for patients.

On February 6th, 2023, a pair of earthquakes occurred in the Pazarcık and Elbistan districts of Kahramanmaraş, Turkey 9 hours apart. The temblors had magnitudes of 7.9 and 7.6, respectively, and incurred irreparable material losses in Kahramanmaraş and the surrounding provinces. Over 50,000 people died as a result and more than 120,000 were seriously injured [3]. The earthquake affected residents living in 11 provinces spread over an area of 110,000 square kilometers. As a result of the shaking, roads were blocked, public transport ceased, medical facilities were damaged, and there were significant delays in delivering technical equipment and personnel. Furthermore, there were difficulties delivering patients to medical institutions, and even medical procedures themselves were interrupted. Musculoskeletal and systemic injuries that required urgent treatment during the earthquake were treated in field hospitals that could be established in the nearby provinces and regions [4,5]. Because Turkey had not faced such a disaster in modern times, there were no protocols in place to continue to treat diseases and conditions that required regular and continuous treatment. There is information in the literature regarding how orthopedic pathologies were treated in Turkey during the COVID-19 pandemic, but there are no guidelines as to what to do with semi-elective orthopedic procedures during natural disasters [6]. Patients who could be moved were either sent to unaffected surrounding provinces for treatment, or their treatment processes were interrupted.

It is morally unethical to deliberately delay clubfoot treatment and to conduct an observational study of the consequences. However, the treatment disruption caused by the recent earthquake in Turkey enables such an investigation. Our goal was to evaluate the delay in the treatment of patients with clubfoot who continued their treatment in a hospital in the earthquake zone and the clinical consequences of that situation.

Materials and methods

We assessed disruptions in the ICF treatment process due to the 2023 Kahramanmaras earthquake by collecting data of ICF patients treated with the Ponseti method in the Orthopedics and Traumatology Outpatient Clinic at Gaziantep Metropolitan Municipality Inayet Topcuoglu Hospital from December 2022 to July 2023.

Study design

After receiving approval from the Gaziantep Islam Science and Technology University non-interventional clinical research ethics committee (approval date: 20.07.2023, protocol No: 2023/280, decision No: 280.27.11), the study was retrospectively collected data from 31 legs of 20 patients. The study included patients who had not previously been treated with ICF at another center, had no additional congenital anomalies, and continued all treatment at the clinic. The study excluded cases of relapse, patients whose first treatment was started after the earthquake, and patients whose completed treatment with the Ponseti method and then underwent abduction foot orthosis before the earthquake.

Patient demographics, the number of plaster casts made before the earthquake, the total number of plaster casts made, delay durations, and costs of treatment were analyzed. The Dimeglio score was used for the morphological classification of clubfoot. The Dimeglio scoring system is based on the severity of four different foot pathologies: 1) equinus deformity in the sagittal plane, 2) varus deviation in the frontal plane, 3) derotation of the calcaneo-pedal block in the horizontal plane, and 4) adduction of the forefoot in the horizontal plane. Each parameter is given a score from 0–4, and weakness in the medial fold, cavus, and cruris muscles is recorded as an additional score [7,8]. The higher the Dimeglio score, the more severe the deformity; the highest possible score is 20 (Table 1).

Table 1: Classification of the severity of clubfoot according to Dimeglio score

Severity level	Type	Total score	Reducibility
I	Benign	< 5	Mild-mild correctable
II	Moderate	5 to < 10	Mild-hard, fixable, partially resistant
III	Severe	10 to <15	Hard-soft, resistant, partially correctable
IV	Very severe	15 to 20	Hard-hard, resistant

Statistical analysis

Descriptive analysis was performed using the median and interquartile range for non-normally distributed variables. The normality of the data was examined using the Kolmogorov-Smirnov/Shapiro-Wilk tests. The Dimeglio score variable was evaluated using the Freidman test. The correlation analyses were performed using the Spearman correlation test. We used SPSS 22.0 (IBM SPSS Corp.; Armonk, NY, USA) software. *P*-values smaller than 0.05 were considered to indicate statistical significance.

Results

The study included 31 feet (16 left and 15 right) of 20 patients (11 males, 9 females) with a mean age of 3.5 months (standard deviation: 1.6 months). The median and minimum/maximum Dimeglio scores were 11 (9, 13), 6 (4, 8), and 9 (7, 11) at first admission, before the earthquake, and after the earthquake, respectively ($P<0.001$) (Table 2). The Dimeglio score of all patients decreased significantly from the first measurement to the second measurement, and a significant increase was observed in all patients at the time of the third measurement performed after the earthquake ($P<0.001$ and $P<0.001$, respectively). The mean number of casts applied before the earthquake was 4.32 (0.32) and the total number of casts was 9.39 (1.38). The delay before retreatment after the earthquake was, on average, 12 weeks (range: 8–15 weeks). There was a

Table 2: Classes of disease severity at the time of first arrival, before and after the earthquake according to Dimeglio

	n	Mean	SD	Minimum	Maximum	Percentiles		
						25th	50th (Median)	75th
First arrival Dimeglio classification	31	11.29	1.131	9	13	10.00	11.00	12.00
Pre-earthquake Dimeglio classification	31	5.61	1.054	4	8	5.00	6.00	6.00
Post-earthquake Dimeglio classification	31	9.03	1.278	7	11	8.00	9.00	10.00

SD: standard deviation

significant positive correlation between the duration of the delay and the Dimeglio score measured after the earthquake (r=0.392, *P*=0.029). The additional cost per patient due to this delay was calculated to be 8290.8 ± 5033.761 TRY (308.78 ± 187.43 USD).

Discussion

While many patients' traumatic injuries were treated immediately in Turkey after the 2023 Kahramanmaras earthquake, that accomplishment was possible only thanks to the significant efforts of medical personnel [4,5]. In addition to the loss of life inflicted by the earthquake, the natural disaster also inflicted a pronounced socio-economic burden on the Turkish economy [9,10]. We experienced a similar situation in healthcare as persisted during the COVID-19 pandemic; however, we had no advance warning [11,12]. Many planned medical procedures were postponed as a result of the earthquake [13]. In this study, we evaluated how ICF treatment, which is a semi-elective treatment, was affected by the 2023 Kahramanmaras earthquake.

Pediatric orthopedic deformities are inherently difficult to track and treat over time, and delays, neglect, and relapses can lead to prolongation of the final treatment and a decrease in clinical satisfaction [14,15]. There were difficulties in accessing health care facilities during the COVID-19 pandemic; a similar situation persisted in the aftermath of the 2023 Kahramanmaras earthquake in Turkey. Following this natural disaster, orthopedic procedures were divided into four categories according to their urgency. Patients with clubfoot admitted for treatment for the first time were included in category 3, which corresponded to semi-elective procedures [16]. It was concluded that a treatment delay of up to 3 months, measured from the time of first admission, would not adversely affect patient outcomes [16]. During the pandemic, Chand et al. [11] showed that the number of new admissions decreased by 60%, follow-up visits decreased by 70%, tenotomies decreased by 80% and other clubfoot surgeries decreased by 90%; relapse rates increased by 27% over the pre-pandemic period. Another study demonstrated that there is variation in achilotomy practices among orthopedic surgeons at the pandemic period [17]. All of the patients in our study experienced some sort of delay in treatment that persisted for anywhere from 8–15 weeks). This delay may have been caused by healthcare facilities being damaged, a lack of medical personnel, or personal situations faced by families due to the earthquake. Some authors suggested trying to at least reduce relapse with simple physical therapy methods enacted via telemedicine [6,18].

Even though the literature shows that treatment of clubfoot with the Ponseti method is effective in patients under 10 years old, follow-up with plastering, surgery, and orthosis becomes more difficult as a patient gets older and treatment is delayed [19,20]. Under normal circumstances, ICF cases are expected to reach the tenotomy stage in an average of 4.8 casts (range: 4–6 casts) with the Ponseti method [21]. In our study, the deformity was almost restored in most patients due to the delay; therefore, the average total number of casts made was 9.39 (standard deviation: 1.38). The cost of treating clubfoot varies by country and can range from $170 to $30,000 [22]. As the total number of plaster casts increases, the cost also increases [21]. Costs are also associated with patients' missed work and transport [23]. The additional cost per patient due to earthquake-induced delays was calculated to be 8290.8 ± 5033.761 TRY (308.78 ± 187.43 USD). Direct and indirect cost increases manifest as financial burdens on the state in countries like Turkey where medical interventions are covered for citizens.

Limitations

Our study has several limitations. First of all, this investigation was designed retrospectively. It is a study without a control group, because under normal circumstances patient-induced delays are rare and often not recorded in hospital records. Furthermore, we did not collect any data from the patients' parents. Additionally, our study was based on records from a single center. Because a prospective study cannot be ethically performed by delaying clubfoot treatment, follow-up analysis can only be performed on larger groups of patients if an event such as a natural disaster or pandemic occurs in the future.

Conclusion

Despite the occurrence of natural calamities and pandemics, individuals born with clubfoot will continue to require medical intervention. In the context of Turkey, political figures and the Ministry of Health possess the capacity to formulate meticulously devised treatment protocols that are tailored to specific diseases, with the aim of mitigating the adverse consequences following occurrences of natural disasters. For example, it is possible to arrange parent education programs focused on clubfoot, develop smartphone applications for this purpose, establish a national clubfoot follow-up system under the supervision of the Ministry of Health to document and track patient data throughout the treatment process. By utilizing recorded data and information, patients can receive appropriate treatment or be referred to alternative centers as necessary. From an orthopedic perspective, it is crucial to provide comprehensive training in the management of clubfoot to both pediatric orthopedic experts and all orthopedists. This training should encompass the necessary knowledge and abilities required to effectively carry out basic dynamic surveillance and treatment for this condition.

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Research article

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Effect of waist circumference and body mass index on respiratory function

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Ethics Committee Approval
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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 increase in waist circumference and obesity are among the important human health problems at present. It cannot be denied that this problem, which has a negative effect on many body systems, may also cause negative effects on the respiratory system. Therefore, we aimed to investigate the effect of waist circumference and body mass index (WC and BMI, respectively) on spirometric parameters, such as the forced expiratory volume in 1 s and forced vital capacity (FEV1 and FVC, respectively).

Methods: In this retrospective cohort study, patients who applied to the chest diseases outpatient clinic of our hospital between January 1 and December 31, 2022 and had existing abdominal computed tomography (CT) and pulmonary function test results recorded in the hospital system were included. The WC of the patients was measured using the abdominal CT results. The BMI of the patients was measured using their height and weight values. The correlation between the WC, BMI, and spirometric parameters (FEV1, FVC) was examined.

Results: A statistically significant correlation between the WC and BMI values of the 90 patients included in the study and their FVC and FEV1 values was found. In the relationship between all evaluated parameters, the *P*-value was <0.001. Based on the Spearman's correlation test, it was concluded that WC showed a highly negative correlation with both FVC and FEV1 (−0.984 and −0.870, respectively). BMI also had a high negative correlation with FVC and FEV1 (−0.905 and −0.867, respectively).

Conclusion: Weight gain, which leads to an increase in WC and BMI, appears to have a negative effect on the respiratory system. To maintain good respiratory function, it is recommended that patients adopt lifestyles that help them avoid gaining weight.

Keywords: waist circumference, body mass index, computed tomography, respiratory function test, spirometer

Introduction

Respiratory function is measured using a spirometer, which measures pulmonary function. This test measures specific parameters, such as the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/FVC, forced mid-expiratory flow ($FEF_{25–75}$), and vital capacity (VC). The calculated values are then compared with reference values obtained from healthy individuals with the same demographic characteristics as the patient. These characteristics include gender, age, weight, height, and race. Pulmonary function test results may indicate whether the patient has obstructive, restrictive, or mixed type respiratory failure [1,2]. Obesity can be defined as hypertrophy and hyperplasia of fat storage cells or excessive fat storage. According to the World Health Organization, people with a body mass index (BMI) greater than 30 kg/m^2 are considered obese [3]. Apart from the BMI, obesity and adipose tissue can be measured with different techniques, which include computed tomography (CT) measurements of abdominal adipose tissue and manual measurement of the waist circumference (WC) [4,5].

Obesity has an impact on many systems in the human body; one of the most important systems that obesity affects is the respiratory system. Obesity and/or adipose tissue may have respiratory-related physiological and anatomical effects, such as an increase in workload and a decrease in lung volume [6,7]. It is also known that weight gain is associated with many respiratory diseases, including asthma, chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and sleep apnea [8]. Aside from their effects on the respiratory system, studies proving the association of weight gain and/or obesity with early mortality in adults have been published [9,10]. Numerous studies have examined the effects of obesity on lung function. However, to the best of our knowledge, studies in which the WC measurements are based on CT results and the effect of such values on pulmonary function test results was determined are very limited in number. Thus, this study was conducted to contribute additional information to the few studies in the literature on the effects of CT-measured WC and BMI on the respiratory system.

Materials and methods

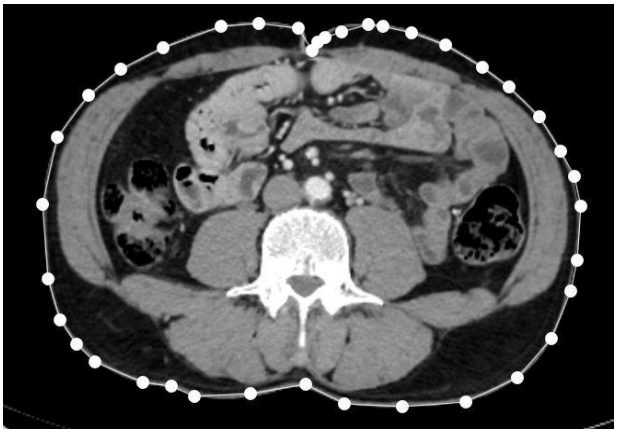
Sample group

This study was designed as a retrospective study with a retrospective cohort. In this study, patients who applied to the chest diseases outpatient clinic of our hospital between January 1 and December 31, 2022 and had both abdominal CT and pulmonary function test results recorded in the hospital system were included. As this study was a retrospective cohort study, it consisted of patients recruited using inclusion criteria without prior calculation of study size or power analysis. Inpatients were not included in the study. Patients who did not have appropriate abdominal CT scans were excluded from the study. Only patients who were over the age of 18 were included in the study. Patients who could not perform the pulmonary function test properly and/or patients with gross intra-abdominal pathology were excluded. Patients with structural and/or interstitial lung diseases or who smoked over 20 packs of cigarettes per year were also excluded. The patients included in the study were divided into two main subgroups: (1) obese and (2) normal groups. Obese patients' BMI and WC measurements were obtained, and the relationship between these two parameters and FVC and FEV1 spirometric parameters was investigated. To avoid potential biases, the radiologist who measured the WC performed the measurements without having any knowledge about the patients. Since BMI was obtained from the files of the patients and consisted of the records obtained before the study, bias did not occur. Ethics committee approval for the study was obtained from Adıyaman University Non-Interventional Clinical Research Ethics Committee (Decision Date: January 24, 2023, Decision No: 2023/1-24)

Imaging

The included patients were imaged using a 16-detector CT scanner (MX16, Philips Medical System, Koninklijke, Netherlands). The CT device parameters were 16 × 0.75 mm beam collimation, 0.75 s turn time, 1 mm slice thickness, 1 mm slice reconstruction, 90–120 kV tube voltage, and 50–110 mAs effective tube current. The abdominal circumference of the patients was measured by analyzing CT images using the Oracle Database program version 1.10.48.299. The abdominal CT images of these patients were evaluated by a radiologist with at least 10 years of experience (Figure 1). Patients who had improper abdominal CT images that prevented evaluation (artifacts, inappropriate image acquisition, and other issues) were not included in the study.

Figure 1: Axial abdomen computed tomography scan cross-section from umbilicus level for measuring waist circumference.



Statistical analysis

A normality test was used to applied to determine whether the variables were not normally distributed. Spearman's correlation analysis was used to determine the correlations between the non-normally distributed variables. Correlation coefficients of 0–0.30, 0.31–0.70, and 0.71–1 were considered low, moderate, and high, respectively [11]. *P*-value <0.05 was considered statistically significant. Statistical analysis of the data was performed using IBM SPSS Statistics for Windows 26.0 (IBM Corp., Armonk, NY, USA).

Results

The study included 90 patients of whom 56 (62%) were male, and 34 (37%) were female. The mean age of the obese patients was 48 years, mean WC was 103.70 mm, mean BMI was 33.04 kg/m^2, mean FVC was 73.24%, and mean FEV1 was 75.20% (Table 1).

Table 1: Demographic characteristics of the participants.

Variable	n	%
Groups		
Healthy	33	36.7
Obese	57	63.3
Gender		
Male	56	62.2
Female	34	37.8
	mean (SD)	
Age	48.00 (11.64)	
WC	103.70 (22.06)	
BMI	33.04 (8.75)	
FVC	73.24 (10.98)	
FEV1	75.20 (9.64)	

n: number of patients, SD: standard deviation

The correlation between WC and the FVC and FEV1 parameters was evaluated. A statistically significant, high, and negative correlation between WC and the lung parameters was found (P<0.001). The correlation between BMI and the same parameters was also evaluated. A significantly high and negative correlation between WC and the lung parameters was also found (P<0.001) as shown in Table 2.

Table 2: Correlation between WC and BMI and the lung parameters, FEV1 and FVC. respectively).

Variable	Value	WC
WC	s	1.000
	P-value	1.000
FVC	S	–0.984
	P-value	<0.001
FEV1	S	–0.870
	P-value	<0.001
Variable	**Value**	**BMI**
BMI	s	1.000
	P-value	1.000
FVC	s	–0.905
	P-value	<0.001
FEV1	S	–0.867
	P-value	<0.001

S: Spearman's correlation, *P*-value: Significance, WC: waist circumference, BMI: body mass index, FEV1: forced expiratory volume in 1 s, FVC: forced vital capacity

Discussion

This study is unique in that the correlation between the WC and BMI parameters of participants and their spirometry test parameters was based on CT scan results that were used to measure WC to acquire more accurate measurements. It was shown that WC and BMI showed highly negative correlations with FVC and FEV1.

In a study by Sutherland et al. [12] on the effect of BMI and WC on lung function in 361 participants, it was found that an increase in BMI and WC caused a significant decrease in the FVC and FEV1 parameters. In another similar study with a sample size of 80 participants, it was reported that an increase in BMI and WC had a negative effect on both FVC and FEV1 [8]. The present study demonstrated similar results. Although the small number of participants compared to the study by Sutherland et al. [12] is a limitation in our study, it is thought that the results of the present study are more specific than those in previous studies since WC measurements were based on CT images.

In a study by Thijs et al. [13], the volume of abdominal adipose tissue of 98 patients was measured using magnetic resonance imaging (MRI), and a volumetric increase in abdominal adipose tissue was found to lead to a significant decrease in the FVC and FEV1 parameters. Considering that the current study included a similar number of patients as their study did and obtained similar results despite using a different test method, the similarity in these findings further proves the relevance of this study.

In a study evaluating 94 patients who underwent surgery for weight reduction, the change in lung function before and after surgery was examined. The BMI, WC, FEV1, and FVC parameters of obese individuals with a BMI >37 kg/m^2 were examined three months after weight reduction surgery, and it was observed that a significant decrease in the BMI and WC of the patients led to significant increase in their FEV1 and FVC parameters [14]. In a similar study, 52 obese patients with obstructive sleep apnea underwent weight reduction surgery. When the pre- and post-operative lung functions of the patients were evaluated, a significant improvement was observed in the patients' FVC and FEV1 parameters [15]. The results of these two studies show that weight loss has a positive effect on lung function. Thus, the finding of the present study, in which participants with lower WC and BMI had better lung function, complements the results of these two previous studies. It is also noteworthy that the number of patients included in these two studies was about the same as the number of participants in our study.

In a study concerning obese patients with asthma and a high BMI, it was observed that weight gain impaired lung function, caused respiratory complaints, and negatively affected the FEV1 and FVC. However, the WC of the patients was not measured in that study [10]. In another similar study, the abdominal adipose tissue of asthmatic patients was volumetrically measured based on CT results. According to the results, the increase in volumetric abdominal adipose tissue led to an increase in the need for inhaled medication in asthmatic patients and led to a decrease in spirometric parameters, such as the FEV1 and FVC [16]. In a study conducted with chronic obstructive pulmonary disease (COPD) patients, who have characteristics similar to asthmatic patients, it was found that a volumetric increase in abdominal adipose tissue caused an increase in respiratory complaints and a significant decrease in parameters, such as the FEV1 and FVC [17]. Although only patients with asthma and COPD were evaluated in the three previously mentioned studies, their results were in line with the present study.

In a study by Ochs-Balcom et al. [18] in which the effect of CT-measured abdominal adipose tissue volume on lung function, was investigated, it was found that increased adipose tissue volume produced a significantly negative effect on the FEV1 and FVC of males, while it had no significant effect on the FEV1 and FVC parameters of females. In the current study, the results were the same for both genders. Therefore, while the results from their study regarding males were in line with our results, the result regarding females were different.

Limitations

Although this study was unique in terms of methodology, it was limited by the fact that it was conducted in a single center, only included a small patient population, and gender and age effects were excluded from evaluation. Researching the correlation between age and gender and the parameters that we evaluated in future studies will contribute new information to the literature. In addition, the results obtained

by including the larger population and multiple centers will be more relevant.

Conclusion

Increasing WC and BMI due to weight gain and obesity, which are among the important problems of present-day human health, have a negative effect on many systems in the body. In this study we investigated the possible negative effects of obesity on the respiratory system. In this study, we revealed negative WC- and BMI-related respiratory system effects, such as causing a decrease in the FVC and FEV1 parameters, as measured in pulmonary function tests.

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Research article

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Is the reduced risk of post-operative nausea and vomiting in low flow anesthesia applications associated with pre-operative neutrophil/lymphocyte ratio values?

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Ethics Committee Approval
The study was approved by the Malatya Turgut Ozal University Clinical Research Ethics Committee (date: April 28, 2022, number: 2022/19).
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: Post-operative nausea and vomiting (PONV) are defined as nausea and/or vomiting occurring within the first 24 h after surgery and are often observed in the first 2 h after surgery. Only a few previous studies on the use of low fresh gas flow that reduces inhaler agent consumption in laparoscopic cholecystectomy patients at high risk of PONV have been published. Our study aimed to determine the incidence of PONV in the first 30 min and again at 24 h in cases of laparoscopic cholecystectomy in which we applied low fresh gas flow (1 L/min). In addition, we wanted to predict whether the pre-operative neutrophil/lymphocyte ratio (NLR) ≥2 is a risk factor for PONV in our patients to whom we applied low fresh gas flow.

Methods: For our prospective cohort study, 80 cases between the ages of 18 and 65, had American Society of Anesthesiologists (ASA) scores of I and II, and who had been scheduled to undergo elective laparoscopic cholecystectomy were included in the study. The NLR limit (calculated by dividing the neutrophil count obtained from the complete blood count before surgery by the lymphocyte count) calculated in the pre-operative period after a patient's informed consent was obtained was accepted as 2 [5]. Patients were classified into two groups: (1) NLR-I with NLR <2 and (2) NLR-II with NLR ≥2. Premedication was not used in either group.

Results: A total of 80 patients were included in the study. They were divided into two groups for classification purposes: (1) NLR-I (n=40) and (2) NLR-II (n=40). The characteristics of the patients in both groups, such as gender distribution, ASA scores, smoking status, mean age, and body mass index (BMI) values, were not different. Sevoflurane consumption in the groups was similar (P=0.169). The time required to complete surgery was longer in the NLR-II group (P=0.025). Nausea/vomiting and antiemetic use were similar in the NLR-I and NLR-II groups in which low fresh gas flow was applied in the first 30 min and 24 h **(***P*=0.500). Although nausea/vomiting was more common in the female and non-smoking group in the first 30 min and 24 h, it was not statistically significantly different from males and smoking groups **(***P*=0.325). However, nausea/vomiting was more common and significantly different in the ASA II versus the ASA I group **(***P*=0.046). The time required to complete surgery was longer, and sevoflurane consumption was higher in patients with nausea and vomiting (P=0.001).

Conclusions: Pre-operative NLR as classified by the two groups was not associated with an increase in the risk of PONV in patients to whom we applied low fresh gas flow. A decrease in sevoflurane consumption due to low fresh gas flow may lead to a reduction in the risk of PONV in at-risk patients.

Keywords: postoperative nausea and vomiting, low fresh gas flow, neutrophil-lymphocyte ratio

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Introduction

Post-operative nausea and vomiting (PONV) are described as nausea and/or vomiting occurring within the first 24 h following surgery with most cases occurring within the first 2 h [1]. Its prevalence has been reported to be around 44%–83% in different studies. The incidence after laparoscopic cholecystectomy is as high as 46% to 72% [2]. PONV leads to a decrease in patient comfort and satisfaction after a one-day laparoscopic cholecystectomy procedure and infrequently results in dehydration, electrolyte imbalances, suture separation, aspiration of gastric contents, esophageal rupture, and hemorrhaging. PONV leads to prolongation of hospital stays and increases procedure-related costs [3]. Important risk factors for PONV include patient-related, anesthetic, and surgical factors [4]. However, PONV has been thought to increase this risk due to it associated inflammation. The neutrophil/lymphocyte ratio (NLR) is a cost-effective parameter that can be used in the follow-up of inflammatory diseases and the limiting value of this ratio has been accepted as 2 [5]. Research has been published that demonstrates a link between the NLR and PONV [6]. A wide range of antiemetics have been studied for the prevention and treatment of PONV [7]; however, none of the available antiemetics are completely effective. Combined antiemetic treatments have been recommended to prevent PONV, particularly in high-risk patients [8,9]. All of these factors have led to the emergence of new studies. However, a few previous studies on the use of low fresh gas flow that reduces inhaler agent consumption in laparoscopic cholecystectomy patients at high risk of PONV have been published.

In our study, we aimed to determine the antiemetic requirement and the incidence of PONV in the first 30 min and 24 h in cases of laparoscopic cholecystectomy in which we applied low fresh gas flow (1L/min). We also wanted to predict whether pre-operative NLR is a risk factor for PONV in the patients to whom we applied low fresh gas flow.

Materials and methods

Ethical approval was received from the Malatya Turgut Ozal University Clinical Research Ethics Committee and dated April 28, 2022 with number 2022/19 for our prospective cohort study. Eighty cases with scores of I/II based on the American Society of Anesthesiologists (ASA) status and those between the ages of 18 and 65 who had been scheduled to undergo elective laparoscopic cholecystectomy were included in the study. Those with a history of PONV and those with hematological problems were excluded from the study. The NLR limit value (calculated by dividing the neutrophil count obtained from the complete blood count as measured before surgery by the lymphocyte count) calculated in the pre-operative period after a patient's informed consent was obtained was accepted as 2 [5]. Patients were divided into two groups for classification purposes: (1) NLR-I (n=40) with NLR <2 and (2) NLR-II with NLR ≥2 (n=40). Premedication was not applied to either group. After a patient was taken to the procedure room, electrocardiography (ECG), heart rate/minute (HR /min.), systolic arterial pressure (SAB-mmHg), diastolic arterial pressure (DAB-mmHg), mean arterial pressure (OAB-mmHg), and peripheral oxygen saturation (SpO_2) were monitored. Age, gender, height, weight, body mass index (BMI), ASA score, smoking status, comorbid diseases, and NLR values of all patients were recorded pre-operatively. Intravenous anesthesia with lidocaine (1 mg/kg), propofol (2 mg kg), fentanyl (1 µg/kg), and vecuronium (0.1 mg/ kg) was administered to both patient groups, and after adequate anesthesia depth was achieved following induction, patients were intubated with the appropriate endotracheal tube and connected to the anesthesia device. End-tidal carbon dioxide ($EtCO_2$), sevoflurane amount, and oxygen flow were continuously monitored after intubation. Fresh gas flow was then adjusted to 1 L min after which 80% O_2 + 20% nitrous oxide3 (N_2O) and 2%–3% sevoflurane were administered. Tramadol (1 mg/kg) for post-operative pain treatment and metoclopramide (10 mg) for PONV were administered. We applied 5 cmH_2O positive-end expiratory pressure (PEEP) to prevent atelectasis during the operation and we managed to keep the bispectral index (BIS) value around 40–50 for the depth of anesthesia throughout the operation. Sugammadeks (Bridion 200 mg/ 2 mL, MerckSharp and DohmeCorp, USA) was used to reverse neuromuscular blockade and patients were transferred to post-operative intensive care after extubation. Sevoflurane consumption, time to complete surgery, nausea, vomiting, and antiemetic requirements of the patients were recorded in the first 30 min in post-operative intensive care and at the first 24 h in the relevant clinic.

Statistical analysis

The conformity of continuous variables such as age, BMI, sevoflurane consumption, and time to complete surgery in the study to normal distribution was evaluated graphically and using the Shapiro–Wilks test. It was determined that age and BMI variables conformed to the normal distribution, and sevoflurane consumption and surgical completion time variables did not conform to such a distribution. Mean, standard deviation (SD) and median (interquartile range [IQR]) values were given in the representation of the descriptive statistics of the variables.

Independent sample t-test was used to compare age and BMI values based on NRL grouping. In addition, the Mann–Whitney U test was used to compare sevoflurane consumption and surgical completion time values based on NLR grouping. The cross tables were created for the comparison of gender, ASA, smoking status, and NLR grouping, and number (n), percentage (%) and chi-squared test statistics were determined. In the comparison of nausea/vomiting conditions between the NLR-I and NLR-II groups, cross tables were created, and number (n), percentage (%) and Fisher's exact test statistics were determined. For statistical analysis and calculations IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used. Statistical significance level was accepted as P <0.05.

Results

A total of 80 patients were included in the study. They were divided into two groups for classification purposes: (1) NLR-I (n=40) and (2) NLR-II (n=40). The characteristics of the patients in both groups, such as gender distribution, ASA scoring, smoking status, mean age, and BMI values were not different (P=0.999) as shown in Table 1 and Figure 1.

Sevoflurane consumption values in the groups were similar (P=0.169). The time required to complete surgery was longer in the NLR-II group (P=0.025) as shown in Table 1 and Figure 2.

Table 1: Characteristic features of neutrophil/lymphocyte ratio I and II (NLR-I and NLR-II) groups

	NLR <2	NLR ≥2	*P*-value
Gender			
Female, n (%)	28 (70.0)	28 (70.0)	0.999*
Male, n (%)	12 (30.0)	12 (30.0)	
ASA			
ASA I, n (%)	11 (27.5)	11 (27.5)	0.999*
ASA II, n (%)	29 (72.5)	29 (72.5)	
Smoking			
No, n (%)	26 (65.0)	26 (65.0)	0.999*
Yes, n (%)	14 (35.0)	14 (35.0)	
Age (years), mean (SD)	48.08 (13.46)	46.05 (13.96)	0.511
BMI, mean (SD)	29.31 (4.31)	28.70 (4.19)	0.523
Sevoflurane consumption (ml), mean (SD) (median)	15.68 (2.03) (15.50)	16.23 (1.82) (16.00)	0.169
Duration of surgery (min), mean (SD) (median)	46.88 (5.82) (47.00)	49.93 (6.08) (49.00)	0.025ǂ

* χ^2 Chi-squared test, ǂ Independent Sample T-Test, Mann–Whitney U test, SD: standard deviation

Figure 1: Distribution of age and body mass index (BMI) values among the neutrophil/lymphocyte ratio I and II (NLR-I and NLR-II) groups

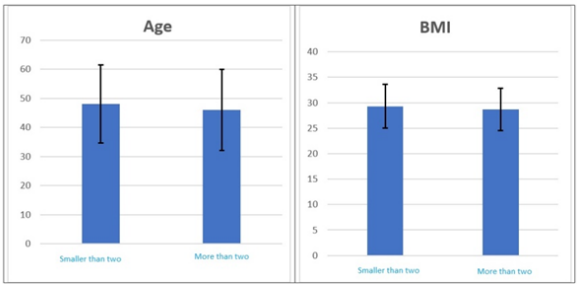
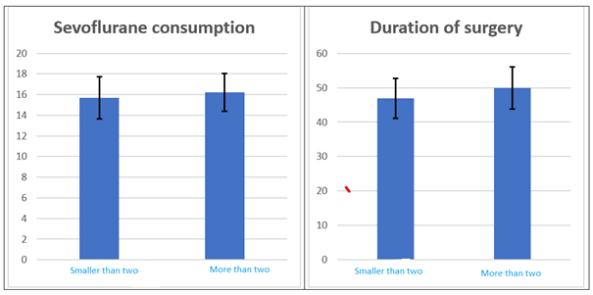


Figure 2: Sevoflurane consumption and duration of operation between NLR-I and NLR-II groups



Nausea/vomiting and antiemetic use were similar in the NLR-I and NLR-II groups in cases in which low fresh gas flow was applied in the first 30 min and at 24 h (*P*=0.500) as shown in Table 2. Although PONV was more common in the female gender and non-smoking group in the first 30 min and at 24 h, PONV was not significantly different than in any other affected patient (*P*=0.325). However, PONV was more common in the ASA II group and was statistically significantly different from the ASA I group (*P*<0.05) as shown in Table 3. The time to complete surgery was longer, and sevoflurane consumption was higher in patients with PONV (*P*=0.001) as shown in Table 3 and Figures 3 and 4.

Table 2: Nausea/vomiting relationship with NLR

	NLR <2 n (%)	NLR ≥2 n (%)	*P*-value
In the first 30 min Nausea/vomiting and antiemetic requirement			
No	36 (90.0)	35 (87.5)	0.500
Yes	4 (10.0)	5 (12.5)	
In 24 h Nausea/vomiting and antiemetic requirement			
No	37 (92.5)	35 (87.5)	0.356
Yes	3 (7.5)	5 (12.5)	

Fisher's exact test

Table 3: The effects of gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI) and smoking status on nausea and vomiting

		In the first 30 min Nausea/vomiting (Yes/No)	In 24 h Nausea/vomiting (Yes/No)
Gender n (%)	**Female**	6 (10.7)/50 (89.3)	5 (8.9)/51 (91.1)
	Male	3 (12.5)/21 (87.5)	3 (12.5)/21 (87.5)
	***P*-value**	0.544	0.450
ASA n (%)	**ASA I**	0 (0.0)/22 (100.0)	0 (0.0)/22 (100.0)
	ASA II	9 (15.5)/49 (84.5)	8 (13.8)/50 (86.2)
	***P*-value**	0.046	0.066
Smoking n (%)	**Yes**	2 (7.1)/26 (92.9)	2 (7.1)/26 (92.9)
	No	7 (13.5)/45 (86.5)	7 (13.5)/45 (86.5)
	***P*-value**	0.325	0.325
BMI	**(median)**	30.70 (5.65)/28.79 (4.02)	31.46 (5.53)/28.74 (4.02)
	***P*-value**	0.206*	0.084*
Sevoflurane consumption	**(median)**	19.78 (1.48)/15.46 (1.36)	20.13 (1.13)/15.49 (1.36)
	***P*-value**	<0.001ǂ	<0.001ǂ
Duration of surgery (min)	**(median)**	60.33 (4.30)/46.89 (4.41)	61.63 (1.99)/46.93 (4.39)
	***P*-value**	<0.001ǂ	<0.001ǂ

* Independent Sample T-Test, ǂ Mann–Whitney U Test, Fisher's exact test

Figure 3: Consumption of sevoflurane with nausea and vomiting in the first 30 min and at 24 h

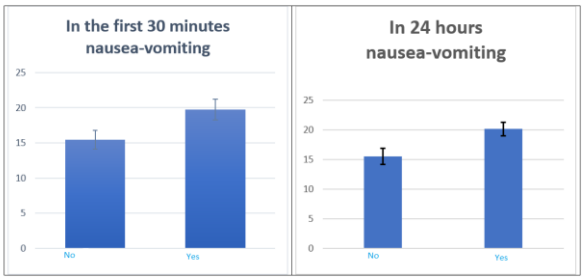
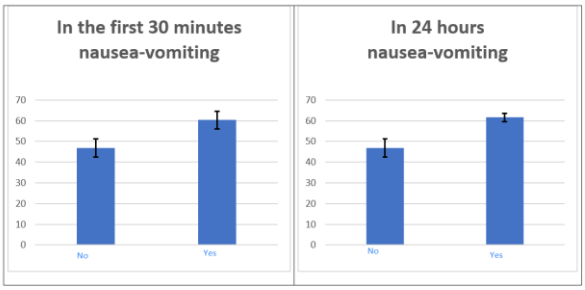


Figure 4: The duration of the operation in patients with nausea and vomiting in the first 30 min and at 24 h



Discussion

The study was conducted prospectively with 80 patients (24 [30%] males and 56 [70%] females) between the ages of 18 and 65 who had been scheduled for elective laparoscopic cholecystectomy. There was similar between the NLR-I and NLR-II groups in terms of gender distribution, ASA score, smoking, mean age and BMI values. In the literature, NLR ≥2 has been shown to be a risk factor for nausea-vomiting [4,6]. However, in our study, it was determined that this risk was significantly reduced with the use of low fresh gas flow. In addition, increased sevoflurane consumption was observed to be correlated with increased PONV. This result indicates that the anesthesia method we applied with low fresh gas flow led to a reduction in the risk of PONV.

Female gender, previous history of PONV and/or car sickness, non-smoking status, and post-operative opioid use are important risk factors associated with the patient predicted to have PONV [10]. A comprehensive meta-analysis of 22 studies addressing risk factors for PONV each involving 500 patients, female gender and non-smoking status were the strongest predictors of PONV among patient-specific risk factors, whereas BMI, and ASA scores were not statistically significant [3]. BMI was not statistically significant in our study. However, PONV was more common in the ASA II risk group. We think that the

existing co-morbidities of the patients in the ASA II risk group had a negative effect on this situation. In addition, although PONV was more common in female patients and non-smokers in our study, female gender and non-smoking status were not identified as risk factors for PONV.

Important risk factors for PONV also include anesthetic and surgical factors. In a comprehensive meta-analysis study in 2012, only three of the 13 surgical categories have been shown to be statistically significant. It has been stated that laparoscopic cholecystectomy, in particular, was the strongest predictor of PONV followed by laparoscopic interventions and gynecological surgery [3]. It has previously been emphasized that antiemetics should be used prophylactically in patients with a high risk of PONV who are undergoing surgery, such as laparoscopic cholecystectomy [11]. Due to the high risk of PONV in our patient group, prophylactic antiemetics were administered. In a study involving 5123 patients, it was shown that 59% of untreated surgical patients complained of nausea and vomiting, while at the same time, only 17% of the patient group who were given antiemetic prophylaxis and avoided emetogenic effects during anesthesia complained of nausea and vomiting [12]. In a study by Erhan et al. [13] that consisted of 80 patients who underwent laparoscopic cholecystectomy, the overall incidence of PONV was 75% with placebo, 35% with ondansetron, 30% with granisetron, and 25% with dexamethasone. In our study, we administered 10 mg of metoclopramide prophylactic to patients with a high risk of PONV, and our PONV rates were 10% in the NLR-I group and 12.5% in the NLR-II group, both of which were quite low. The low consumption of inhalers due to the anesthesia method we applied with low fresh gas flow suggests that this method can lead to a reduction in the risk of PONV.

The use of inhalation agents was identified as the major dose-dependent risk factor for vomiting in the early post-operative interval (0–2 h) in a study enrolling 1180 patients. It was discussed that in the delayed post-operative period (2–24 h), it would be prudent to avoid inhalation anesthesia rather than add an antiemetic to prevent or treat delayed vomiting [14]. In another study, it was shown that the main anesthetic triggers for PONV were inhalation agents, and no significant differences were found between the type of agent [15]. Again, in the study conducted by Apfel et al. [3] in 2012, it was shown that the use of inhalation agents, which is an anesthesia-related risk factor, is the strongest predictor of PONV followed by the duration of anesthesia. The results of our study are also significant in terms of increased antiemetic requirement, increased PONV risk with high sevoflurane consumption, and prolonged surgical time in the early post-operative period (first 30 min) and in the delayed post-operative 24-h period.

In a study by Nelskyla et al. [16] in 2001 with 62 patients, they found that optimized application of sevoflurane with BIS monitoring led to a reduction in PONV and allowed for early recovery in patients who underwent outpatient gynecological laparoscopy. In our study, in which we applied low fresh gas flow with BIS monitoring and optimum sevoflurane consumption, our PONV incidence was quite low.

Opinions differ as to the effect of nitrous oxide (N_2O) use on PONV. In a study conducted by Taylor et al. [17] with 50 patients who underwent laparoscopic cholecystectomy, the incidence of PONV was similar in the group with and without N_2O. However, Apfel et al. [15] mentioned the relative risk for N_2O. A recent study by Peyton et al. [18] revealed that the risk of PONV due to N_2O was time dependent. We think that the use of N_2O, which produced a surgical time of 50 min less than other agents, only had a limited effect on PONV in our study.

The fourth consensus guidance on the management of PONV in adults and children was updated in 2020 by Gan et al. [19] focuses on risk assessment, key-risk prevention, and pharmaco-prophylaxis. In our patient group with a high risk of PONV, we managed to reduce the consumption of inhaler agents, which is one of the key-risks for PONV, by applying low fresh gas flow under BIS monitoring. In addition, the incidence of PONV was found to be very low after prophylactic antiemetic administration.

NLR and platelet to lymphocyte ratio (PLR) are pre-operative inflammatory markers [20]. NLR and PLR can be measured easily and inexpensively and can quickly provide the necessary information for interventions within the first few hours after hospitalization [21]. In their study by Arpaci et al. [22] consisting of 64 patients, it was found that the risk of PONV was significantly higher in patients with NLR ≥2. They have suggested that NLR could be an indicator for PONV, and antiemetic prophylaxis could be given after evaluating the NLR ratio. In another study with 80 patients, the patients were classified into two groups based on their pre-operative NLR values. The need for antiemetics and the risk of PONV was found to be significantly higher in the patient group with NLR ≥2 in the recovery room and at 24-h [6]. In our study, although the patient group with NLR ≥2 had a higher rate of antiemetic requirement and PONV risk in the first 30 min and at 24 h than the NLR<2 group, the difference between these two groups was not statistically significant. Our study suggests that decreased inhalation agent consumption due to low flow anesthesia leads to a reduction in the risk of PONV; thus, high NLR values do not appear to be correlated with an increase in the risk of PONV. However, due to the small number of patients, this result needs to be supported by more comprehensive studies.

Limitation

The fact that our study was conducted in a single center in addition to the relatively small number of patients were restrictive factors. We think that future studies need to be done more comprehensively and prospectively.

Conclusions

Pre-operative NLR was not associated with an increased risk of PONV in patients to whom we applied low fresh gas flow. Decreased sevoflurane consumption due to low fresh gas flow may lead to a reduction in the risk of PONV in at-risk patients.

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Evaluation of alanine aminotransferase responses in chronic hepatitis B patients using entecavir or tenofovir disoproxil fumarate

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Ethics Committee Approval
The study was approved by the Izmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (December 07, 2022 and 2022/170).
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: An estimated 300 million individuals worldwide live with hepatitis B virus (HBV) infection. Alanine aminotransferase (ALT) levels, which indicate liver damage when elevated, are among the crucial laboratory parameters frequently monitored in the follow-up of chronic hepatitis B patients. The primary objectives of antiviral treatment are to reduce liver inflammation and prevent the development of hepatocellular carcinoma or cirrhosis by inhibiting HBV replication. This study evaluated ALT responses and identified factors influencing patient responses following initiating entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment.

Methods: This retrospective cohort study collected data from treatment-naive and treatment-experienced patients with elevated ALT levels who received either ETV (0.5 or 1 mg per day) or TDF (245 mg per day) treatment between 2008 and 2018. Pregnant women and patients under 18 were excluded from the study. Elevated ALT levels were defined as greater than 35 IU/L for men and 25 IU/L for women. All patients underwent examinations for ALT, HBV DNA levels, HBeAg, and antiHBe at baseline and every 3–6 months. ALT levels of the patients were monitored for 60 months, and the presence of fatty liver was also documented.

Results: Our study comprised 192 patients with a mean age of 53.7 (13.42) years. The majority of patients, 130 (67.7%), were male. Of these, 97 (50.5%) started ETV treatment, while 95 (49.5%) began TDF treatment. The median baseline ALT levels of the patients were 68 (44–133.5) IU/L, and the median ALT levels at the 60th month were 24 (18–32) IU/L. The median initial HBV DNA level was 114,282 (267.5–5,029,875) IU/mL, and the median HBV DNA levels from the 6th month onwards were 0 (0–0). ALT normalization was observed in 44.8% of men and 28.1% of women at 3 months, which was statistically significant (P=0.034). Normalization rates by gender remained consistent in all other months. No significant differences were noted in this regard. ALT normalization rates were 58.5% at the 6th month and 74.7% at the 24th month in the ETV group, significantly higher than in the TDF group (P=0.01, P=0.02, respectively). In patients with fatty liver, ALT normalization rates were significantly lower at 6, 12, 24, and 48 months than those without fatty liver (P=0.01, P=0.01, P=0.009, P=0.002, respectively).

Conclusion: Although ALT responses to ETV treatment were more pronounced in specific months, both drugs demonstrated overall efficacy. ALT levels in patients with fatty liver remained elevated despite antiviral treatment. Therefore, patients with chronic hepatitis B and fatty liver may require additional support beyond antiviral therapy, including metabolic, nutritional, and lifestyle recommendations.

Keywords: hepatitis B, fatty liver, alanine transaminase, tenofovir, entecavir

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Introduction

Currently, it is estimated that approximately 300 million individuals are affected by the hepatitis B virus (HBV) worldwide. In Turkey, the seroprevalence of hepatitis B is approximately 4% [1]. HBV is a DNA virus belonging to the *Hepadnaviridae* family and often presents asymptomatically in infected individuals. The most concerning outcomes associated with this virus are the development of cirrhosis and hepatocellular carcinoma [2]. HBV can be transmitted through various means, including blood contact, sexual transmission, mother-to-baby transmission, and horizontal transmission within families.

Tenofovir and entecavir (ETV) are the most frequently utilized potent antiviral drugs against hepatitis B [3,4]. The primary objectives of antiviral therapy are to diminish liver inflammation and thwart the development of hepatocellular carcinoma or cirrhosis by impeding viral replication. These medications exhibit a high resistance barrier, often necessitating lifelong treatment for patients [5].

Alanine aminotransferase (ALT) stands as one of the paramount laboratory parameters routinely monitored during the follow-up of patients with chronic hepatitis B. Elevated levels of this enzyme can serve as an indicator of liver damage, making regular monitoring an essential tool for healthcare providers in managing this condition and facilitating any required treatment adjustments. The expectation is that using potent antiviral medications, which inhibit viral replication, will suppress liver damage.

The study aimed to evaluate ALT responses and identify factors influencing these responses in patients following the initiation of either entecavir (ETV) or tenofovir disoproxil fumarate (TDF) treatment.

Materials and methods

We collected data from treatment-naive and treatment-experienced patients who exhibited elevated ALT levels and were initiated on either ETV (0.5 or 1 mg per day) or TDF (245 mg per day) treatment between 2008 and 2018. Pregnant women and individuals under 18 were excluded from this study. Treatment-experienced patients had previously received either lamivudine or adefovir dipivoxil. The reasons for patients switching to TDF or ETV included high ALT levels, elevated HBV DNA levels, and/or the presence of side effects. Ethical approval for this study was granted by the local ethics committee on 7/12/2022 under reference number 2022/170 (Ethics Committee of Izmir Bozyaka Training and Research Hospital).

We employed a modified ISHAK scoring system to assess liver biopsies. Following this system, fibrosis stage 3 and beyond signify the progressive impact on the liver [6]. A Histological Activity Index (HAI) score of ≥6 indicated significant hepatic inflammation. Liver biopsy results were included for those individuals for whom data were accessible.

All patients underwent periodic examinations for ALT, HBV DNA levels, HBeAg, and antiHBe at baseline and every 3–6 months. HBV DNA quantification was performed using the *Artus* HBV RG PCR Kit with the QIAGEN Rotor-Gene Q 6000 device (Valencia, CA, USA), which boasts the lowest detection limit of 3.8 IU/mL.

Elevated ALT levels were defined as exceeding 35 IU/L for men and 25 IU/L for women, as per reference [7]. ALT levels of the patients were monitored over 60 months.

Cirrhosis was defined by a nodular liver structure as observed in ultrasonography, signs of portal hypertension such as splenomegaly or varices, and/or a thrombocytopenia count of less than 150,000/mm^3. Additionally, individuals with a fibrosis stage of 4 or higher in liver biopsy results were categorized as having cirrhosis. Patients with fatty liver were also documented.

Diagnosing hepatocellular carcinoma (HCC) was established through dynamic liver magnetic resonance imaging or liver biopsy.

Statistical analysis

Categorical variables were analyzed using descriptive statistics, presented as numbers and percentages. For continuous variables, those conforming to a normal distribution are reported as mean and standard deviation, while those not following a normal distribution are presented as median and interquartile range (IQR). When there were two independent groups, categorical variables were compared using the Pearson chi-square test, while the Cohran Q test was employed for dependent variables with more than two measurements. Statistical analysis was conducted using SPSS 22.0 (IBM Corporation, Armonk, New York, United States), and a two-tailed $P<0.05$ was considered statistically significant.

Results

Our study involved 192 patients with an average age of 53.7 years (standard deviation: 13.42). Most patients, specifically 130 individuals (67.7%), were male. The rate of individuals who initiated either ETV or TDF treatment was 50.5% (n=97) and 49.5% (n=95), respectively. The proportion of patients with prior treatment experience was 46.4% (n=89). In non-naive patients, the mean duration of treatment before changing therapy was 5.26 years (standard deviation: 3.25).

Table 1: Demographic and clinical characteristics of the patients.

Characteristic	n (%)
Age (mean [SD])	53.7 (13.42
Gender	
Female	62 (32.3)
Male	130 (67.7)
Treatment experience	
Yes	89 (46.4)
No	103 (53.6)
Antiviral treatment	
ETV	97 (50.5)
TDF	95 (49.5)
Fatty liver	
0	134 (70.2)
1	42 (22)
2	11 (5.8)
3	4 (2.1)
Cirrhosis	
Yes	14 (7.3)
No	178 (92.7)
HCC	
Yes	5 (2.6)
No	187 (97.4)
E serology before treatment	
HBeAg	54 (29)
Anti hBe	126 (67.7)
HBeag+Anti hBe	6 (3.2)
F score median (IQR)	2 (1-3)
HAI median (IQR)	8 (6-9)

n: number, SD: standard deviation, IQR: interquartile range

Cirrhosis was observed in 14 cases (7.3%), while five cases (2.6%) had HCC. Table 1 presents the demographic and clinical characteristics of the patients.

The patients had a median baseline ALT level of 68 IU/L (range: 44–133.5 IU/L), and at the 60th month, the median ALT level was 24 IU/L (range: 18–32 IU/L). The median initial HBV DNA level was 114,282 IU/mL (range: 267.5–5,029,875 IU/mL), and from the 6th month onwards, the median HBV DNA levels were consistently at 0 (range: 0–0 IU/mL). The 5-year ALT and 2-year HBV DNA follow-up results of the patients are given in Table 2.

Although all patients initially had elevated ALT levels, the ALT normalization rate at 12 months reached 67.7%, and at 60 months, it increased to 73.2%. A statistically significant increase in ALT normalization rates was observed over the 5-year follow-up period (P<0.001) (Table 3).

Table 2: Five-year ALT and 2-year HBV DNA follow-up results.

Months	ALT levels-IU/L Median (IQR)	HBV-DNA levels-IU/mL Median (IQR)
0(n=192)	68 (44-133.5)	114282 (267.5-5029875)
3(n=173)	35 (26-53)	29 (0-514.5)
6(n=188)	29 (23-41.7)	0 (0-46)
12(n=186)	27 (21-36.2)	0 (0-0)
24(n=185)	24 (20-36)	0 (0-0)
48(n=175)	25 (19-34)	-
60(n=157)	24 (18-32)	-

IQR: interquartile range, ALT: alanine aminotransferase

Table 3: ALT normalization rates by months.

	ALT normalization		
Months	**Yes n (%)**	**No n (%)**	***P*-value**
0	0 (0)	192 (100)	<0.001
3	68 (39.3)	105 (60.7)	
6	93 (49.5)	95 (50.5)	
12	126 (67.7)	60 (32.3)	
24	123 (66.5)	62 (33.5)	
48	118 (67.4)	57 (32.6)	
60	115 (73.2)	42 (26.8)	

ALT: alanine aminotransferase

ALT normalization was observed in 44.8% of men and 28.1% of women at 3 months, and this difference was statistically significant (P=0.034). Normalization rates based on gender remained consistent throughout the remaining months, with no notable differences observed. In the ETV group, ALT normalization rates were 58.5% at the 6th month and 74.7% at the 24th month, significantly higher than those in the TDF group (P=0.01, P=0.02, respectively).

For patients with fatty liver, ALT normalization rates were consistently lower at 6, 12, 24, and 48 months than those without fatty liver (P=0.01, P=0.01, P=0.009, P=0.002, respectively). A comprehensive comparison of ALT normalization rates during the follow-up period based on the demographic and clinical characteristics of the patients is provided in Table 4.

No significant differences were observed between the groups with and without ALT normalization at the 3rd, 6th, 12th, 24th, 48th, and 60th months regarding age, F score, and HAI scores. ALT normalization status based on age, F score, and HAI scores is presented in Table 5.

Table 4: Comparison of ALT normalization rates during the follow-up regarding patients' demographic and clinical characteristics.

	ALT normalization											
Variables	**3rd month**		**6th month**		**12th month**		**24th month**		**48th month**		**60th month**	
	Yes n (%)	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**	**No n (%)**
Gender												
Female	16(28.1)	41(71.9)	26(41.9)	36(58.1)	37 (61.7)	23(38.3)	39 (65)	21(35)	37 (64.9)	20(35.1)	37 (72.5)	14(27.5)
Male	52(44.8)	64(55.2)	67(53.2)	59(46.8)	89 (70.6)	59 (29.4)	84 (67.2)	41(32.8)	81 (68.6)	37 (31.4)	78 (73.6)	28 (26.4)
P-value	0.034		0.14		0.22		0.76		0.62		0.89	
Treatment experience												
No	34 (36.2)	60(63.8)	54 (54)	46(46)	72 (72.7)	27(27.3)	67 (68.4)	31(31.6)	62 (68.1)	29(31.9)	62 (78.5)	17(21.5)
Yes	34 (43)	45 (57)	39(44.3)	49(55.7)	54 (62.1)	33 (37.9)	56 (64.4)	31(35.6)	56 (66.7)	28 (33.3)	53 (67.9)	25 (32.1)
P-value	0.35		0.18		0.12		0.56		0.83		0.14	
Antiviral treatment												
ETV	33 (37.9)	54 (62.1)	55(58.5)	39(41.5)	67 (72.8)	25 (27.2)	68 (74.7)	23(25.3)	59 (68.6)	27(31.4)	58 (75.3)	19(24.7)
TDF	35 (40.7)	51 (59.3)	38(40.4)	56(59.6)	59 (62.8)	35 (37.2)	55 (58.5)	39(41.5)	59 (66.3)	30 (33.7)	57 (71.3)	23 (28.7)
P-value	0.71		0.001		0.14		0.02		0.74		0.56	
Fatty liver												
No	52 (41.9)	72 (58.1)	73(55.3)	59(44.7)	96 (73.8)	34 (26.2)	92 (72.4)	35(27.6)	91 (74.6)	31 (25.4)	83 (76.9)	25 (23.1)
Yes	16 (33.3)	32 (66.7)	20(36.4)	35(63.6)	30 (54.5)	25(45.5)	30 (52.6)	27(47.4)	26 (50)	26 (50)	31 (64.6)	17 (35.4)
P-value	0.30		0.01		0.01		0.009		0.002		0.11	

Table 5: ALT normalization status according to age, F, and HAI scores.

	ALT normalization											
Variables	**3rd month**		**6th month**		**12th month**		**24th month**		**48th month**		**60th month**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Age Mean(SD)	56.1 (14.2)	52.5 (12.6)	53.7 (14)	53.6 (13.7)	54 (13.6)	53.6 (13)	54 (8)	53.1 (13)	55.4 (12.8)	52.8 (13.8)	55.7 (12.9)	51.4 (12.9)
P-value	0.09		0.95		0.95		0.42		0.20		0.068	
F scores Median(IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-2.25)	2 (1-3)	2 (1-3)	2(1-3)	2 (1-3)	2 (1-3)	2 (1-3)
P-value	0.71		0.44		0.66		0.48		0.87		0.47	
HAI scores Median (IQR)	8 (6-10)	7 (6-9)	8(6-9.25)	7 (6-9)	8 (6-9)	8 (6-9)	8 (6-9)	8(6-10)	8 (6-9)	7.5 (6-9)	8 (6-9)	8 (6-9)
P-value	0.06		0.91		0.81		0.6		0.59		0.47	

IQR: interquartile range, ALT: alanine aminotransferase, SD: standard deviation

Discussion

It is essential to emphasize that despite reducing the overall prevalence of hepatitis B, the number of affected patients, morbidity, and mortality rates remain significant. Antiviral treatments can lead to successful virological, serological, and biochemical responses. This can be crucial in preventing adverse outcomes like cirrhosis and hepatocellular carcinoma (HCC), offering substantial relief to individuals afflicted by hepatitis B [8].

Expectations are that chronic hepatitis B patients who consistently adhere to their antiviral treatment regimen will exhibit treatment responses over several years. It is worth highlighting that achieving virological, serological, and biochemical responses is pivotal for effectively managing hepatitis B. Our study assessed ALT responses over 5 years, revealing that ETV demonstrated superior efficacy at the 6th and 24th months, while both drugs exhibited ALT responses during the remaining months. Furthermore, both ETV and TDF treatments displayed substantial reductions in HBV DNA levels starting from the 6th month. A study conducted by Batirel et al. [9] found no significant difference in ALT responses between patients receiving ETV and those receiving TDF. Virological responses were also comparable across all groups. Another study assessing histological responses in patients receiving TDF or ETV revealed that both groups exhibited similar ALT and virological responses [10]. Based on the findings from these studies, it is evident that both drugs have demonstrated success in terms of virological and biochemical responses.

Hepatocellular carcinoma (HCC) is indeed a worrisome consequence of hepatitis B. Several studies propose that the early normalization of ALT levels following treatment could potentially reduce the risk of HCC in individuals with hepatitis B [11]. The results of our study underscore a notable contrast in the utilization of ETV between patients who achieved ALT normalization and those who did not. It is important to note that only five patients in our study developed HCC; some had pre-existing HCC at the outset of their ETV/TDF treatments. Consequently, no statistical analysis was conducted in this regard.

Hepatitis B and fatty liver can coexist, potentially leading to more severe liver damage. Fatty liver often results from metabolic disorders, nutritional issues, and a sedentary lifestyle. Elevated ALT levels can commonly occur due to hepatitis B or fatty liver [12]. Our research revealed that patients with fatty liver experienced persistent high ALT levels despite consistent antiviral treatment. Another study, encompassing patients with metabolic dysfunction-associated fatty liver and hepatitis B, demonstrated that the coexistence of chronic hepatitis B and hepatic steatosis led to elevated ALT enzyme levels and adverse outcomes [13]. Monitoring liver enzymes in chronic hepatitis B patients and conducting annual abdominal ultrasounds to detect fatty liver are crucial practices. Furthermore, investigating metabolic conditions can assist in identifying necessary dietary adjustments and lifestyle changes to enhance liver health.

Limitations

It is important to recognize that our study has certain limitations warrant consideration. Firstly, the study was conducted at a single center, which may restrict the generalizability of our findings to other populations or settings. Additionally, the sample size of patients was relatively small, potentially affecting the statistical robustness of our results. Furthermore, it is essential to note that the study group was not homogeneous, comprising patients with varying treatment experiences and some individuals with pre-existing HCC and/or cirrhosis at ETV/TDF therapy initiation.

Conclusion

Although we observed more pronounced ALT responses to ETV treatment during specific months, both drugs succeeded. Nevertheless, it is worth highlighting that patients with fatty liver continued to exhibit elevated ALT levels despite receiving antiviral treatment. This suggests that individuals with chronic hepatitis B and fatty liver may necessitate additional interventions beyond antiviral therapy, such as addressing metabolic, nutritional, and lifestyle factors. Tailoring support to meet each patient's unique needs and providing comprehensive care for their overall health and well-being is imperative. Furthermore, there is potential for conducting prospective cohort studies involving homogeneous patient groups to investigate how fatty liver impacts the biochemical response to antiviral treatments in hepatitis B patients.

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Research article

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Primary closure method after asymmetrical excision of a pilonidal sinus treatment: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Bursa City Hospital Ethics Committee with the following decision number: 2022-13/1.
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: There is no gold standard method in pilonidal sinus surgery, because each technique has a recurrence rate. This study aims to evaluate the outcomes of pilonidal sinus surgeries performed by a single surgeon using excision and primary closure technique in a state hospital.

Methods: The study included 159 pilonidal sinus patients operated on by a single surgeon in the General Surgery Department between September 2014 and May 2022. The patients were investigated retrospectively, and age, gender, surgical technique, type of anesthesia administered, time needed to return to normal life, history of previous abscess drainage, long-term complaints in the incision area, number of intergluteal sinuses, postoperative complications and recurrence rates were recorded. Missing information was completed with polyclinic medical records and phone calls. Patients with incomplete data were excluded from the study. An excision and primary closure method was performed on all patients included in the study.

Results: Sixty-seven (42.1%) of the patients were male and 92 (57.9%) were female. The mean age was 27.8 (8.97) years. Twenty-one (13.2%) patients were operated on under local anesthesia, whereas 138 (86.8%) received spinal anesthesia. The mean operative time was 28.87 (8.01) minutes (range: 14-47 minutes). The mean length of hospital stay was determined to be one day (range: 6-24 hours). Surgical-site infections developed in 4 (2.5%) patients and wound dehiscence developed in 14 (8.8%) patients during the postoperative period. Patients developing these conditions were followed up with dressing and antibiotic treatment. The mean postoperative follow-up period was 67 months (range: 1-105 months). Recurrence was detected in six patients during the follow-up period, representing a recurrence rate of 3.8%.

Conclusion: Primary closure after asymmetrical excision of the pilonidal sinus is an easily performed technique with minimal postoperative pain and early wound healing. Additionally, this method has early return-to-work rates and low recurrence rates. We think that this method would be more applicable in pilonidal sinus surgery due to these advantages.

Keywords: pilonidal sinus, primary closure, recurrence

Introduction

A pilonidal sinus is a chronic condition that limits daily activity, causes discomfort, and can result in long-term loss of work. It is most commonly seen in the sacrococcygeal area. It especially affects the teenage to young adult population, ages 15-25 years, and commonly occurs in Turkey. Although there are many techniques described for the treatment of a pilonidal sinus, an ideal treatment modality has yet to be found, due to the high recurrence rates. The cyst should be totally excised during treatment, and different methods are used for the closure. Currently, marsupialization, primary closure, and flap methods are the most frequently used surgical techniques [1,2]. Flap methods have some disadvantages, such as the need for experience, performing wide surgical excision in the gluteal region, complaints of pain and numbness during the postoperative period, and cosmetic problems. Longer healing periods result from techniques where the wound is left completely or partially open, and this is the most significant disadvantage [1-3]. In recent years, studies have been reported that favorably regard the primary closure method, although it has a high recurrence rate [3-5]. This study aims to evaluate the outcomes of patients who underwent surgery using the primary closure method.

Materials and methods

The files of 159 pilonidal sinus patients operated on by a single surgeon using excision and the primary closure method in the General Surgery Department of Çekirge State Hospital between September 2014 and May 2022 were retrospectively investigated. The ages, genders, surgical techniques, types of anesthesia administered, hospitalization periods, postoperative complications, time needed to return to normal life, long-term complaints in the incision area, numbers of intergluteal sinuses, histories of previous abscess drainage of patients, and development of recurrence were evaluated. Missing information was completed with polyclinic medical records and phone calls.

The gluteal region was shaved 12-18 hours before the surgery in all of the patients. A written informed consent form was received from the patients. The surgeries were performed under local and spinal anesthesia. One g IV cefazolin sodium was administered to the patients at anesthesia induction for prophylaxis. The intergluteal region was made more visible in the jackknife position with the help of thick adhesive tapes.

Excision of an elliptical wedge of skin and subcutaneous tissue down to the sacrococcygeal fascia was performed (Figure 1). The surgeon tried to prevent dead space by passing the 0/0 Vicryl sutures through the subcutaneous tissue in the deep plane. The skin was sutured using 3/0 prolene sutures (Figure 2). The patients received ciprofloxacin 750 mg/day tablet for infection prophylaxis postoperatively for five days. Patients were asked to come for a control visit on the tenth postoperative day. Those who were determined to have wound infection and wound dehiscence had weekly follow-up control visits. The patients who had a recurrence were reoperated on.

Ethics committee approval of the study was obtained from Bursa City Hospital Ethics Committee (decision number: 2022-13/1).

Figure 1: Excision of an elliptical wedge of skin

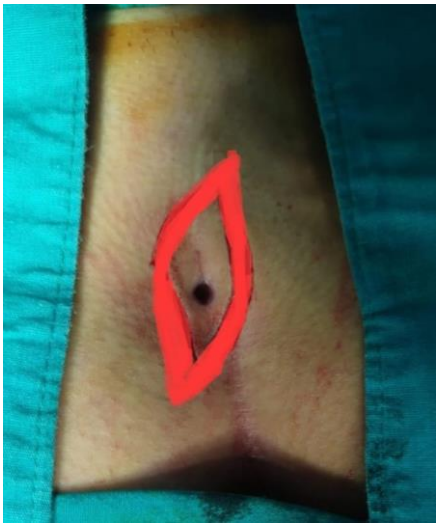
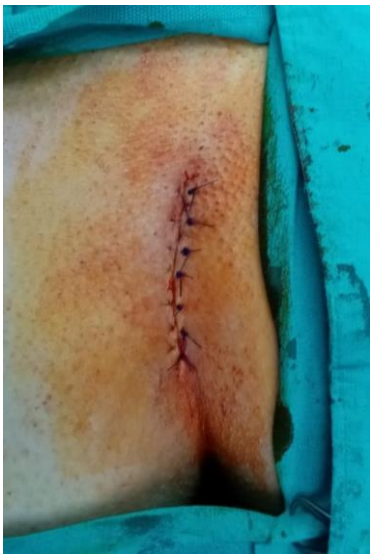


Figure 2: The appearance after surgical excision



Statistical analysis

Conformity of the qualitative data to the normal distribution was evaluated with the Shapiro-Wilk test. Descriptive statistical methods were expressed as mean and standard deviation, or median (minimum and maximum) for quantitative data, and as frequency and percentage for qualitative data. The Mann-Whitney U test was used for the variables without normal distribution. Pearson's chi-square test, the Fisher-Freeman-Halton test, and Fisher's Exact test were used to analyze categorical data. The significance level was determined to be α=0.05. The IBM SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) statistical package program was used for statistical analysis of data.

Results

Sixty-seven (42.1%) of the patients were males and 92 (57.9%) were females. The mean age was 27.85 (8.97) years (range: 15-54 years). All operations were performed by the same surgeon under local anesthesia in 21 (13.2%) patients and spinal anesthesia in 138 (86.8%) patients. The mean operative period was 28.87 (8.01) minutes (range: 14-47 minutes). The mean length of hospital stay was one day (range: 6-24 hours). Surgical-site infections developed in 4 (2.5%) patients and wound dehiscence developed in 14 (8.8%) during the postoperative period. Patients developing surgical-site infection and wound

dehiscence were followed up with dressing and antibiotic treatment. The mean postoperative follow-up period was 67 months (range: 1-105 months).

When patients developing recurrence were compared regarding complications, no statistically significant difference (P=0.223) was found; however, a statistically significant difference was determined regarding the history of previous abscess drainage (P=0.035). The mean period of return-to-work time was six days (range: 1-19 days).

The mean postoperative follow-up period of patients was 67 months (range: 1-105 months). Recurrence was detected in six patients during the clinical follow-ups, representing a recurrence rate of 3.8% in the study. Four of the patients developing recurrence were males and two were females. No statistically significant difference was found between the patients with and without recurrence regarding age, gender, or body mass index (BMI).

Twenty-two (13.8%) patients had a history of previous abscess drainage prior to the surgery. The presence of an abscess in the patients with recurrence (50%) was higher compared to the patients without recurrence (12.4%). This difference was found to be statistically significant (P=0.035).

No statistically significant difference was determined between patients regarding the type of anesthesia administered, hospitalization period, follow-up period, or time needed to return to normal life.

The number of intergluteal sinus pits was found to be higher in patients with recurrence compared to those without recurrence. This difference was considered to be statistically significant (P=0.008).

Discussion

A pilonidal sinus is a chronic condition that deteriorates the quality of life due to reasons, such as recurrent discharge and abscess formation, and can lead to social and psychological problems in the long term. It is more commonly seen among the young adult and male population [6]. While many theories have been proposed related to the development of the condition, today it is thought that the chronic inflammation process starts with the penetration of free hairs into the subcutaneous tissue through the intergluteal sulcus. Clinically, although it can be asymptomatic, it can also manifest itself with various symptoms, such as pain, discharge, and abscess.

Many therapy methods including noninvasive and surgical ones have been offered as treatment for the condition. The most commonly used conservative method is the local application of phenol into the cyst through the sinus orifices [7]. A wide resection to include all sinus orifices is recommended in the surgical treatment. Different surgical techniques, such as excision with open healing, partial closure (marsupialization), primary closure, and flap methods are applied. There is a likelihood of recurrence in all methods. Primary closure has many advantages, such as ease of application, short operative time, no need for further experience, less postoperative pain, earlier wound healing, and earlier return to daily life. The most important complications observed after primary closure are surgical-site infection and wound dehiscence. These complications delay the wound healing, increase the recurrence development, and prolong the time needed to return to daily life. Wound healing problems after the primary closure technique were reported with a rate of 11-34% [4,8]. In our study, this rate was 11.3% and was consistent with previous data in the literature.

Staphylococci and Bacteroides species were determined with a rate of 50% in bacteriological studies performed in the pilonidal sinuses [4,9]. The use of antibiotics Staphylococci and Bacteroides decreases the infection rates [4]. In our study, an oral ciprofloxacin tablet was started in all patients with a dose of 750 mg twice a day during the postoperative period. During this period, surgical-site infection, wound dehiscence, and recurrence in the long follow-up period were detected in 4 (2.5%), 14 (8.8%), and 6 patients; respectively.

Patients developing surgical-site infection and wound dehiscence were followed up with dressing and antibiotic treatment. The mean postoperative follow-up period was 67 months (range: 1-105 months), and recurrence was detected in six patients during this time. The recurrence rate was found to be 3.8% in the current study. Re-excision and primary closure were performed in patients with recurrence. Other complications were treated conservatively.

In a study comparing the primary closure and Limberg flap reconstruction treatment methods, the likelihood of development of infection was shown to be ten times less in patients treated with the Limberg flap reconstruction method than those treated with the primary closure method (10). In a study comparing four surgical methods, the infection rate in primary closure, marsupialization, excision without closure, and the Limberg flap reconstruction methods was 14%, 9%, 3%, and 8%, respectively [11]. In our series, surgical-site infection was observed with a rate of 2.5%.

The development of recurrence after pilonidal sinus surgery is one of the most important problems to date. The diagnosis of recurrence is made with the formation of a new cyst after the penetration of the hair follicle into the subcutaneous tissue or the presence of a hair follicle in the granulation tissue after surgery. Recurrence after primary closure was reported with a rate of 0-42% in the literature [1,4,5,12]. Although some studies demonstrating higher recurrence rates after primary closure have been presented, studies supporting the primary closure method have also been published, especially in recent years. While Nihat et al. [1] reported the average recurrence rate after primary closure as 3%, the recurrence rate was reported to be 7.4% in the study performed by Bulent et al. [6]. These different results detected in the recurrence rates after primary closure are still a topic of discussion. This condition can be explained by differences in the selection of patient groups, surgical techniques, and follow-up periods. In our study, the recurrence rate was found to be 3.8%.

Wound healing takes an average of 40-60 days after open healing or marsupialization following pilonidal sinus excision. The patients have more frequent dressing in this period and the defect is expected to heal with granulation tissue. The wound heals on average in ten days after primary closure, and thus return-to-work time is earlier [4,14]. In the current study, the mean period of return to daily life was determined to be six days. These results show that primary closure is more

advantageous than open healing and marsupialization techniques. Complaints, such as pain, numbness, and paresthesia on the incision line are more commonly encountered, especially in patients undergoing the flap method. In our study, no patients described complaints of paresthesia, numbness, or pain related to the wound site during the long postoperative period. When compared with the primary closure, the flap method results in wide scar tissue formations in the gluteal region, which is cosmetically undesirable. Hence, cosmetic dissatisfaction was reported as an important disadvantage in a study conducted on the Limberg flap reconstruction method [14]. No patients stated dissatisfaction with the surgery in our study.

Strengths and Limitations

The greatest strength of the study is that all cases were performed by a single surgeon with the same technique. The study has a number of possible limitations. Our data contains only cases taking place at the Çekirge State Hospital. In addition, the number of cases was limited due to the fact that it was a study performed by a single surgeon. Consequently, the need for future prospective studies with more patients is needed.

Conclusion

Currently, many different surgical techniques are used in pilonidal sinus surgery. The primary closure technique is a treatment method that can be easily performed in pilonidal sinus surgery due to the advantages of minimal postoperative pain, early wound healing, early return-to-work time, and acceptable recurrence rates.

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Research article

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Monocyte to high-density lipoprotein ratio and neutrophil to lymphocyte ratio in trigeminal neuralgia patients: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the Dokuz Eylül University Faculty of Medicine ethics committee (date: March 5, 2018, number: 32151665-210.03-18389).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Trigeminal neuralgia (TN) is a prevalent cranial nerve disorder. While inflammation has been implicated in neuropathic pain in numerous recent studies, its role in TN has remained uncertain. Given the increasing significance of neuroinflammation, this study aims to explore the association between inflammation and TN and to assess whether there are disparities in the monocyte to high-density lipoprotein ratio (MHR) and neutrophil to lymphocyte ratio (NLR) values between TN patients and healthy individuals. There is a dearth of literature concerning the link with MHR, a parameter extensively studied in cardiac research but unexplored in the context of TN.

Methods: This retrospective cohort study encompassed 48 patients diagnosed with classical TN and 40 healthy controls treated at the neurology and pain clinic of Dokuz Eylül University. Demographic and clinical variables, such as age and gender, along with monocyte, neutrophil, lymphocyte, and high-density lipoprotein (HDL) levels, were retrospectively retrieved from medical records. Inflammation markers, namely MHR and NLR, were calculated. Nonparametric tests were employed to compare these markers between TN patients and healthy controls.

Results: Regarding sociodemographic data, the average age of the patient group was 59.8, while that of the healthy group was 47.4. A significant age difference was observed between the patient and healthy groups (P<0.001). However, no significant differences between the groups regarding MHR or NLR values were detected.

Conclusions: These findings may suggest the presence of an inflammatory process characterized by local neurogenic inflammation in the pathophysiology of TN. Further comprehensive studies are required to assess the utility of MHR as a readily applicable marker in neurological disorders with neuroinflammatory and neuropathic pain etiologies.

Keywords: inflammation, neutrophil to lymphocyte ratio, monocyte to high-density lipoprotein ratio, trigeminal neuralgia

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Introduction

Trigeminal neuralgia (TN), defined by the third edition of the International Classification of Headache Disorders (ICHD-3), is characterized by recurrent, unilateral pain that abruptly initiates and terminates, resembling a brief electric shock. This pain is localized to one or more branches of the trigeminal nerve and can be triggered by seemingly innocuous sensory stimuli [1]. The second and third branches of the trigeminal nerve are predominantly affected. Incidence rates in various studies range from 4.3 to 27 per 100,000 individuals, with a lifetime prevalence estimated between 0.016% and 3% in population-based studies. While the age of onset can vary, classical trigeminal neuralgias typically manifest around age 53, whereas secondary trigeminal neuralgias tend to appear at age 43. The primary cause of classical TN is often attributed to the trigeminal nerve compression by arterial structures in the cerebellopontine system or morphological alterations. Anatomical investigations have revealed a gradual transition from Schwann cell myelinization to oligodendroglia within the proximal 25% of the nerve. This transition zone is considered vulnerable to compression, particularly by vascular structures [2].

Irrespective of the underlying etiology, a common thread emerges in numerous neurophysiological, neuroimaging, and histological studies: the central pathophysiological mechanism revolves around focal demyelination of the primary trigeminal afferent at the point where the trigeminal root enters the pons. Consequently, the nerve becomes hyperexcitable as demyelination progresses to a stage where ions are permitted to flow in and out within the axon, making it challenging to maintain the resting potential at the Ranvier nodes. This phenomenon may play a role in the pathophysiological processes associated with ephaptic conduction and secondary central sensitization [2].

Recent evidence suggests a correlation between neuroinflammation mediated by the chemokine-cytokine network and neuropathic pain. In the peripheral nervous system, inflammatory cells begin to aggregate around the affected nerve following nerve damage, releasing chemokines and cytokines, ultimately leading to chronic neuroinflammation and peripheral sensitization. Initially, the myelin component in sensory nerves, composed of Schwann cells and resident macrophages, becomes activated. Subsequently, circulating leukocytes, primarily neutrophils during the initial stages, accumulate around the injured nerve. Previously activated leukocytes then bolster macrophages. Macrophages play a pivotal role in driving the progression of neuroinflammation, clearing debris, facilitating tissue repair in Wallerian degeneration, and activating lymphocytes. Ultimately, lymphocytes congregate around the damaged nerve, contributing to the development of neuropathic pain [3]. In 2011, it was observed that patients with complex regional pain syndrome exhibited a significantly higher inflammatory phenotype in their monocytes compared to healthy controls [4].

Microglial cells are specialized, resident macrophage-like cells within the central nervous system (CNS). They are responsible for maintaining the CNS microenvironment and regulating immunity. Microglial cells initiate a classical pro-inflammatory response in response to threats or pathogens. Ideally, once the threat is controlled, an immunomodulatory response should engage, dampening the inflammatory reaction and restoring homeostasis. However, any disruptions in this process can lead to increased damage, potentially resulting in cell death and neurodegeneration. It is believed that the pro-inflammatory activation of microglia may contribute to the pathogenesis of neurodegenerative diseases such as Parkinson's disease and multiple sclerosis (MS) [5].

Previous studies have identified leukocytes and specific lymphocyte subtypes as inflammatory markers in cardiovascular diseases. The neutrophil to lymphocyte ratio (NLR) can be readily determined by assessing neutrophil and lymphocyte counts in peripheral blood samples. Previous research has underscored its potential as a novel inflammatory marker in cardiac conditions and non-cardiac diseases [6].

Collateral neuronal damage often accompanies primary neuroinflammatory diseases and may also represent a potential outcome of primary neurodegeneration. Current research has shed light on intriguing parallels between Alzheimer's disease and MS [7].

Seeking to shift the phenotype of macrophages from a pro-inflammatory state to an anti-inflammatory one may present a more favorable therapeutic approach than outright inhibition of their function within the damaged nerve. This is crucial because macrophages are pivotal in nerve repair [8].

Recently, the monocyte to high-density lipoprotein ratio (MHR) value, calculated by dividing the monocyte count by the high-density lipoprotein (HDL) level, has emerged as a noteworthy inflammatory marker in the cardiovascular domain. Several studies in the field of neurology have suggested its potential significance as a novel prognostic marker [9]. While the involvement of inflammation in neuropathic pain has been proposed in numerous recent investigations, its role in TN has remained elusive. Given the growing emphasis on neuroinflammation, the current study explores the connection between inflammation and TN, aiming to discern any disparities in MHR and NLR values between TN patients and healthy individuals.

Materials and methods

This retrospective cohort study was conducted at the Dokuz Eylül University Faculty of Medicine, Department of Neurology and Pain in İzmir, Turkey. The study received approval from the Dokuz Eylül University Faculty of Medicine Ethics Committee on 5 March 2018, with the reference number 32151665-210.03-18389, and it was carried out following the principles outlined in the Helsinki Declaration.

In this study, we conducted a retrospective analysis of blood values in patients who presented to our Pain and Neurology Headache Outpatient Clinic and were diagnosed with classical TN. We focused on patients undergoing blood tests to assess their MHR and NLR values. We examined patient records from 2007 to 2017, extracting demographic and clinical data, including age, gender, monocyte levels, neutrophil levels, lymphocyte levels, and HDL levels from their medical records. To serve as a control group, we calculated MHR and NLR values, which serve as inflammation markers, for 40 healthy

individuals who met similar exclusion criteria, had no comorbidities, and had visited the outpatient clinic within the last month.

The exclusion criteria for this study encompassed individuals with the following conditions: diagnosed chronic inflammatory diseases, infections, diabetes mellitus, severe liver and chronic kidney diseases, rheumatic and hematological diseases, coronary artery disease, heart disease, individuals undergoing steroid therapy, and those with a history of cancer.

The patient group's follow-up period was meticulously documented. During their visits to the outpatient clinic, blood tests and lipid profiles, including low-density lipoprotein (LDL) and HDL, were assessed either on the date of their appointment or within a 6-month timeframe. Furthermore, we calculated the average HDL values from their multiple hospital admissions between 2007 and 2017. Any additional coexisting medical conditions were duly recorded.

To ensure accuracy and reliability, we separately calculated the MHR at the first presentation and the MHR based on mean HDL values. Multiple HDL measurements were averaged to enhance the precision of our calculations.

Statistical analysis

We employed IBM SPSS Statistics software version 24.0 (IBM SPSS, Inc., Tokyo, Japan) for our statistical analyses. Descriptive statistics were presented using mean values, standard deviations, and medians. Due to the non-normal distribution observed between the patient and healthy groups, we applied the independent samples Mann-Whitney U test, a nonparametric statistical method. Results with a *P*-value below 0.05 were considered statistically significant.

Results

In a retrospective review of records spanning the past 10 years, 90 patients diagnosed with classical TN were included in the study. Twenty-four patients were excluded due to concurrent medical conditions, while 18 patients were excluded due to incomplete blood test results. The final patient group comprised 48 individuals. Additionally, 40 individuals without any concurrent medical conditions were selected as healthy controls from the retrospective records.

The average age of the patient group was 59.8 years (range: 24.0 to 85.6), while the healthy group had an average age of 47.4 years (range: 23.3 to 69.8). The patient and healthy groups had a significant age difference ($P<0.001$). Gender distribution among healthy subjects and patients, along with age averages and the patient's years of follow-up, are presented in Tables 1–3.

Table 1: Numbers and percentages of healthy and patient groups (number given as n)

	Healthy group	Patient group
Gender		
Female, n (%)	22 (55)	28 (58.3)
Male, n (%)	18 (45)	20 (41.7)
Total, n	40	48

Table 2: The mean age, minimum, maximum and standard deviation values of the healthy and patient groups

	Healthy group		Patient group	
Variable	**Min.-Max.**	**Mean (SD)**	**Min.-Max.**	**Mean (SD)**
Age	23.3-69.8	47.4 (12.1)	24.0-85.6	59.8 (15.4)

SD: standard deviation

Table 3: Number of patient group follow-up years

Patient group	n (%)
Follow-up years	
0-1 years, n (%)	23 (47.9)
2-5 years, n (%)	17 (35.4)
> 5 years, n (%)	7 (14.6)
>10 years, n (%)	1 (2.1)
Total n	48

The Mann-Whitney U test, a nonparametric statistical method, was employed for the independent samples. The analysis revealed no significant differences in white blood cell and monocyte values between the patient and healthy groups.

HDL data was available for 29 patients in the patient group and 39 subjects in the healthy group. No significant differences were observed between the groups regarding either MHR or NLR values. For the average HDL and MHR values, data was obtained from the records of 20 patients in the patient group and 12 subjects in the healthy group. The results and corresponding *P*-values are in Tables 4 to 6 and Figures 1 and 2.

Table 4: The median, minimum and maximum values of the NLR, MHR initial and MHR average of the healthy and patient group are shown

	Healthy group		Patient group	
	Median	Min.-Max	Median	Min.-Max
NLR	1.82	1.00-7.75	1.81	0.85-4.5
MHR initial	0.146	0.059-0.278	0.142	0.060-0.286
MHR average	0.009	0.006-0.029	0.008	0.003-0.018

NLR: neutrophil to lymphocyte ratio, MHR: monocyte to high-density lipoprotein ratio

Table 5: The *P*-values in the comparison between the healthy and the patient group using the independent samples Mann-Whitney U test are shown

	P-value
HDL initial	0.118
HDL average	0.192
LDL initial	0.687
LDL average	0.922
NLR	0.880
MHR initial	0.828
MHR average	0.058

LDL: low-density lipoprotein, HDL: high-density lipoprotein, NLR: neutrophil to lymphocyte ratio, MHR: monocyte to high-density lipoprotein ratio

Table 6: Comparison of NLR and MHR values between genders in the patient group

Patient group	Gender	N	Mean (SD)	*P*-value
NLR	female	28	1.80 (0.66)	0.110
	male	20	2.2 (0.90)	
	n	48		
MHR initial	female	17	0.11 (0.033)	0.338
	male	12	0.17 (0.046)	
	n	29		
MHR average	female	12	0.006 (0.002)	0.066
	male	8	0.010 (0.004)	
	n	20		

NLR: neutrophil to lymphocyte ratio, MHR: monocyte to high-density lipoprotein ratio, SD: standard deviation

Figure 1: NLR frequency graphic for healthy and patient group (Graphic with blue color is patient group, and Graphic with green color is healthy group)

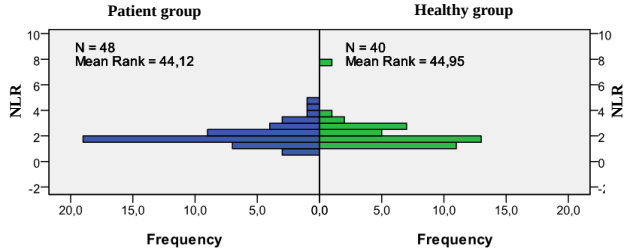
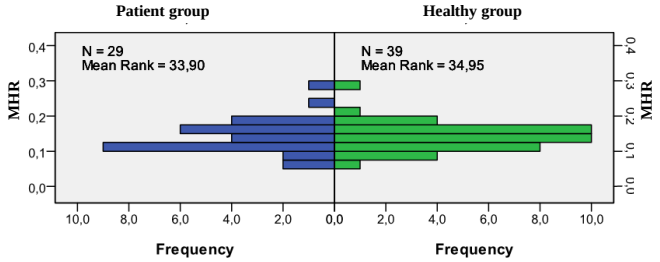


Figure 2: MHR frequency graphic for healthy and patient group (Graphic with blue color is patient group, and Graphic with green color is healthy group)



Discussion

The peripheral immune system has long been examined as a potential source of biomarkers for various disease states. NLR and MHR, which are used as noninvasive, inexpensive, and easily accessible peripheral biomarkers for many diseases, are among them. The CNS is immunologically protected, and circulating immune cells are not typically found within the CNS. However, activated microglia can secrete inflammatory mediators and induce secondary inflammatory responses in the CNS. Immune processes that impact neurodegeneration occur in the periphery and CNS.

While NLR serves as a parameter of systemic inflammation, the results from studies on Alzheimer's disease, intracranial atherosclerosis, and other neurological diseases have shown inconsistency [10-12].

Over the past two decades, there has been a growing focus on the role of glial cells in the development and persistence of chronic pain. Accumulating evidence suggests that dysregulated glial activity may contribute to chronic pain, highlighting the central role of neuroinflammation in its onset and maintenance, affecting both the CNS and peripheral nervous system. Microglial cells and other non-neuronal immune system cells are the primary sources of pro-inflammatory cytokines and chemokines, which, when released, lead to increased sensitivity to pain by activating nociceptive neurons in both the peripheral and CNS.

In the peripheral nervous system, such as in cases like sciatica and dorsal root ganglia, immune cells infiltrate the area, while in the CNS, glial cells and astrocytes become activated, resulting in the production and release of pro-inflammatory cytokines and chemokines. Numerous studies have demonstrated the involvement of microglial mitogen-activated protein kinase (MAPK) activation in the pathogenesis of neuropathic pain [5,13].

Studies have demonstrated a strong association between chronic constriction damage to the sciatic nerve and increased infiltration of macrophages after 28 days, along with the emergence of neuropathic pain-like behaviors in mice. In inflammatory events, neutrophils are often prominent but typically absent from the sciatic nerve. However, in animal experiments involving sciatic nerve damage, neutrophils appear to be implicated in the induction of neuropathic pain-like behaviors.

Depletion of neutrophils has been shown to result in a reduction in the development of thermal hypersensitivity. Nevertheless, research suggests neutrophils may primarily contribute to the initial phase of neuropathic pain rather than its sustained presence. They release many chemokines and activate other immune cells, such as macrophages, which exhibit algogenic effects similar to mast cells [8].

T lymphocyte cells, constituting 80% of circulating lymphocytes in the blood, can be categorized into two groups with pro-inflammatory and anti-inflammatory functions. They hold a crucial position in the context of autoimmune diseases. Research has indicated a notable elevation in the number of T cells in neuropathic pain models compared to control groups, and this rise is linked to heightened sensitivity to both mechanical and thermal pain. Experiments involving mice deficient in T cells reduced neuropathic pain-like behavior [8].

In neuroinflammation, macrophages and microglia play more prominent roles than T lymphocytes. Microglia, a non-migrating glial cell, are partially derived from circulating monocytes. They adopt the morphology of activated macrophages and exhibit heightened sensitivity to damage within the CNS. In addition to the conventional "outside-in" pathology involving myelin sheath to axon interactions, Tsunado Fujinami et al. [7] have proposed an "inside-out" pathology based on observations of secondary demyelination following virus-mediated neuronal and axonal damage. Such lesions may also involve neuronal injury and oligodendroglial damage, triggering an immune response that can potentially progress to autoimmunity under specific environmental conditions.

Macrophages play a crucial role in the onset and persistence of neuropathic pain. Traumatic damage to the peripheral nerve results in the detachment of axons from the cell body and the accompanying myelin sheath, a process known as Wallerian degeneration. Macrophages assume a vital role in the phagocytosis and clearance of myelin debris. This clearance is significant because myelin debris can hinder axon regeneration, making removing such debris essential for nerve repair [8].

Numerous inflammatory pain mediators encompass a wide range of molecules, from small compounds like bradykinin and prostanoids to cytokines, chemokines, and growth factors, with their diversity steadily increasing. This group comprises many immune cells, glial cells, and neurons. Throughout this process, these inflammatory mediators exert various effects, including the sensitization and activation of nociceptive terminals, the regulation of the primary nociceptive phenotype, control over presynaptic transmitter release in the spinal cord nociceptor, and modulation of postsynaptic neuronal excitability. A crucial challenge lies in elucidating the intricate interplay among these diverse mediators and mechanisms, particularly in pain-related situations [8].

The NLR in peripheral blood has been proposed as a potential systemic inflammatory marker in various diseases, with a specific focus on rheumatological conditions [14] and cancer research [15]. The physiological immune response of circulating leukocytes to systemic inflammation typically involves increased neutrophil counts and decreased lymphocyte counts. Lymphopenia indicates weakened cellular immunity, while neutrophilia reflects the body's response to systemic inflammation. Consequently, NLR is put forward as a fundamental marker of systemic inflammation and stress across numerous diseases. Many studies interpret the ratio of these two values as a measure of the competency of the cellular immune response [16–18]. In short, NLR serves as an indirect indicator of the host's immune response [19].

Moreover, NLR offers a cost-effective means of identifying critically ill patients, as it is a readily measurable and reproducible indicator of subclinical inflammation. Its potential utility has also been explored in neurological conditions like ischemic stroke [20]. Goyal and colleagues [21] discovered that NLR on admission could be a prognostic biomarker for outcomes in patients with large vessel occlusion strokes.

Although few studies have investigated NLR in patients with MS, they have proposed a potential role in disease diagnosis and the detection of disease activity [22–27]. NLR has been validated as a poor prognostic marker for cancer and cerebrovascular diseases [28-30]. Furthermore, it has been linked to the presence and severity of atherosclerosis in carotid arteries, coronary arteries, and even peripheral arteries, suggesting that atherosclerosis is an inflammatory disorder [31-35].

In our study, we explored the role of systemic inflammation in the pathophysiology of TN using inflammatory markers such as NLR and MHR calculated from blood tests and lipid profile measurements. We did not observe any significant differences when comparing NLR and MHR values between TN patients and the control group. A similar study involving 141 TN patients found that NLR and other inflammatory markers could predict TN diagnosis and showed a close association with inflammation [36]. The variation in results between these studies may be attributed to differences in patient sample sizes. Additionally, it is worth considering that hematological parameters, such as neutrophils (NEU) and lymphocytes (LYM), which a wide range of conditions can influence, may have played a role in these findings.

The brain is the body's most cholesterol-rich organ, containing nearly 25% of the total cholesterol [37]. A significant portion (70–80%) of this cholesterol resides within myelin, which plays a crucial role in insulation [38]. Astrocytes and oligodendrocytes locally synthesize brain cholesterol and is largely isolated from other cholesterol pools in the body [39]. The prevailing consensus suggests minimal net cholesterol transfer from the peripheral bloodstream to the CNS due to the blood-brain barrier, which restricts the passage of plasma lipoproteins into the brain. HDL forms both in the systemic circulation and the brain. HDL serves a diverse range of functions, including anti-oxidation, anti-inflammation, promoting endothelial function, anti-thrombosis, and modulation of immune function. Substantial evidence supports that elevated plasma levels of HDL offer protection against cardiovascular disease. An increasing body of evidence suggests that HDL also plays a beneficial role in various systems, including the CNS. Plasma HDL levels have been linked to neurodegenerative diseases such as MS [40]. Individuals in the acute stage of MS have been reported to exhibit lower HDL levels than those in remission, with a higher likelihood of developing acute inflammatory lesions, as assessed by Magnetic Resonance Imaging [40-42]. HDL promotes the formation of M2-polarized macrophages, characterized by a reduced pro-inflammatory profile, and inhibits the cytokine-induced expression of adhesion molecules in endothelial cells [43-45]. These properties may contribute to immune system suppression, thereby preventing MS relapses. Additionally, abnormalities in HDL levels have been observed in patients with psychiatric disorders [46].

The MHR has emerged as a novel inflammation marker, and its association with various diseases has been explored. One study investigated the relationship between MHR and intracerebral hemorrhage (ICH) outcomes, revealing that elevated MHR was independently linked to disability or mortality at hospital discharge and 3 months post-stroke among acute ICH patients [9]. MHR has also been strongly correlated with cardiovascular conditions. Kanbay et al. [47] were the first to report a relationship between high MHR and cardiovascular events in patients with chronic kidney disease. Canpolat et al. [48] additionally highlighted MHR as an independent predictor of atrial fibrillation recurrence following cryoballoon-based catheter ablation. Moreover, other studies have found that increased MHR is independently associated with major adverse cardiovascular events during hospitalization in patients with coronary artery disease [49,50]. Despite previous studies suggesting that MHR may serve as a novel prognostic marker for cardiovascular and neurological vascular diseases, our study found no significant difference between patients diagnosed with classical TN and healthy subjects.

Limitations

The sample size within our TN cohort was limited. Several factors contributed to the reduction in the number of patients, including the extensive exclusion criteria, incomplete data, and the absence of HDL values for all patients. Additionally, there was a notable difference in mean age between the patient and healthy groups, constituting the study's weakness. Furthermore, this study has several limitations, including the lack of evaluation of other inflammation biomarkers such as C-reactive protein, procalcitonin, sedimentation rate, and interleukin levels. We also could not exclude asymptomatic subjects with a nonspecific inflammatory response. However, the study's primary strength lies in its 10-year retrospective analysis of archived cases diagnosed with classical TN. While we aimed to maintain group homogeneity, the strict exclusion criteria resulted in a relatively small number of included patients. Nevertheless, it's worth noting that this study represents the first investigation of the MHR in the context of TN.

Conclusions

As a result, it is imperative to conduct further investigations with larger sample sizes to corroborate these preliminary findings. Expansive studies are necessary to thoroughly evaluate the significance of the MHR as a readily applicable marker in neurological diseases characterized by neuroinflammation and neuropathic pain pathogenesis. Subsequent studies could prove valuable, particularly when the differential diagnosis of classical TN is challenging or regarding its potential role in predicting acute exacerbations.

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Musculoskeletal injuries profile of patients applying to a sports medicine outpatient clinic

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Ethics Committee Approval
The study was approved by The Atatürk Education and Research Hospital Ethics Committee (date: August 8, 2023 and no: 0371). 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: Sports injuries represent a significant public health concern, and their prevalence is on the rise due to the growing global population and increased participation in amateur and professional sports. Epidemiological studies on sports injuries are crucial in identifying priority areas for injury prevention efforts. While there is a wealth of research on musculoskeletal injuries specific to various sports, there is a scarcity of epidemiological studies focusing on patients seeking care at sports medicine outpatient clinics. This study aims to define and categorize the diagnoses of patients presenting to a sports medicine outpatient clinic for musculoskeletal injuries.

Methods: This retrospective cohort study included all patient visits for musculoskeletal injuries at the sports medicine outpatient clinic between 1 July 2022 and 30 June 2023. Patients with complaints other than musculoskeletal injuries and those lacking sufficient data (diagnosis or injury type) in the data recording system were excluded. Data recorded for each participant included age, sex, symptoms, injured body region, and injury type. Diagnoses were categorized using the Orchard Sports Injury and Illness Classification System (OSIICS) v.13. Descriptive analyses provided a detailed overview of reported injuries, including counts and proportions within specific injury categories. Categorical variables are presented as 'n' and (%), while continuous variables are expressed as medians with interquartile ranges (IQRs).

Results: Data from 1,203 patients (395 females and 808 males) were analyzed, with a mean age of 24 (2.2) years. A total of 1393 injuries were documented, with the knee being the most commonly injured body region (n=398, 30.7%). Among the OSIICS v.13 injury categories, muscle/tendon injuries constituted 33.7% (n=466) of all injuries, followed by cartilage/synovium/bursa injuries (n=432, 31.2%).

Conclusion: This study revealed that the knee was the most frequently injured body region among patients seeking care at the sports medicine clinic for musculoskeletal injuries. Muscle/tendon injuries were the predominant type of injury observed.

Keywords: athletic injuries, classification, injuries, musculoskeletal system, sports medicine

Introduction

Sports injuries represent a significant public health concern, with the global population's steady growth contributing to a continuous rise in amateur and professional sports participation [1,2]. While data on elite, professional, or college-level athletes are readily available, information about other levels of play remains limited. Detailed data, especially for individuals engaging in sports at the community level, are scarce. Additionally, the incidence of comorbidities and musculoskeletal injuries stemming from sedentary lifestyles has been on the rise, resulting in an increased demand for healthcare services [3].

The International Federation of Sports Medicine (FIMS) has defined sports medicine as a discipline that investigates the impact of exercise, training, sports, and sedentary lifestyles on healthy and unwell individuals. This field encompasses prevention, diagnosis, treatment, and rehabilitation across all age groups and genders, focusing on those engaged in physical activity. Sports medicine is a multidisciplinary field, blending theory and practice to generate research that benefits individuals [4]. Following the European Federation of Sports Medicine Associations' definition, sports medicine encompasses the diagnosis, treatment, prevention, and rehabilitation of injuries and health issues resulting from engagement in physical exercise and activities, spanning all levels of participation. It also strives to promote the adoption of an active lifestyle among the general public [5].

The Centers for Disease Control and Prevention (CDC) defines musculoskeletal injuries as injuries that impact the soft tissues, including muscles, tendons, nerves, joints, and cartilage. These injuries can result from sudden events or sustained repetitive motions, external forces, improper postures, or exposure to vibrations [6].

Numerous studies have explored musculoskeletal injuries associated with various sports; however, there is a notable scarcity of epidemiological investigations focusing on patients seeking care at sports medicine outpatient clinics [7-12]. This study's primary objective is to delineate and categorize the diagnoses of individuals who sought treatment at sports medicine outpatient clinics for musculoskeletal injuries.

Materials and methods

This is a retrospective cohort study. The sample size was determined by the number of patients who sought treatment at the sports medicine outpatient clinic for musculoskeletal injuries during the study period. The study population encompassed all patient presentations for musculoskeletal injuries at the sports medicine outpatient clinic from 1 July 2022 to 30 June 2023. The records of 1,203 patients who met the inclusion criteria were examined. The study protocol received approval from the Atatürk Education and Research Hospital Ethics Committee (Approval no.: 0371, approval date: August 18, 2023), and the study adhered to the guidelines outlined in the Declaration of Helsinki, 2013.

This record-based study analyzed all patient presentations in the clinic's online data recording system. It specifically focused on patients who sought treatment at the sports medicine clinic for musculoskeletal injuries. Patients with complaints unrelated to musculoskeletal injuries and those lacking sufficient data (diagnosis and injury type) in the data recording system were excluded from the study.

The study collected patients' age, sex, symptoms, injured body region, and injury type. To prevent duplication, patients with multiple diagnoses simultaneously or those seeking treatment at different times for a previous diagnosis were considered single patients. Each diagnosis was documented separately, and the total number of diagnoses was manually calculated.

Musculoskeletal injuries were defined according to the CDC definition [6]. These injuries were further classified using the Orchard Sports Injury and Illness Classification System (OSIICS) v.13 [13]. This system categorizes injuries based on the injured body region, tissue type, and pathology type. The injury data were meticulously assigned to the most relevant cell within the matrix. Raw numbers for each injury type were calculated and expressed as a percentage of the total injuries.

Statistical analysis

The data were initially organized within a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). Subsequently, the researchers meticulously reviewed the data for accuracy and conducted a manual cleaning process to remove duplicate entries and records that did not meet the eligibility criteria. Following this data preparation phase, the dataset was imported into SPSS v.21 (IBM, Armonk, NY, USA).

Descriptive analyses were carried out to provide a comprehensive overview of the reported injuries. These analyses included counts and proportions of injuries categorized by specific criteria. Categorical variables are presented as "n" and the corresponding percentage within parentheses (%), while continuous variables are represented as medians accompanied by interquartile ranges (IQRs).

Results

Over 12 months, a total of 3,605 patients admitted were assessed. Among these patients, 1,578 were excluded from the study due to athlete's license examinations, 461 were excluded for reasons unrelated to the musculoskeletal system, and 363 were excluded because they were undergoing follow-up examinations after their initial admission. Consequently, the study comprised 1,203 patients.

Of the patients, 67% (808 out of 1,203) were male. The average age of the patients was 31.3 (14.3) years, with an age range of 6 to 77 years. Among the patients, 29% (352 out of 1,203) were not engaged in any sports, and the most common sport was soccer (n=255, 30%) (Table 1). A total of 1,383 injuries were recorded, with the highest number of clinic visits occurring in June (14.7%) (Figure 1). Most musculoskeletal injuries (n=398; 30.7%) affected the knee (Figure 2). Injuries categorized under OSIICS v.13 as muscle/tendon accounted for 33.7% (n=466) of the injuries, followed by cartilage/synovium/bursa (n=432; 31.2%) (Table 2).

Figure 1: Distribution of the number of patient applications by months.

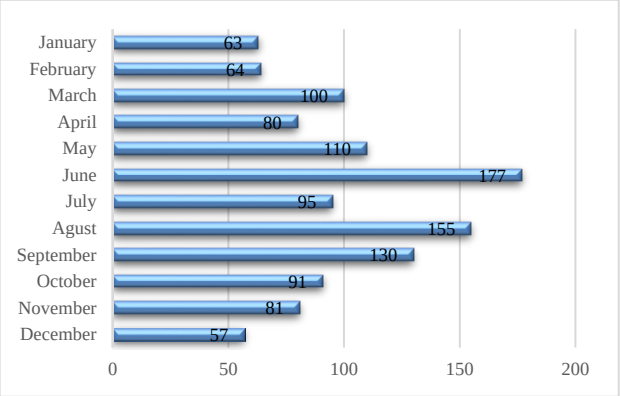

Table 1: The sports branches of participants.

Branches of sports	Participants, n=850	(%)
Soccer	255	30
Fitness	156	18.4
Volleyball	48	5.6
Basketball	44	5.2
Running	36	4.3
Preparation for police/military service	31	3.6
Athletics	26	3
Pilates	25	2.9
Walking	25	2.9
Kick boks	23	2.7
Tennis	18	2.2
Swimming	14	1.7
Military personnel	14	1.7
Taekwondo	12	1.4
Gymnastics	12	1.4
Cycling	12	1.4
American football	11	1.3
Yoga	9	1
Boks	8	0.9
Trekking	8	0.9
Hiking	6	0.7
Karate	6	0.7
Police	5	0.5
Dancing	5	0.5
Triathlon	4	0.4
Water ball	4	0.4
Martial arts	4	0.4
Crossfit	4	0.4
Sailing	4	0.4
Fencing	4	0.4
Wrestling	3	0.3
Orienteering	3	0.3
Archery	2	0.2
Paragliding	1	0.1
Folk dancing	1	0.1
Ballet	1	0.1
Underwater rugby	1	0.1
Judo	1	0.1
Table tennis	1	0.1
Capeora	1	0.1
Barbell	1	0.1
Figure skating	1	0.1

n: number, %: percent.

Figure 2: Number of injuries classified by body region.

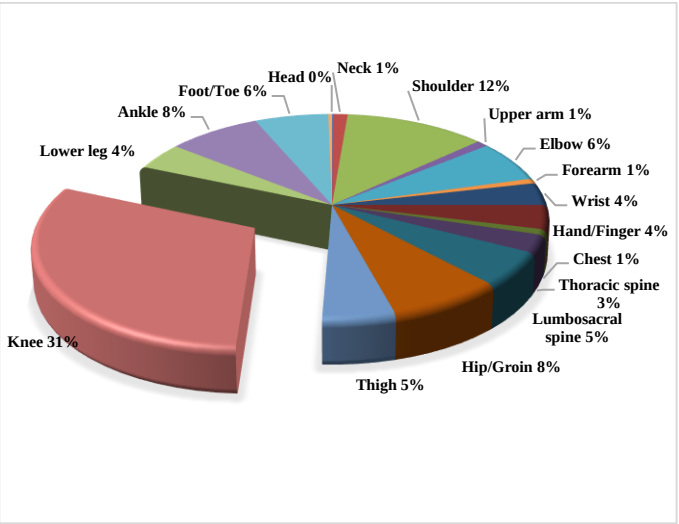

Table 2: Categories of injury types.

Tissue	Pathology type	n=1.383	(%)
Muscle/tendon		**466**	33.7
	Muscle injury	116	
	Muscle strain	*109*	
	Muscle rupture	*7*	
	Myofascial pain syndrome	49	
	Muscle spasm	21	
	Delayed onset muscle soreness (DOMS)	2	
	Fibromyalgia	1	
	Compartment syndrome multiple sites lower leg	1	
	Tendinopathy	202	
	Achilles tendinopathy	*32*	
	Medial tibial stress syndrome (Shin splints)	*16*	
	Adductor longus tendinopathy	*16*	
	Patellar tendinopathy	*15*	
	Rotator cuff syndrome	64	
	Tendon rupture	7	
	Snapping hip syndrome	2	
	Trigger finger	1	
Nerve		**36**	2.6
	Peripheral nerve injury	36	
	Lumbar disc herniation	*25*	
	Piriformis syndrome	*11*	
	Cervical disc herniation	*5*	
	Carpal tunnel syndrome	*4*	
	Tarsal tunnel syndrome	*3*	
Bone		**141**	10.1
	Acute fracture	31	
	SIAS epiphyseal separation	*3*	
	Bone stress injury	54	
	Stress fracture	*20*	
	Spondylolysis	*5*	
	Stress reactions	*30*	
	Bone contusion	20	
	Bone deformity	14	
	Scoliosis	*8*	
	Hallucs valgus	*5*	
	Kyphosis	*1*	
	Enthesopathy	22	
	Epin calcanei	*9*	
	Haglund deformity	*1*	
	Apophysitis	17	
	Os good schlatter syndrome	*12*	
	Sever disease	*5*	
Cartilage/Synovium/Bursa		**432**	31.2
	Cartilage injury	217	
	Patellofemoral pain syndrome	*201*	
	Chondromalazia patella	*42*	
	Osteochondral dissecans (OCD)	*10*	
	Triangular fibrocartilage complex (TFCC)	*6*	
	Arthritis	58	
	Synovitis/Capsulitis	11	
	Femur-acetabulum impingement	*6*	
	Sacroileitis	*3*	
	Adhezive capsulitis (shoulder)	*2*	
	Medial and lateral meniscal tears	82	
	Degenerative meniscal tear	34	
	Bursitis	26	
	Iliotibial band (ITB) syndrome	*11*	
	Sinovial cyst	*4*	
Ligament/Joint capsule		**177**	12.7
	Plantar fasia injuries	6	
	Plantar fasiit	*5*	
	Plantar fasia rupture	*1*	
	Joint sprain	65	
	ATFL sprain	*42*	
	Acromioclavicular sprain	*22*	
	Lisfranc injury	*1*	
	Acut joint dislocation	23	
	Chronic instability	83	
	ACL rupture	*52*	
	PCL rupture	*7*	
	Radioulnar instability	*7*	
	SLAP tear	*7*	
	Patellar tilt	*5*	
	Patella alta	*3*	
	Sternocostal joint subluxation	*1*	
	Spondylolisthesis	*1*	
Superficial tissues/skin		**95**	6.8
	Contusion	95	
Non-specific		**36**	2.6
	Ganglion cyst	11	
	Synovial plica of knee	6	
	Tumour lower leg	4	
	Pes planus	4	
	Hoffa syndrome	3	
	Glomus tumour	1	
	Tumour thigh	1	
	Avascular necrosis	1	
	Winging scapula	1	
	Restless leg syndrome	1	
	Ankylosing spondylitis	1	
	Metatarsalgia	1	

ACL: Anterior cruciate ligament, ATFL: Anterior talofibular ligament, PCL: Posterior cruciate ligament, SLAP: Superior labrum anterior to posterior, %: percent. Note: Musculoskeletal injuries are classified according to OSIICS v.13 (Orchard Sports Injury and Illness Classification System version 13).

Discussion

This study investigated musculoskeletal injuries in patients seeking treatment at sports medicine outpatient clinics. Muscle and tendon injuries were the most common, followed by cartilage, synovium, and bursa injuries. The knee was the most frequently injured body region. To the best of our knowledge, this is the first study to examine the musculoskeletal injury profile of all patients visiting the sports medicine outpatient clinic, and their diagnoses were categorized using OSIICS v.13.

Epidemiological studies play a crucial role in understanding sports injuries. Primarily, they serve as a roadmap for research to prevent sports injuries and enhance sports safety. These studies offer fundamental insights essential for sports physicians, assisting them in resource allocation for injury treatment and management. Additionally, they aid in pinpointing key areas for research within particular sports disciplines. Sports organizations can use this data to underscore their commitment to providing a secure sports environment for participants. Furthermore, these studies are indispensable for evaluating the effectiveness of interventions, such as rule modifications. They also serve as the foundation for designing tailored sports injury prevention programs [3].

In Turkey, two similar studies were conducted by Tahirbegolli et al. [14,15]. One of these studies focused on injuries among athletes seeking treatment at sports medicine facilities [14], while the other examined injuries in sedentary individuals [15]. Like our study, both investigations employed a retrospective design and encompassed patients seeking treatment over 1 year. The participant cohorts included 1,302 athletes and 744 sedentary individuals, with a male predominance. In all three studies, the knee emerged as the most frequently injured body region, and soccer was the most prevalent sport, aligning with our findings. Notably, neither of the previous studies utilized a classification method for injuries.

In the studies by Tahirbegolli et al. [14,15], ligament injuries predominated among athletes, while sedentary individuals frequently reported patellofemoral pain syndrome. In contrast, our current study identified muscle-tendon injuries as the most common, cartilage/synovium/bursa injuries as the second most frequent, and ligament injuries as the third most common. While the classification systems employed in these studies differ, the variance in injury types between them and our current study remains unexplained. Possible factors contributing to these differences may include variations in the geographic locations where the studies were conducted and differences in the study populations.

Interestingly, Tahirbegolli et al. [14] reported the highest outpatient clinic applications in April, whereas our study observed the highest number of applications in June, followed closely by August. Several factors may explain this discrepancy. Firstly, it could be attributed to students attending sports schools during the summer months or the region's popularity as a holiday destination. Additionally, increased city population and activities during this season may play a role. Compared to June and August, the lower number of applications in July could be due to researcher availability and potential days off during that month.

Numerous epidemiological studies conducted in various countries have examined musculoskeletal injuries in patients seeking treatment at sports clinics. Consistent patterns emerge from these studies: a predominance of male patients (69% to 85%), the knee as the most frequently injured body region (23.2% to 32%), and soccer as the most common cause of injuries (14% to 50%) [7-12]. These findings mirror the results of our study. Soccer enjoys widespread popularity and enthusiastic participation in Turkey and internationally [16]. Consequently, injuries are more prevalent in this sport.

Some studies in the literature were designed prospectively [7,9,11], while others adopted a retrospective approach [8]. However, it's noteworthy that none of these studies employed a classification method for injuries. For example, Garrido et al. [11] also refrained from using a classification method and categorized injuries broadly as ligament/tendon/muscle, with ligament injuries being the most frequently reported. Additionally, Kannus et al. [7] reported that while acute contusions, dislocations, and fractures were more common in men, stress fractures and nerve compression syndromes were more prevalent in women.

Muscle injuries account for 31% of all sports-related injuries, with hamstring muscle injuries being the most prevalent type [17]. Our study also identified the hamstring muscle group as the most commonly injured (23%). Furthermore, the Achilles tendon ranks as the most frequently injured tendon, with a prevalence of 21.5% [18]. This finding aligns with our study, where Achilles tendon injuries were the most common type (18%). These findings from our study are consistent with existing literature in this regard.

The International Statistical Classification of Diseases and Related Health Problems (ICD) is a frequently employed tool in passive surveillance but tends to be less specific when classifying musculoskeletal injuries [19]. In contrast, the Delphi study recommends using ICD or OSIICS for active surveillance, with a preference for OSIICS when more detailed injury categorization is necessary [20]. OSIICS was designed to provide a more comprehensive definition of sports injuries [13]. Consequently, while several studies examining patient injury profiles did not utilize any classification system, ICD was employed in some instances [12]. This variability can lead to different interpretations of the study results.

Limitations

Our study possesses several strengths, including a well-defined characterization of musculoskeletal injuries and the utilization of a classification system specifically designed to describe sports-related injuries. However, it also exhibits several limitations. Firstly, a single physician diagnosed all injuries, and alternative diagnoses could not be independently verified; diagnoses were reliant on the knowledge of a single physician. We excluded patients with missing data from our analysis to mitigate information bias within our extensive population-based cohorts. Furthermore, there was a reduction in the number of applications during certain months due to the physician's scheduled leaves. It is important to note that the findings of this study may not apply to the entire country, various sports disciplines, or other medical specialties.

We contend that employing the OSIICS represents a more precise method for categorizing injuries arising from exercise or sports activities. The utilization of a standardized

classification system in epidemiological investigations focused on these types of injuries, coupled with a consistent approach in selecting such a system, can yield more reliable findings for interpreting and comparing studies in this domain.

Conclusion

In summary, the knee emerged as the most commonly affected body region among patients seeking treatment for musculoskeletal injuries at the sports medicine outpatient clinic, with muscle/tendon injuries being the prevailing injury type. It is imperative to comprehensively assess the musculoskeletal injury landscape in patients to identify and address potential risk factors and prevention strategies. Adopting a classification system in epidemiological studies investigating these injuries, combined with a consistent approach in selecting such a system, can enhance the accuracy of results when interpreting and comparing these studies.

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Fibrinogen to albumin and C-reactive protein to albumin ratio can play an important role in catheterization decisions in COVID-19 pneumonia patients: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the Harran University Clinical Research Ethics Committee (HRÜ/22.19.05-03.10.2022).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Elevated troponin T (Tp) is an important indicator in the decision to catheterize. However, since COVID-19 infection may cause elevated Tp, different biomarkers are needed to make the decision for catheterization. We aimed to investigate the importance of fibrinogen-to-albumin ratio (FAR) and CRP-to-albumin ratio (CAR) values in predicting obstructive coronary artery disease (CAD) in patients hospitalized with COVID-19 pneumonia and catheterized with the suspicion of acute coronary syndrome (ACS).

Methods: In this retrospective cohort study, clinical, laboratory, catheterization, and electrocardiography data of all patients were analyzed. Patients with obstructive CAD were defined as the MI group, and patients with normal coronary arteries were defined as the normal group.

Results: The MI group consisted of 49 patients (66.2%), and the normal group consisted of 25 patients (33.8%). Both FAR and CAR were significantly higher in the MI group (P=0.007; P=0.009, respectively). FAR and CAR were found to be independent predictors of obstructive CAD (95% CI 0.06 [0.000-34.052], P=0.024; 95% CI 1.35 [0.803-2.255], P=0.025, retrospectively). A cut-off value of 0.64 for FAR has an 80% sensitivity and a 40% specificity, and a cut-off value of 0.65 for CAR has an 83% sensitivity and a 41% specificity in predicting obstructive CAD.

Conclusion: A decision for ACS and catheterization in patients hospitalized with COVID-19 pneumonia in the ICU should not be based only on elevated Tp, as it is useful to evaluate FAR and CAR values in addition to Tp.

Keywords: COVID-19 pneumonia, catheterization, fibrinogen, albumin, C-reactive protein, hospitalization

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Introduction

Coronavirus-19 (COVID-19) was first identified in 2019 in Wuhan, China, and the first case was seen in Turkey in March 2020 [1]. The number of cases increased rapidly in Turkey and in the whole world, and isolation measures and quarantine processes were put in place. The quarantine brought a significant decrease in emergency department admissions; however, it has been observed that the number of emergency service admissions due to acute coronary syndrome (ACS) has also decreased [2].

Patients with moderate-to-severe pneumonia developing secondary to COVID-19 were hospitalized in pandemic wards and intensive care units (ICU). These patients may develop myocardial damage due to either the direct effect of the virus or the systemic inflammation caused by the infection. The presence of myocardial damage as assessed by troponin (Tp) elevation is common in patients with COVID-19 and is associated with poor prognosis [3]. COVID-19 can cause cardiac diseases such as myocardial infarction, pericarditis, myocarditis, and arrhythmia other than pneumonia [4]. Tp elevation in COVID patients may also be caused by other factors (such as pulmonary embolism, right ventricular dysfunction due to lung disease, etc.) [5]. For the reasons mentioned above, it is very difficult to diagnose ACS in COVID-19 patients by evaluating only Tp values. Due to the intensity of the health system during the pandemic and to prevent individuals from being infected by COVID-19, especially healthcare professionals, and ensure that personal protective gear can be used more effectively, it has become more important to recognize genuine ACS patients and to use additional laboratory parameters to support the diagnosis of ACS in COVID-19 patients with elevated Tp.

Fibrinogen is a plasma protein synthesized in the liver. It is a substrate of thrombin in the coagulation cascade and an acute phase reactant (APR), and its plasma level increases in inflammatory conditions. It plays a role in the development of vascular inflammation and atherosclerosis [6]. Many studies show that a high serum fibrinogen level is associated with disease severity in coronary artery disease (CAD), which is an inflammatory process [7, 8]. Albumin is the main protein in the extracellular matrix and is a negative APR. Albumin accelerates fibrinolysis, reduces platelet and red blood cell aggregation, and neutralizes fibrinogen binding sites in the endothelium [9]. Studies have shown that high fibrinogen and low albumin levels are associated with CAD [10–12]. CRP is a positive APR protein; its plasma level is increased in inflammatory conditions such as ischemia and infection [13]. Many studies in the literature show a relationship between CRP-to-albumin ratio (CAR) and ACS, which is an ischemic and inflammatory process [14, 15].

In clinical routine practice, the decision for cardiac catheterization is based on cardiac biomarkers, electrocardiography (ECG) changes, and the presence of typical angina. However, there is no study investigating other biomarkers, such as FAR and CAR, in determining whether to catheterize patients hospitalized in the ICU due to COVID-19 pneumonia. In our study, we investigated the fibrinogen-to-albumin (FAR) and CAR parameters to predict obstructive CAD and use that information in making the decision to catheterize COVID-19 pneumonia patients hospitalized in the ICU and suspected of ACS due to elevated Tp.

Materials and methods

Source of data and study population

Our study is a retrospective cohort study. Patients over 18 years of age who were hospitalized in the ICU due to COVID-19 pneumonia, had elevated Tp, and underwent coronary angiography (CAG) between April 2020 and September 2022 with the suspicion of myocardial infarction without ST-segment elevation (NSTEMI) were included the study. CAG was performed on patients who were hospitalized in the ICU with positive COVID-19 polymerase chain reaction (PCR) test results, with moderate or advanced lung involvement, receiving high-dose reservoir oxygen therapy, receiving continuous positive airway pressure (CPAP) therapy, under high-flow nasal oxygen device therapy, or intubated; they were included in the study. Those with negative PCR test results were not included. The mean hospitalization time in the ICU was 23 (2.2) in the MI group and 20 (3.1) in the normal group. The patients had undergone CAG within 24 to 36 hours.

In the diagnosis of NSTEMI, increases in the control Tp values as well as the basal Tp elevation were also taken into consideration. The diagnosis of NSTEMI was accepted according to the current cardiovascular guidelines. Nine patients were excluded from the study because CAG was performed due to ST-segment elevation on ECG, and five patients were excluded because their CAG results were reported as stable angina pectoris. In addition, those who developed additional diseases such as myocarditis, pulmonary thromboembolisms, and cerebrovascular events that cause Tp elevation were not included in the study. According to CAG results, patients with obstructive epicardial coronary stenosis were labeled the “MI group,” and those without such stenosis were labeled the “normal group.”

Clinical, laboratory, and ECG data of all patients were scanned and analyzed retrospectively. Our study was approved by the local ethics committee (Harran University, Ethics Committee, date: 03.10.2022, number: HRÜ/22.19.05). Our study complies with the Declaration of Helsinki Principles.

Statistical analysis

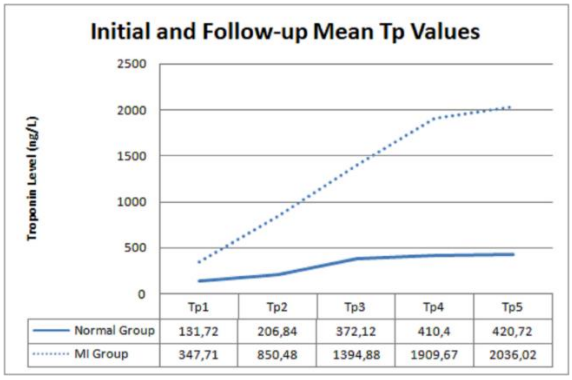
Statistical analysis was performed using the 20.0 SPSS for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical variables were presented as counts and percentages. Continuous variables were evaluated for normal distribution using the Kolmogorov-Smirnov test and presented as mean (standard deviation) or median with interquartile range. The Students’ t-test was used for normally distributed variables, the Mann-Whitney U test for non-normally distributed variables, and the chi-square test for categorical variables to assess the differentiation between the groups. The Spearmen correlation test was used for correlation analysis between FAR, CAR, and other variables. Receiver operating characteristics (ROC) were generated to determine cut-off values of FAR and CAR for the obstructive CAD. In addition, univariate and multivariate binary regression analyses were used to define independent predictors of obstructive CAD. Variables resulting in a *P*-value less than 0.10 in univariate analysis were included in the multivariate

analysis. A *P*-value less than 0.5 was accepted as statistically significant.

Results

Seventy-four COVID-19 pneumonia patients who underwent CAG with the suspicion of NSTEMI were included. Obstructive epicardial coronary stenosis was detected in 49 patients (66.2%), while normal coronary artery was detected in 25 patients (33.8%). The rates of diabetes mellitus (DM), hypertension (HT), and chronic renal disease (CRD), which are classical risk factors for CAD, were found to be significantly higher in the MI group (*P*=0.006, *P*=0.001, *P*=0.006, respectively). Laboratory parameters ferritin, D-dimer, and procalcitonin levels were found to be significantly higher in the MI group, while albumin levels were lower (*P*=0.006, *P*=0.008, *P*=0.021, *P*=0.001, respectively). Tp levels (Tp1) measured at admission were found to be above the upper reference limit (14 ng/L) in both groups and were significantly higher in the MI group than in the normal group. There was an increase in follow-up Tp levels in both groups compared to the initial value, but these increases were higher in the MI group (Figure 1).

Figure 1: Initial and follow-up mean troponin values in the MI group and normal group.



In addition, both FAR and CAR values were significantly higher in the MI group (*P*=0.007, *P*=0.009, respectively). Baseline characteristics, laboratory parameters, angiographic data, and clinical features of the patients are shown in Table 1.

The perioperative mortality rate was found to be significantly higher in the MI group. The proportion of patients requiring intubation and patients who were intubated at the time of angiography and then extubated during follow-up was similar in the two groups. In the MI group, three vessel disease was the most common. LAD was the vessel most frequently revascularized, and RCA was the second most frequently revascularized vessel (Table 1).

The Spearmen correlation analysis revealed that procalcitonin, creatinine, and ferritin were positively correlated with both FAR and CAR. Hemoglobin was negatively correlated with FAR. D-dimer and NLR were positively correlated with CAR, while lymphocyte was negatively correlated with CAR. All correlated parameters are presented in Table 2.

Univariate and multivariate analyses were performed to predict the presence of obstructive CAD. Creatinine, FAR, and CAR were found to be independent predictors of obstructive CAD (95% CI: 0.06 [0.000-34.052], *P*=0.024; 95% CI: 1.35 [0.803-2.255], *P*=0.025, respectively) (Table 3). No significant *P*-value (*P*<0.10) was obtained with age, gender, and other cardiovascular risk factors in univariate analysis.

Table 1: Baseline clinical, catheterization, and laboratory characteristics of COVID-19 positive patients who underwent catheterization.

Variables	MI group (n=49)	Normal group (n=25)	*P*-value
Age (year)	66.6 (10.8)	64.4 (12.5)	0.452
Gender (male), n (%)	27 (36.5)	13 (17.6)	0.811
BMI (kg/m^2)	28.2 (5.6)	27.5 (5.2)	0.468
DM, n (%)	24 (49.0)	4 (16.0)	**0.006**
HT, n (%)	30 (61.0)	5 (20.0)	**0.001**
HPL, n (%)	7 (14.3)	3 (12.0)	0.546
Smoking, n (%)	7 (14.3)	1 (4.0)	0.172
CKD, n (%)	4 (8.2)	2 (8)	0.676
CVD, n (%)	1 (2.0)	0 (0.0)	0.662
Creatinine (mg/dL)	1.33 (1.00-1.69)	0.91 (0.88-1.09)	**0.006**
Hgb (g/dL)	12.5 (2.6)	12.9 (2.5)	0.480
Platelet (10^3/uL)	265.33 (116.11)	298.24 (93.29)	0.193
Neutrophil (10^3/uL)	11.52 (5.40)	10.27 (4.85)	0.317
Lymphocyte (10^3/uL)	1.75 (1.50)	1.51 (1.05)	0.452
MPV (fL)	10.7 (0.9)	10.3 (1.2)	0.158
CRP (mg/L)	56.0 (14.5-109.5)	21.0 (10.0-79.0)	0.073
Ferritin (ng/mL)	386.0 (143.0-828.5)	168.0 (82.5-389.5)	**0.004**
Fibrinogen (mg/dL)	5.0 (1.7)	4.2 (1.4)	0.067
Albumin (g/L)	3.3 (0.6)	3.7 (0.3)	**0.001**
Procalcitonin (ng/mL)	0.55 (0.15-1.20)	0.14 (0.05-0.55)	**0.021**
D-dimer (ug/mL)	2.10 (0.79-5.50)	0.97 (0.58-1.82)	**0.008**
Trop 1 (ng/L)	100.0 (37.5-312.0)	44.0 (16.5-185.5)	**0.025**
Mass CK-MB 1 (ng/mL)	6.0 (2.8-17.0)	7.0 (2.0-11.0)	0.109
NLR	7.9 (4.5-14.5)	7.3 (3.9-17.0)	0.787
PLR	185.0 (120.3-315.4)	270.4 (140.5-383.5)	0.077
FAR	1.59 (0.82)	1.16 (0.48)	**0.007**
CAR	24.90 (13.34)	12.5 (8.20)	**0.009**
LVEF (%)	43.4 (7.4)	42.5 (5.9)	0.578
Discharge status, n (%)			
Discharged	30 (40.5)	23 (25.7)	**0.006**
Deceased	19 (31.1)	2 (2.7)	
Intubation status, n (%)			
Extubated	31 (41.9)	21 (28.4)	0.105
Intubated	18 (24.3)	4 (5.4)	
Culprit lesion, n (%)			
LAD	8 (10.8)		
LCx	2 (2.7)		
RCA	6 (8.1)		
LAD-LCx	7 (9.5)		
LAD-RCA	4 (5.4)		
LCx-RCA	3 (4.1)		
LAD-LCx-RCA	19 (25.7)		
Revascularized vessel, n (%)			
LAD	21 (28.4)		
LCx	9 (12.2)		
RCA	12 (16.2)		
LAD-LCx	1 (1.4)		
LAD-RCA	1 (1.4)		
LCx-RCA	1 (1.4)		
CABG	4 (5.4)		

MI: myocardial infarction; BMI: body mass index; DM: diabetes mellitus; HT: hypertension; HPL: hyperlipidemia; CKD: chronic kidney disease; CVD: cerebrovascular disease; Hgb: hemoglobin; MVP: mean platelet volume; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet to lymphocyte ratio; FAR: fibrinogen to albumin ratio; CAR: CRP to albumin ratio; LVEF: left ventricular ejection fraction; LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery; CABG: coronary artery bypass grafting. Bold fonts indicate a *P*-value lesser than 0.05

Table 2: The Spearmen correlation analysis of FAR and CAR with other parameters.

FAR			CAR		
Variables	**Rho**	***P*-value**	**Variables**	**Rho**	***P*-value**
CAR	0.684	<0.001	FAR	0.684	**<0.001**
Procalcitonin	0.274	0.018	Procalcitonin	0.430	**<0.001**
CRP	0.655	<0.001	Creatinine	0.266	**0.022**
Creatinine	0.283	0.015	Ferritin	0.591	**<0.001**
Ferritin	0.391	0.001	Fibrinogen	0.568	**<0.001**
Hgb	-0.244	0.036	D-dimer	0.315	**0.006**
			Lymphocyte	-0.240	**0.040**
			NLR	0.295	**0.011**

FAR: fibrinogen-to-albumin ratio; CAR: CRP-to-albumin ratio; CRP: C-reactive protein; Hgb: hemoglobin; NLR: neutrophil-to-lymphocyte ratio. Bold fonts indicate a *P*-value lesser than 0.05

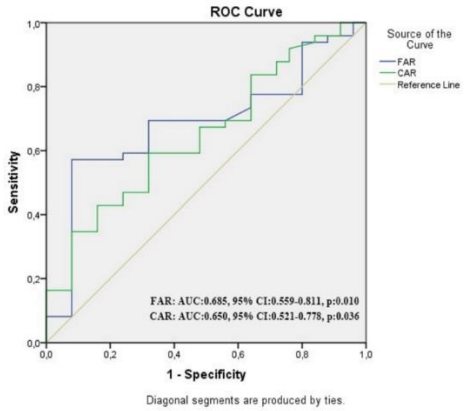
Table 3: The predictors of obstructive CAD in binary logistic regression analysis.

Variables	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
CRP	1.01 (0.999-1.019)	0.076	0.92 (0.793-1.065)	0.260
Creatinine	29.25 (3.534-242.211)	0.002	34.48 (2.562-464.161)	**0.008**
Ferritin	1.001 (1.000-1.003)	0.092	1.00 (0.999-1.002)	0.547
Fibrinogen	1.34 (0.974-1.854)	0.072	5.04 (0.378-67.398)	0.221
Albumin	0.18 (0.055-0.620)	0.006	0.27 (0.020-3.848)	0.339
FAR	3.48 (1.213-9.992)	0.020	0.06 (0.000-34.052)	**0.024**
CAR	1.035 (1.002-1.068)	0.036	1.35 (0.803-2.255)	**0.025**

CAD: coronary artery disease; CRP: C-reactive protein; FAR: fibrinogen-to-albumin ratio; CAR: CRP-to-albumin ratio; OR: odds ratio; CI: confident interval. Bold fonts indicate a *P*-value lesser than 0.05

The ROC analysis indicated that a cut-off value of 0.64 for FAR has an 80% sensitivity and a 40% specificity in predicting obstructive epicardial coronary stenosis (AUC: 0.685, 95% CI: 0.559-0.811, *P*=0.010). A cut-off value of 0.65 for CAR has an 83% sensitivity and a 41% specificity (AUC: 0.650, 95% CI: 0.521-0.778, *P*=0.036) (Figure 2).

Figure 2: ROC analysis of FAR and CAR values.



Discussion

The main purpose of the present study is to investigate the predictive value of FAR and CAR in patients with COVID-19 pneumonia who underwent coronary catheterization due to elevated Tp levels. We found that FAR and CAR levels were higher in patients with obstructive CAD than in patients with normal coronary function. Additionally, FAR and CAR had a significant correlation with other laboratory parameters in CAD patients. In the ROC analysis, FAR and CAR had a good sensitivity in predicting obstructive CAD and were independent predictors of obstructive CAD in multivariate regression analysis.

CAD and ACS are the leading causes of mortality and morbidity worldwide. The main symptom in ACS is acute chest discomfort. Acute myocardial infarction (AMI) defines cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischemia. It is diagnosed by the presence of myocardial ischemia symptoms, ECG changes, detection of wall motion abnormalities by echocardiography, and presence of Tp elevation [16]. According to the fourth universal definition of AMI published in 2018, Type-1 MI is myocardial necrosis that occurs as a result of disruption of flow in the epicardial coronary arteries caused by intramural thrombus developing due to atherosclerotic plaque erosion or rupture. Type-2 MI is myocardial necrosis caused by an imbalance between oxygen supply and demand without plaque instability [17]. The diagnosis of STEMI is easily made by ECG, but the ECG may be completely normal in patients without ST elevation. In this case, the parameter supporting the diagnosis is Tp. However, it should be kept in mind that Tp levels increase in various clinical conditions (such as kidney diseases, tachycardia, and bradycardia) [16,18]. Tp elevation is also common in patients hospitalized with COVID-19 pneumonia for various reasons [19]. It is difficult to diagnose ACS in these patients who were hospitalized in the ICU as intubated due to moderate-to-severe pneumonia, had no findings of myocardial ischemia in the ECG, could not communicate verbally due to respiratory support, and had increased Tp in follow-up blood tests. For this reason, it is important to use laboratory parameters other than Tp to support the diagnosis of obstructive CAD.

In our study, no obstructive epicardial coronary stenosis was found in 25 (33.8%) of 74 patients who were hospitalized for COVID-19 pneumonia and underwent CAG with the suspicion of NSTEMI. The most striking point was that both the MI group and the normal group had Tp values above the normal reference range at the time of admission, along with an increase in follow-up Tp values. Although the Tp value was found to be higher than the reference value in both groups at the time of admission, it was significantly higher in the MI group than in the normal group. Considering other laboratory parameters, ferritin, D-dimer, and procalcitonin levels, which are positive APRs, were found to be significantly higher in the MI group, while albumin, which is a negative APR, was found to be lower. In the literature, it has been shown that the frequency of CAD is higher in people with high serum ferritin levels [20,21]. Zakai et al. [22] showed in their study that D-dimer elevation increased the risk of CAD independently of other cardiovascular risk factors. Similarly, high procalcitonin level has been shown to be associated with the severity of CAD in ACS patients [23]. Duan et al. [24] observed that the severity of CAD was higher in ACS patients with low serum albumin levels. The fact that the results of our study are similar to the literature data supports the reliability of our data and results.

Previous studies have shown that both FAR and CAR levels are high in patients with CAD and/or ACS [11–15,25]. In a study evaluating the relationship between CAD burden and FAR in NSTEMI patients, it was found that FAR was higher in patients with medium-high (22 and above) SYNTAX scores [25]. Similarly, it has been shown that there is a correlation between the severity of CAD and CAR in patients with NSTEMI [26]. In our study, both FAR and CAR rates were higher in the MI group than the normal group. The risk of mortality is higher in COVID-19 patients with high FAR [27]. Similarly, there are studies showing that the risk of COVID-19 mortality increases with high CAR [28]. In our study, the in-hospital mortality rate was higher in the group with higher FAR and CAR values.

In the correlation analyses, we found that the parameters of procalcitonin, CRP, creatinine, ferritin, fibrinogen, and albumin were associated with both FAR and CAR. We also found that hemoglobin was associated with FAR, and D-dimer, NLR, and lymphocyte were associated with CAR. In the regression analysis, the independent predictors of the presence of obstructive CAD were serum creatinine level, FAR, and CAR.

In ROC analyses, we found that the cut-off value of 0.64 for FAR had an 80% sensitivity and a 40% specificity, and the cut-off value of 0.65 for CAR had an 83% sensitivity and a 41% specificity in predicting obstructive CAD. Duan et al. [24] found that a FAR value of 0.706 predicted a high Gensini score in ACS patients. Previous studies have shown that FAR value has higher specificity and sensitivity than albumin alone or fibrinogen alone in predicting cardiac events [29, 30]. In the study of Karabağ et al. [15], the sensitivity of CAR value over 0.63 in predicting >22 SYNTAX score was 86.8% and the specificity was 43.4% [15].

Limitations

The main limitations of our study were its retrospective nature, its single-center scope, and its relatively small number of patients. The lack of serial follow-up of FAR and CAR was another limitation. The value of our study would have increased if patients had undergone intracoronary imaging. However, considering the general condition of the patients and the risk of spreading COVID-19, the shortest possible procedure time was pursued, and therefore intracoronary imaging was not performed.

Conclusions

Since COVID-19 pneumonia is an infective and inflammatory disease, a significant increase in Tp is observed in these patients. FAR and CAR values have a predictive value for obstructive CAD and can be evaluated in order to understand whether Tp elevation is associated with obstructive CAD or COVID-19 pneumonia. FAR and CAR can help medical staff decide on whether catheterization is necessary for a given patient. In this way, the number of unnecessary CAGs and the risk of infecting personnel will be minimized. Further studies are needed on biomarkers other than Tp in catheterization decisions in infectious diseases such as COVID-19 pneumonia.

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Volumetric apparent diffusion coefficient histogram analysis for determining the degree of differentiation of periampullary carcinomas

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Ethics Committee Approval
The study was approved by the Ethics Committee at Bakirkoy Dr. Sadi Konuk Training and Research Hospital of the University of Health Sciences on April 11, 2023 (Decision No: 2023/94).
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 classification of periampullary adenocarcinomas into pancreatobiliary-type periampullary adenocarcinoma and intestinal-type periampullary adenocarcinoma (PPAC and IPAC, respectively) has gained significant acceptance in the medical community. A patient's prognosis is determined by the degree of differentiation of these tumor types. The objective of the present investigation was to assess the efficacy of volumetric apparent diffusion coefficient (ADC) histogram analysis in assessing the degree of differentiation for these two tumor types.
Methods: This retrospective cohort research evaluated 54 PPAC (45 well-differentiated and nine poorly differentiated) and 15 IPAC (11 well-differentiated and four poorly differentiated) patients. Magnetic resonance imaging (1.5 T MRI) scans were used to evaluate the results. The features of the histogram for the ADC values were computed and incorporated several statistical measures, such as the mean, minimum, median, maximum, and percentiles in addition to the skewness, kurtosis, and variance.
Results: In both PPAC and IPAC patients, the ADC values exhibited lower values in the poorly differentiated group when compared with the well-differentiated group. However, the changes between groups did not reach statistical significance. Among IPAC patients, the well-differentiated group had a larger kurtosis (P=0.048). In IPAC patients, the calculated value for the area under the curve (AUC) of kurtosis was determined to be 0.818. When the threshold was set at 0.123, the specificity and sensitivity were observed to be 90% and 75%, respectively.
Conclusion: Our research indicates that the kurtosis of ADC is an effective indicator to determine the level of IPAC differentiation. Analysis of the histogram at increased b values can provide valuable insights to help determine the degree of differentiation of IPAC using a noninvasive technique.

Keywords: apparent diffusion coefficient, differentiation degree, periampullary adenocarcinoma, volumetric histogram

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Introduction

Periampullary adenocarcinoma (PAC) includes pancreatic ductal adenocarcinoma (PDAC), distal cholangiocarcinoma, ampullary carcinoma, and duodenal adenocarcinoma and accounts for 5% of all gastrointestinal tract malignancies [1]. Pancreatic head adenocarcinoma is the most frequent source of periampullary-type malignancies. However, pre-operative imaging differentiation between these origins is difficult due to their close anatomical proximity. The primary tumor origin affects patient prognosis and survival rates. Consequently, pathological evaluation is frequently required [2].

In over 50% of cases, PDAC is typically detected in its advanced stages, and despite advancements in treatment approaches, the 5-year relative survival rate remains around 20%. Early detection of patients who are eligible for curative surgery is limited to around 15% of cases to be performed immediately [3]. Although a considerable proportion of patients who have undergone surgical resection for PDAC experience the development of both local and systemic metastases, which ultimately lead to mortality within the initial year post-surgery, improvements in adjuvant therapies have been associated with an increase in survival [4,5]. The ampullary area is characterized by its intricate nature. Misdiagnosis of the primary tumor site could indeed occur during clinical practice [6]. A new classification was introduced to divide adenocarcinomas into two subtypes based on their histological differentiation: (1) pancreatobiliary-type periampullary adenocarcinoma (PPAC) and (2) intestinal-type periampullary adenocarcinoma (IPAC). This classification is now widely accepted for identifying periampullary adenocarcinomas [7].

Pancreatoduodenectomy is utilized to treat periampullary adenocarcinomas that are resectable. However, this treatment varies based on the survival rates and the histological characteristics of the adenocarcinoma's genesis [8]. Assessing the prognosis of patients with resectable periampullary adenocarcinomas is one of the greatest concerns when attempting to bring about a decrease in the need for unwarranted surgical interventions in individuals with a high probability of early tumor recurrence. The precise etiology of early recurrence is not completely understood but presumably involves histological and genetic tumor heterogeneity with micrometastases that remain imperceptible by imaging techniques even in cases in which they are amenable to surgical removal. Regrettably, the genetic characteristics of PAC can only be evaluated based on histological specimens, which are often not obtained for resectable adenocarcinomas [9–11]. Hence, it would be advantageous if non-invasive techniques could enhance the prognostic classification of such individuals.

Histogram analysis is an efficient method for the analyzing the spread of levels of gray within a specific region of interest (ROI) on cross-sectional images that can be used by employing descriptive characteristics. Analysis of these histograms can provide useful information concerning gene expression, angiogenesis, metabolism, and tumor heterogeneity [12]. Variations in histogram parameters represent histological and functional distinctions in tumor composition that are associated with aggressiveness and prognosis; these may be applicable to treatment alternatives. Diffusion-weighted imaging (DWI) is a type of magnetic resonance imaging (MRI) that measures the phenomenon of Brownian motion, which refers to the random movement exhibited by water molecules within a tissue voxel. Whole-lesion volumetric histogram assessment eliminates ROI placement subjectivity to assure consistency and computation accuracy, a technique that may eliminate sampling bias [13].

To our knowledge, only one study that includes apparent diffusion coefficient (ADC) histogram analysis for PPAC and IPAC without involving the degree of differentiation of periampullary adenocarcinomas is available [14]. Our objective was to evaluate the usefulness of the analysis of volumetric ADC histograms for differentiating between degrees of differentiation in PPAC and IPAC.

Materials and methods

The retrospective cohort research was approved by the Human Subjects Ethics Committee at the Bakirkoy Dr. Sadi Konuk Training and Research Hospital of the University of Health Sciences on April 11, 2023 (Decision No: 2023/94). Moreover, the guidelines of the Helsinki Declarations were followed. One-hundred eighty-two patients were evaluated for the study between July 2015 and January 2023. Among them, 113 patients were excluded. The exclusion criteria for these patients are summarized in Table 1. The study comprised 69 patients who were histopathologically diagnosed with PPAC (54 patients) or IPAC (11 patients) following surgery and who underwent pre-operative MRI. The time interval between the pre-operative MRI and the surgical procedure varied from 7 to 15 days. Patients were classified into two subgroups (well-differentiated and poorly differentiated) based on their degree of differentiation. Patients with moderately differentiated histopathology were included in the well-differentiated group.

Table 1: Data from patients who were excluded from the study

Patients excluded from the study		**n**
Patients treated in other hospitals		22
Patients without an MRI examination		33
MRI without DWI		5
Patients who received invasive treatment before MRI		18
Poor image quality		9
Pathologically confirmed other than IPAC or PPAC	neuroendocrine tumor	12
	gastrointestinal stromal tumor	7
	squamous cell carcinoma with ampullary adenocarcinoma	3
	high-grade pancreatic intraepithelial neoplasia	4

MRI: magnetic resonance imaging; DWI: Diffusion-weighted imaging; IPAC: intestinal-type periampullary adenocarcinoma; PPAC: pancreatobiliary-type periampullary adenocarcinoma

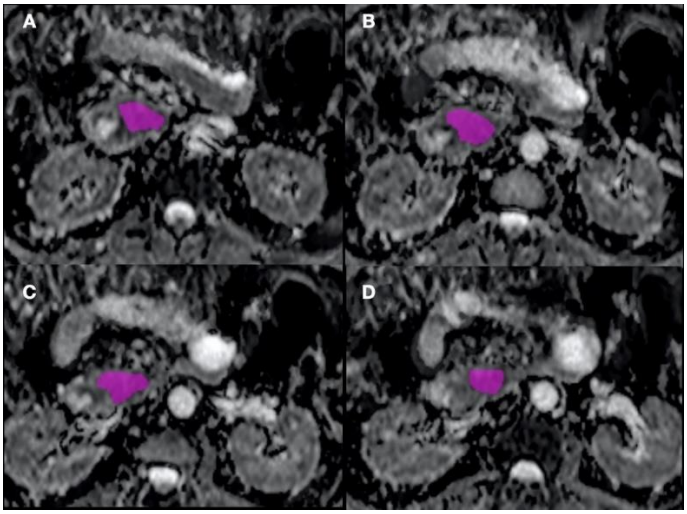
MRI was conducted using a 1.5-T MR system (Verio; Siemens Medical Solutions, Erlangen, Germany). With b-values of 1000 s/mm^2, diffusion-weighted imaging was performed. The imaging protocol consisted of acquiring thin-section turbo spin-echo T2-weighted (TSE) images in the sagittal, coronal, and transverse planes. A total of 20 slices were obtained, each with a thickness of 4 mm and no intersection gap. The imaging parameters for the TSE sequence were specific: (1) repetition time (TR) of 6000 ms, (2) echo time (TE) of 150 ms, and (3) the number of signals acquired of 2. The resulting picture resolution was 0.8 mm x 0.8 mm. For diffusion-weighted imaging, axial plane acquisitions were conducted using respiratory-triggered single-shot echo-planar sequences. The acquisition parameters were a matrix size of 180 x 200, a field of view (FOV) ranging

from 40 to 44 cm, a slice thickness of 4 mm, an intersection gap of 1 mm, a bandwidth of 350 kHz/pixel, an acquisition duration of 6-8 minutes, a flip angle of 90°, and the number of excitations (NEX) of 5.

Image Analysis

The DWI raw data were transferred from the picture archiving and communication system (PACS) to a personal computer (PC) for processing using the open-source LIFEx 7.3.0 voxel program (https://lifesoft.org). Two radiologists with 14 and eight years of experience, respectively, who were blind to the pathological results independently reviewed all MRI images. The researchers manually outlined the ROI using T2-weighted axial images as a guide. The voxel data were automatically aggregated to create a volumetric ROI encompassing the whole tumor. A volumetric ADC map was then created (Figure 1).

Figure 1: An example of manually drawn regions of interest (ROIs) on the apparent diffusion coefficient (ADC) maps for evaluating the volumetric ADC histogram analysis of the periampullary adenocarcinomas. The whole tumor was manually evaluated as an ROI for each slice of the ADC map. The axial T2-weighted and contrast-enhanced images were referred to for details.



The study involved determination of various statistical measures for ADC values, including the 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentiles. Additionally, the study examined the ADC_{max}, ADC_{mean}, ADC_{median}, and ADC_{min} values in addition to variance, kurtosis, and skewness. The n^{th} percentile represents the threshold at which n% of the voxel values from the histogram were seen on the lower end. Skewness indicates that the distribution possesses a rightward tail that is either flatter or longer in comparison to the leftward tail. Kurtosis is a statistical measure that quantifies the degree of peakedness in the distribution of a histogram. A high kurtosis value indicates a prominent peak near the mean, a rapid decline in values away from the peak, and heavy tails in the distribution.

Statistical analysis

Statistical analysis was performed using IBM SPSS 23.0 software (Chicago, IL, USA). Histograms were constructed from the combined ADC values of patients in the well-differentiated and poorly differentiated groups of IPAC and PPAC. The histograms demonstrated that the distribution of all measurements varied. Based on the measurements, descriptive statistics were performed for every set of patients, including measures such as mean, minimum, median, maximum, standard deviation, skewness, kurtosis, and percentiles. These descriptive data were then visually represented to illustrate the variances among the patient groups. The statistics from the previously mentioned group were computed based on data pertaining to individual participants. The t-test for independent samples was employed to assess the potential differences in the statistics obtained from individuals across various groups. Receiver operating characteristic (ROC) curves were produced based on individual statistics, and the cut-off parameters for the resulting statistics were computed.

Results

Population Information

Fifteen cumulative instances were incorporated in the IPAC group, consisting of 11 well-differentiated cases (as shown in Figure 2) and four poorly differentiated cases (as shown in Figure 3). Similarly, the PPAC group comprised 54 cases with 45 well-differentiated cases (as depicted in Figure 4) and nine poorly differentiated cases (as illustrated in Figure 5). The study consisted of a total of 44 male participants and 25 female participants. No statistically significant differences in terms of gender (P=0.555) or age (P=0.560) were found (Table 2).

Figure 2: A 67-year-old female patient with well-differentiated intestinal-type periampullary adenocarcinoma (IPAC). The lesion was isointense (white arrow) on the axial T2-weighted images (a), and the double duct sign was observed on the magnetic resonance cholangiopancreatography (MRCP) (b) image. The lesion showed progressive enhancement (white arrows) in the contrast-enhanced magnetic resonance imaging (MRI) sequences (c,d). The diffusion-weighted image (DWI) as shown in indicated hyperintensity, and the apparent diffusion coefficient image (f) showed hypointensity consistent with diffusion restriction (white arrows).

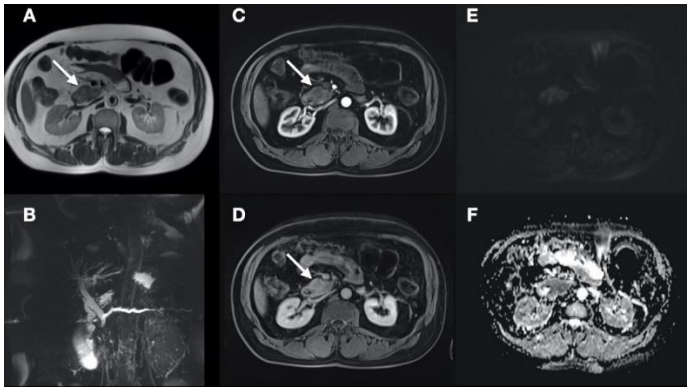


Figure 3: A 54-year-old male patient with poorly differentiated IPAC. The lesion displayed hyperintensity (white arrows) on the T2-weighted images (a–b) and continuous enhancement (white arrows) in the contrast-enhanced MRI sequences (c–d). Diffusion restriction was observed on the DWIs (e,f).

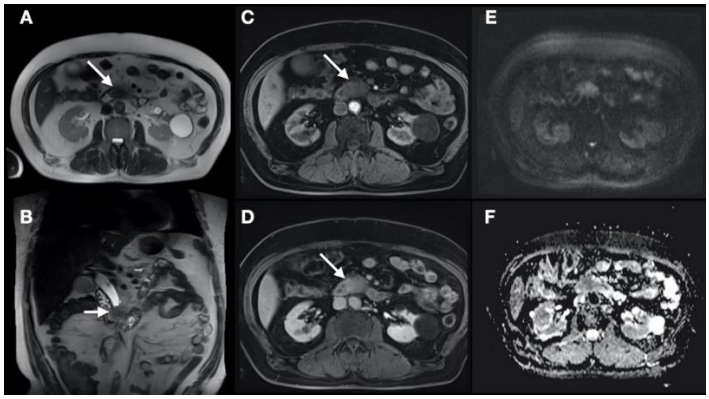


Figure 4: A 73-year-old male patient with well-differentiated pancreatobiliary-type periampullary adenocarcinoma (PPAC). The lesion was hyperintense (white arrow) on T2-weighted images (a), hypointense (white arrow) on T1-weighted images (b) and showed progressive enhancement (white arrows) on the (c,d) contrast-enhanced MRI sequences. The DWI (e) demonstrated hyperintensity, while the apparent diffusion coefficient image (f) exhibited hypointensity, both of which indicate diffusion restriction.

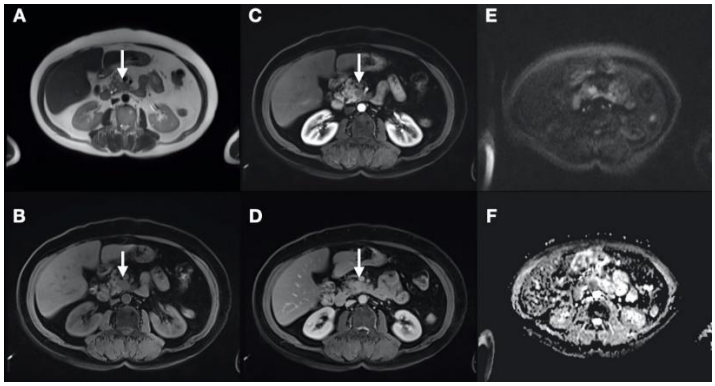
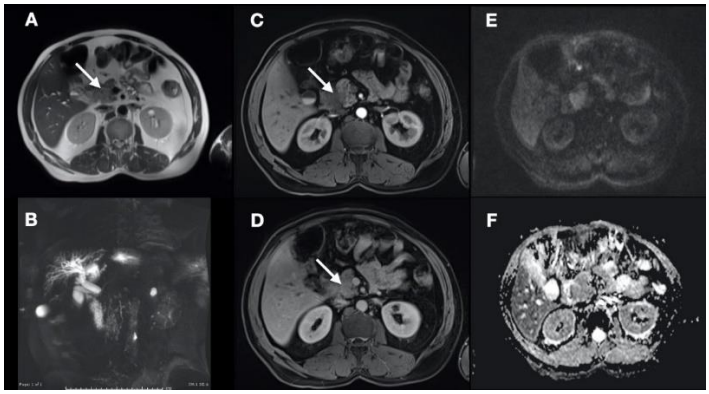


Figure 5: A 58-year-old female patient with poorly differentiated intestinal-type periampullary adenocarcinoma. The lesion was hyperintense (white arrow) on the axial T2-weighted images (a), and MRCP (b) images showed that the common bile duct has an abrupt ending. On contrast-enhanced MRI sequences, the lesion exhibited gradual enhancement (white arrows as shown in c,d). On the DWIs, diffusion restriction was detected (e,f).



Interobserver agreement

The assessment of agreement between the two observers was conducted utilizing the interclass correlation coefficient (ICC). All metrics exhibited ICCs that surpassed the threshold of 0.8, signifying a high level of agreement that approached perfection.

Tumor diameter results

While no difference in tumor size between well- and poorly differentiated groups for intestinal-type periampullary carcinomas was detected, the poorly differentiated group had a greater tumor diameter than the well-differentiated group (P=0.044) for pancreatic-type periampullary adenocarcinomas (Table 1).

ADC histogram parameters results

The ADC_{min}, ADC_{mean}, ADC_{median}, and ADC_{max} together with the percentiles of ADC values in the poorly differentiated group exhibited lower values when compared with those of the well-differentiated group in both PPAC and IPAC patients. However, the difference between the two groups was not statistically significant. No significant distinction could be observed between the variance and skewness metrics. Kurtosis in patients with IPAC was found to be significantly higher in the well-differentiated group (P=0.048) when compared with the poorly differentiated group. The descriptive features of both well-differentiated and poorly differentiated groups of both types of periampullary carcinoma patients are summarized in Tables 2 and 3.

The ROC curve demonstrated the effectiveness of the histogram settings for determining differentiation degree of periampullary carcinomas. In IPAC patients, the greatest value for the area under the curve (AUC) of kurtosis was found to be 0.818. When the cut-off value was set at 0.123, the sensitivity and specificity were observed to be 75% and 90%, respectively.

Table 2: Demographic, radiological, and pathological data of IPAC and PPAC patients

			Well-differentiated	Poorly differentiated	
			n (%) / mean (SD)	n (%) / mean (SD)	*P*-value
IPAC	Age		66.18 (9.14)	65 (4.24)	0.555[a]
	Sex	Male	8 (72.7)	2 (50.0)	0.560[b]
		Female	3 (27.3)	2 (50.0)	
	Tumor diameter (mm)		20.22 (6.94)	19.37 (11.82)	0.695[a]
PPAC	Age		60.78 (8.24)	63.33 (7.48)	0.416a
	Sex	Male	27 (60.0)	7 (77.8)	0.458[b]
		Female	3 (27.3)	2 (22.2)	
	Tumor diameter (mm)		24.99 (8.62)	32.33 (11.83)	0.044[a]

[a] Mann–Whitney U Test; [b]Chi-squared test. IPAC: intestinal-type periampullary adenocarcinoma; PPAC: pancreatobiliary-type periampullary adenocarcinoma, SD: standard deviation

Table 3: Comparisons of apparent diffusion coefficient (ADC) histogram parameters between well-differentiated and poorly differentiated IPAC groups.

ADC (10^{-3} mm^2/s)	Well-differentiated	Poorly differentiated	Total	*P*-value
Mean	1.277 (0.372)	1.177 (0.198)	1.204 (0.244)	0.514
SD	0.212 (0.56)	0.233 (0.74)	0.228 (0.686)	0.602
Median	1.279 (0.365)	1.153 (0.200)	1.186 (0.246)	0.514
Minimum	0.783 (0.358)	0.723 (0.257)	0.739 (0.274)	0.794
Maximum	1.760 (0.384)	1.783 (0.288)	1.777 (0.301)	0.896
Skewness	−0.5 (0.3)	−0.5 (0.5)	−0.5 (0.5)	0.896
Kurtosis	0.0 (0.3)	0.3 (0.3)	0.2 (0.3)	0.048
5th	0.920 (0.283)	0.834 (0.232)	0.858 (0.239)	0.896
10th	0.997 (0.309)	0.891 (0.232)	0.919 (0.248)	0.695
25th	1.119 (0.339)	0.988 (0.223)	1.023 (0.252)	0.514
50th	1.279 (0.365)	1.153 (0.200)	1.186 (0.246)	0.514
75th	1.450 (0.420)	1.358 (0.218)	1.383 (0.271)	0.695
90th	1.577 (0.457)	1.501 (0.232)	1.521 (0.291)	0.695
95th	1.623 (0.464)	1.585 (0.217)	1.595 (0.283)	0.896

ADC: apparent diffusion coefficient, SD: standard deviation

Table 4: Comparisons of ADC histogram parameters between well-differentiated and poorly differentiated groups of PPAC patients

ADC (10^{-3} mm^2/s)	Well-differentiated	Poorly differentiated	Total	*P*-value
Mean	1.314 (0.241)	1.287 (0.306)	1.310 (0.250)	0.359
SD	0.194 (0.46)	0.200 (0.37)	0.195 (0.45)	0.702
Median	1.306 (0.249)	1.275 (0.318)	1.300 (0.258)	0.275
Minimum	0.822 (0.242)	0.748 (0.267)	0.810 (0.245)	0.236
Maximum	1.878 (0.314)	1.832 (0.362)	1.870 (0.319)	0.523
Skewness	0.2 (0.4)	0.1 (0.4)	0.1 (0.4)	0.944
Kurtosis	0.1 (0.6)	−0.2 (0.5)	0.0 (0.6)	0.280
5th	1.010 (0.219)	0.967 (0.245)	1.003 (0.222)	0.223
10th	1.069 (0.222)	1.036 (0.262)	1.063 (0.227)	0.313
25th	1.178 (0.238)	1.147 (0.321)	1.173 (0.250)	0.246
50th	1.306 (0.249)	1.275 (0.318)	1.300 (0.258)	0.275
75th	1.441 (0.258)	1.426 (0.317)	1.438 (0.265)	0.472
90th	1.570 (0.263)	1.552 (0.334)	1.567 (0.273)	0.451
95th	1.650 (0.270)	1.633 (0.338)	1.647 (0.279)	0.451

ADC: apparent diffusion coefficient, SD: standard deviation

Discussion

This study provides a novel investigation into the potential implications of volumetric ADC histogram analysis as no prior research has been conducted for determining the degree of differentiation of periampullary tumors. Histogram parameters that are generated from ADC maps can provide data about the intrinsically pathogenic aspects of pancreatic adenocarcinomas have been extensively studied, revealing significant advancements in terms of enhanced characterization and prognosis according to previous research.

To verify the diagnosis, imaging techniques can effectively detect and localize focal periampullary tumors. Furthermore, imaging techniques are of paramount importance in the determination of therapy allocation for patients as they provide valuable insights into the local tumor stage and the exclusion of distant metastases [15,16]. Multi-detector computed

tomography (MDCT) is the most often used imaging modality followed by MRI and magnetic resonance cholangiopancreatography (MRCP).

The 5-year survival rate of resectable periampullary carcinomas is reported to be 20%–50%. Hence, adjuvant treatment has been suggested to increase overall survival; however, adjuvant treatment may be costly and ineffective. No realistic adjuvant treatment guidelines exist since a lack of consensus regarding the optimal and efficacious chemotherapy protocol and limited data is not available [17].

The intestinal transcription factor, known as CDX2, plays a crucial role in histological identification of challenging instances. Histological subtypes can be differentiated by the presence of mucin (MUC2) and intermediate filament biomarkers [18]. This marker's expression predicts longer overall survival independent of morphology [19]. In addition, some chromosomal abnormalities, such as the gains of 13q and 3q and the deletion of 5q, were detected to be specific to IPAC [20–22]. Nevertheless, it is impossible to examine these characteristics of periampullary carcinomas prior to surgery.

The characteristics of ADC are associated with various aspects of the tumor microenvironment, such as cell membrane stability, cellular proliferation rate, and extracellular matrix composition. The resulting phenomenon exhibits a resemblance to the Brownian motion of water particles [23,24]. Within the range of b-values ranging from 200 to 1000 s/mm^2, the signal attenuation associated with diffusion exhibits a linear pattern, which aligns with the principles of Gaussian diffusion. Non-Gaussian diffusion is observed when b-values exceed 1000 s/mm^2, leading to a commensurate decrease in the ADC value [25]. The primary objective of our investigation was the examination of volumetric ADC histograms and its utility in discerning the differentiation level between well-differentiated and poorly differentiated groups among patients with IPAC and PPAC. It was observed that the ADC values of the poorly differentiated groups, specifically the percentiles of ADC values in addition to ADC_{min}, ADC_{median}, ADC_{mean}, and ADC_{max}, exhibited lower values compared to the highly differentiated groups. However, the difference between the groups was not statistically significant. Kurtosis of ADC was a significant predictor of IPAC differentiation degree. The carcinoma was more likely to be poorly differentiated if the skewness was greater than 0.2.

According to the findings of Shindo et al. [26], utilization of ADC histogram-derived characteristics proved to be effective in differentiating between pancreatic neuroendocrine neoplasms and pancreatic ductal adenocarcinomas. Pancreatic neuroendocrine neoplasms had considerably higher mean ADC_{200} and ADC_{400} values. Pancreatic ductal adenocarcinomas demonstrated elevated levels of skewness and kurtosis when assessed with ADC_{400}. The study conducted by Lu et al. [14] determined that the maximum area under the curve (AUC) for differentiating between IPAC and PPAC was observed at the 75th percentile with an AUC value of 0.781. The sensitivity and specificity were found to be 91% and 59%, respectively, with a cut-off value of 1.50 x 10^{-3} mm²/s. In their study, Bi et al. [27] revealed that the average ADC was not able to differentiate these groups. However, they noticed that the ADC_{min} showed potential in terms of differentiating between the groups with a sensitivity of 85.2%, specificity of 50%, and an AUC of 0.672.

One of the most salient features of the study of the ADC histogram is the assessment of the biological activity of pancreatic cancer. Previous studies have indicated that a range of ADC histogram metrics have the potential to detect cancers exhibiting unfavorable clinical characteristics and a poor prognosis [28–31]. The study conducted by De Robertis et al. [30] demonstrated that the entropy of the ADC was significantly elevated in G2-3 pancreatic neuroendocrine neoplasms. The AUC for these neoplasms was found to be 0.757, indicating moderate discriminatory power. The sensitivity and specificity of the ADC entropy in differentiation between G2 and G3 pancreatic neuroendocrine neoplasms were determined to be 83.3% and 61.1%, respectively. Pereira et al. [28] reported a correlation between the histological grade of pancreatic neuroendocrine tumors and data from the histogram analysis. The average ADC and the 75th, 90th, and 95th percentiles exhibited notably higher values in G1 tumors when compared with either G2 or G3 cancers. Additionally, substantial differences in the skewness and kurtosis measures were found between G1 and G3 tumors.

The whole-lesion ADC entropy, the mean of the bottom 10th percentile, and the mean of the 10th–25th percentile indicated substantial variations between benign and malignant pancreatic intraductal papillary mucosal neoplasms (IPMNs) as reported by Hoffman et al. [29]. ADC entropy was the most effective parameter for predicting malignancy with 83% accuracy, 100% sensitivity, and 70% specificity. A study conducted by Igarashi et al. [32] provided evidence supporting the accurate prediction of high-grade dysplasia in IPMNs with the use of ADC entropy, achieving an accuracy rate of 73%.

In previous research, an ADC histogram analysis was used to compare neoplastic processes to periampullary adenocarcinomas. While misdiagnosis might lead to unnecessary and invasive surgery, the imaging properties of mass-forming pancreatitis based on the use of MRI are essential for differentiating pancreatitis from adenocarcinomas [33–36]. Many researchers have reported different ADC optimum threshold values, ranging from 0.88 to 1.26 10^{-3} mm^2/s to distinguish mass-forming autoimmune pancreatitis (AIP) from PDAC [37–41].

Limitations

This study has some strengths and limitations. This work describes the initial investigation into the possible usefulness of volumetric ADC histogram analysis based on the available knowledge in determining the degree of differentiation of periampullary carcinomas. In this study, the patients were chosen using a retrospective analytic methodology, which presents the potential for bias. We evaluated only the ADC parameters generated from higher b-values as no significant differences between investigations with lower b values could be found. Patients who were too advanced to receive surgery were excluded from the study. Additional research is required to substantiate the results of this research.

Conclusion

This research suggests that the kurtosis of ADC is a reliable indicator of IPAC's differentiation degree. When the kurtosis was >0.2, the carcinoma was more likely to be poorly

differentiated. The utilization of the analysis of volumetric ADC histograms may offer a noninvasive method for assessing the degree of differentiation in IPACs prior to surgical intervention and provide information about patients' prognosis and treatment management.

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Value of ischemia-modified albumin in ankylosing spondylitis

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Ethics Committee Approval
The study was approved by the Ethics Committee of Mersin University Mersin University (Approval number: 2023/78, Date: February 1, 2023).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Ankylosing spondylitis (AS) is a chronic inflammatory illness with a poorly known pathogenesis. Current biomarkers that are used to estimate inflammation are normal in some patients despite having active disease. Recent studies have revealed that oxidative stress may have a role in AS and that there is a close relationship between oxidative stress and inflammation. Ischemia-modified albumin (IMA) is a promising new biomarker for oxidative stress. Thus, the aim of this study was to assess IMA levels and their relationship with disease activity and other inflammatory markers in patients with AS.
Methods: This prospective case-control study included 48 patients with AS and 25 healthy controls (HCs). The measured serum levels of IMA, interleukin (IL)-17, and IL-23 were compared between patients with AS and the HC group. We also analyzed the correlation between IMA and disease activity, acute phase reactants, and HLA-B27 positivity. The Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were used to determine disease activity.
Results: There was no difference in serum IMA levels between the AS and HC groups (25.08 [20.49-46.83] vs. 29.89 [29.89-42.0], *P*=0.146). Only IL-23 was significantly higher in patients with AS (10.81 [7.25-14.06] vs. 7.95 [6.85-10.46], *P*=0.039). Furthermore, there was no correlation between IMA and IL-23, IL-17, CRP, ESR, BASDAI, or ASDAS-CRP (r=-0.079, *P*=0.593; r=-0.043, *P*=0.771; r=-0.018, *P*=0.906; r=0.047, *P*=0.751; r=0.281, *P*=0.053; r=0.162, *P*=0.271). There was no significant difference between IMA, IL-17, and IL-23 levels in patients with low disease activity (BASDAI <4, ASDAS-CRP <2.1) and high disease activity (BASDAI ≥4, ASDAS-CRP ≥2.1) (BASDAI: *P*=0.146, *P*=0.303, *P*=0.071, and ASDAS-CRP: *P*=0.451, *P*=0.410, *P*=0.324, respectively). There was no difference in IMA levels between HLA-B27-positive patients and HLA-B27-negative patients (*P*=0.070).
Conclusion: Although oxidative stress has been suggested to play a role in AS pathogenesis, we did not find an increase in serum levels of IMA, an oxidative stress biomarker, in patients with AS. Our results suggest that IMA may not be a reliable indicator of inflammation. Further research is needed to determine whether IMA may have a role as a biomarker in AS.

Keywords: ankylosing spondylitis, disease activity, ischemia-modified albumin, oxidative stress

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that has a hallmark of low back pain and leads to reduced quality of life. It primarily involves the axial skeleton and may result in structural and functional limitations due to the formation of new bone and ankylosis [1]. Although the pathophysiology of AS has not been fully elucidated, the factors that have been identified include genetic susceptibility and interactions of various immunological and environmental factors. Human leukocyte antigen B27 (HLA-B27) and the interleukin (IL)-23/17 axis have been proposed to have crucial roles in the pathogenesis of AS [2].

Oxidative stress is defined as a perturbation of the balance between pro-oxidant and antioxidant systems that favors oxidation. Free radicals and reactive oxygen species are generated as a consequence of oxidative stress and can cause cellular damage [3]. Recent research has indicated that immunological and oxidative stress factors have an important role in the etiology of AS, which is likely to be mediated by inflammation [4,5]. Oxidative stress is induced by the activation of neutrophils in patients with AS, which generate toxic free radicals such as reactive nitrogen and oxygen species, especially during the active phase of AS [5,6].

Transitional metals such as cobalt, copper, and nickel tend to bind mainly to the amino-terminal ("N-terminal") end of the albumin molecule. Exposure to ischemia alters the N-terminus of albumin, which reduces its ability to bind metals and leads to the production of ischemia-modified albumin (IMA) [7]. Hypoxia, superoxide radical damage, and acidosis have been suggested as factors that cause the conversion of serum albumin to IMA. The production of IMA is closely correlated with a high state of oxidative stress, which could affect various tissues [8].

It has been established that patients with AS have a disturbed balance of antioxidants and oxidants, and various biomarkers of oxidative stress are elevated [9]. However, studies exploring the value of IMA in AS are very limited. The aim of this study was to investigate the levels of serum IMA in patients with AS and the relationship between acute-phase reactants, serum levels of IL-17 and IL-23, and disease activity. As far as we know, this is the first study to investigate the relationship between IMA and interleukin levels.

Materials and methods

Study protocol

The study was approved by the Ethics Committee of Mersin University Mersin University (Approval number: 2023/78, Date: 01/02/2023). All participants were informed about the concept of the study. Informed written consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

This prospective case-control study was carried out at Mersin University between March and May 2023. The study comprised a total of 25 healthy controls (HC) and 48 patients with AS who satisfied the modified New York criteria [10]. Patients who were receiving non-steroidal anti-inflammatory treatment were included. Patients were excluded if they had peripheral joint involvement, infections, cardiac disease, severe renal or hepatic insufficiency, malignancies, diabetes, or rheumatic diseases other than AS. The healthy control group consisted of individuals with no rheumatic illness or known comorbidities. AS was excluded from the controls based on history and examination. All patients with AS were assessed radiologically.

Demographic features (age, sex) and clinical data were recorded. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores and the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) were used to assess disease activity. ASDAS-CRP ≥2.1 and BASDAI ≥4 were considered as indicating high disease activity, and ASDAS-CRP <2.1 and BASDAI <4 indicated low disease activity.

IMA and IL measurements

Blood samples were centrifuged at 4000 rpm for 10 minutes after being collected in biochemistry tubes. Until the day of analysis, aliquots of serum were stored at -80°C. On the day of testing, samples were reduced to room temperature. An investigator who was blinded to the study groups measured IMA and interleukins using ELISA processing equipment (BT-Lab, Bioassay Technology Laboratory Shanghai, China).

C-reactive protein and erythrocyte sedimentation rate measurements

CRP was analyzed using the immunoturbidimetric method on a Cobas Integra 800 device (Roche Diagnostics Mannheim, GmbH) within 2 hours of obtaining a serum sample on the same day with IMA and ILs. The erythrocyte sedimentation rate (ESR) was measured using an infrared reading technique using serum collected in EDTA tubes.

Statistical analysis

The sample size was determined using a power analysis in the software G*Power 3.1 (Franz Faul, University of Kiel, Germany). A sample size of at least 21 participants per group was required to achieve 80% power with a two-tailed significance threshold of 0.05 and an effect size of 0.92. IBM SPSS software v22.0 for Windows (SPSS Inc., Chicago, USA) was used for analysis.

The Kolmogorov-Smirnov test was used to identify the normality of the data distribution. Categorical data are presented as numbers (n) or percentages (%), and continuous data are given as the mean (standard deviation (SD)) or the median for normally distributed data. Otherwise, they are given as a median and interquartile range (IQR). The Student's t-test was used for normally distributed or the Mann-Whitney U for non-normally distributed data to determine the difference in continuous variables between groups. Pearson's correlation was used for relationships between normally distributed data; otherwise, Spearman's test was used. $P<0.05$ was used as a criterion for statistical significance.

Results

Table 1 shows the demographic and clinical features of the HC group and patients with AS. ESR , CRP, and IL-23 were higher in patients with AS than in HCs ($P<0.001$, $P<0.001$, and $P=0.039$, respectively). However, there was no difference in IMA and IL-17 levels between the patients with AS and HCs (25.08 [20.49-46.83] vs. 29.89 [29.89-42.0], $P=0.146$, 0.22 [0.08-0.78] vs. 0.28 [0.13-0.54], $P=0.843$) (Table 2).

Table 1: Demographic and clinical characteristics of AS patients and healthy controls

	AS patients (n=48)	Healthy control (n=25)	*P*-value
Age (years) (median, IQR)	40 (30.5-52.4)	37 (30.5-42.5)	0.191
Gender (Female/Male, n,%)	23/25 (47.9% F, 52.1% M)	11/14 (44% F, 56% M)	0.626
Disease duration (months) median, (min-max)	60 (24-120)	N/A	
HLA-B27 positivity (n,%)	37 (77.1%)	N/A	
BASDAI, mean (SD)	3.84 (1.53)	N/A	
ASDAS-CRP, mean (SD)	2.80 (0.97)	N/A	

AS: Ankylosing Spondylitis; HLA-B27: Human Leukocyte Antigen-B27; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-reactive protein; N/A: not assessed; IQR: Interquartile range; *P* <0.05 considered statistically significant

Table 2: Differences in laboratory variables of AS patients and healthy controls

	AS Patients (n=48) Median (IQR)	Healthy Control (n=25) Median (IQR)	*P*-value
ESR, mm/h	12.0 (8-20)	3.0 (2-4.5)	<0.001 ⁋
CRP, mg/L	5.80 (2-15.25)	1.20 (0.45-2.95)	<0.001 ⁋
IMA, ng/mL	25.08 (20.49-46.83)	29.89 (24.97-42.0)	0.146
IL-17, pg/mL	0.22 (0.08-0.78)	0.28 (0.13-0.54)	0.843
IL-23, pg/mL	10.81 (7.25-14.06)	7.95 (6.85-10.46)	0.039 ⁋

AS: Ankylosing Spondylitis; IQR: Interquartile range; ESR: Erythrocyte sedimentation rate; CRP: C-Reactive protein; IMA: Ischemia-modified albumin; IL-17: Interleukin 17; IL-23: Interleukin 23; *P* <0.05 considered statistically significant; ⁋ Mann Whitney U Test.

There was no significant difference between IMA, IL-17, and IL-23 levels in patients with low disease activity (BASDAI <4, ASDAS-CRP <2.1) and high disease activity (BASDAI ≥4, ASDAS-CRP ≥2.1) (BASDAI: *P*=0.146, *P*=0.303, *P*=0.0.71, and ASDAS-CRP: *P*=0.451, *P*=0.410, *P*=0.324, respectively) (Table 3). No correlation was observed between IMA and IL-23, IL-17, CRP, ESR, ASDAS-CRP, or BASDAI (r=-0.079, *P*=0.593; r=-0.043, *P*=0.771; r=-0.018, *P*=0.906; r=0.047, *P*=0.751; r=0.162, *P*=0.271, r=0.281, *P*=0.053) (Table 4). There was a significant positive correlation between ESR and CRP levels (r=0.595, *P*<0.001). There were no differences in IMA, IL-17, and IL-23 levels, ESR, and CRP between patients with HLA-B27 positivity and HLA-B27 negativity (*P*=0.070, *P*=0.957, *P*=0.714, *P*=0.105, *P*=0.871 respectively).

Table 3: Comparison of IMA, IL-17, and IL-23 levels according to BASDAI and ASDAS-CRP

	BASDAI Scores			ASDAS-CRP Scores		
	Low Activity (n=24)	High Activity (n=24)	*P*-value	Low Activity (n=13)	High Activity (n=35)	*P*-value
IMA (ng/mL)	24.52 (19.92-33.73)	28.13 (21.32-66.81)	0.146⁋	24.95 (20.16-32.27)	25.09 (20.46-65.72)	0.451⁋
IL-17 (ng/mL)	0.21 (0.08-0.54)	0.32 (0.09-1.40)	0.303⁋	0.20 (0.07-0.46)	0.32 (0.08-0.93)	0.410⁋
IL-23 (ng/mL)	9.46 (6.78-13.27)	12.93 (7.68-16.77)	0.071⁋	9.45 (6.93-13.55)	10.95 (7.33-15.18)	0.324⁋
ESR, mm/h	11.0 (7.25-19.75)	14.0 (10.25-23.75)	0.176⁋	8.0 (3.5-16)	13.0 (10-21)	0.029⁋
CRP, mg/L	4.7 (1.75-11.5)	8.9 (2.37-19.75)	0.146⁋	1.9 (1.70-4.7)	11 (2.9-19.0)	0.001⁋

Values are presented as Median (IQR). IQR: Interquartile range; IMA: Ischemia-modified albumin, IL-17: Interleukin 17, IL-23: Interleukin 23, ESR: Erythrocyte sedimentation rate; CRP: C-Reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-reactive protein ⁋ Mann Whitney U Test, *P* < 0.05 considered statistically significant

Table 4: Correlations between IMA and IL levels, acute phase reactants, disease activity scores of AS patients

	IMA (ng/mL)	
	r	*P*-value
Age	0.057	0.699
IL-17, pg/mL	-0.079	0.593
IL-23, pg/mL	-0.043	0.771
CRP, mg/L	-0.018	0.906
ESR, mm/h	0.047	0.751
BASDAI	0.281	0.053
ASDAS-CRP	0.162	0.271

IMA: Ischemia-modified albumin, IL-17: Interleukin 17, IL-23: Interleukin 23, CRP: C-Reactive protein, ESR: Erythrocyte sedimentation rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score; *r*: Correlation coefficient.

Discussion

In this study, there was no significant difference between the IMA levels of patients with AS and the HC group. IMA was not correlated with IL-17, IL-23, disease activity, ESR, CRP, or HLA-B27 positivity. There is limited research on IMA in patients with AS [11,12], and as far as we know, this is the first study investigating the relationship of IMA with serum IL-17 and IL-23 in patients with AS.

Despite the evidence for autoimmune factors, genetic pathways, and the generation of various cytokines of inflammation, the pathogenesis of AS remains elusive. Inflammation promotes the generation of pro-inflammatory cytokines, which trigger tissue damage by accelerating the generation of free radicals [13]. Reduced antioxidant and enhanced oxidant capacity have been implicated in the pathophysiology of AS. Karakoc et al. [14] demonstrated that total oxidative status and oxidative stress index were higher in patients with AS than HCs, whereas total antioxidant status was decreased. However, no correlation was found between oxidant and antioxidant markers and disease activity in their study.

Reactive oxygen species serve as signaling compounds in the early stages of the inflammatory response and modulate essential processes like phagocytosis, secretion, gene expression, and apoptosis, consequently promoting dysregulation of the inflammatory response [15]. But the redox state of a specific organ or tissue may not be accurately reflected by the systemic redox status by analyzing one or more pro-oxidant and antioxidant indicators [16]. Plasma cysteine and glutathione redox states have been shown in studies to be reliable indicators of oxidative stress, but they are not equilibrated in either cells or plasma [17]. Similarly, without broad alterations in the thiol/disulfide redox couples, excessive oxidation may occur, and redox signaling may take place via particular signaling pathways.

Despite the lack of achieving a state of equilibrium and disruption of redox circuits, oxidative stress might occur in the absence of an overall imbalance between pro-oxidants and antioxidants. Thus, it is suggested that oxidative stress can be better defined as a condition that disrupts redox signaling and control [18]. Despite the fact that oxidative stress is implicated in the pathogenesis of ankylosing spondylitis, plasma levels of oxidative stress biomarkers may not be elevated. This hypothesis may explain why serum IMA levels were not substantially different between patients with AS and the HC group in our study.

Adıgüzel et al. [19] found that patients with AS had lower serum total antioxidant status (TAS) levels and higher oxidative stress index (OSI) scores than healthy individuals. However, there was no significant difference in total oxidant status (TOS) between the two groups. The study also reported a moderate negative correlation between ASDAS and TAS levels, but no correlation was observed between ASDAS, TOS, and OSI. Yazici et al. [20] proposed that inflammation and the activation of neutrophils contribute to oxidative stress in AS. This is supported by elevated levels of myeloperoxidase and advanced oxidation protein products, along with reduced thiol levels, particularly in patients with active disease.

Ozgocmen et al. [21] found no difference in malondialdehyde nitrite (MDA) levels and serum nitric oxide, catalase, or superoxide dismutase activities between untreated patients with AS with inactive disease and HCs. Catalase and MDA enzyme activities were only higher in patients with active

AS than in HCs. None of the oxidant/antioxidant parameters were correlated with disease activity, ESR, or CRP.

Ischemia-modified albumin (IMA), which is generated during ischemia, has been linked to hypoxia, acidosis, and the formation of reactive oxygen species during ischemia and reperfusion. Although initially identified as a promising biomarker for acute myocardial ischemia, recent studies have shown that IMA is elevated in many rheumatic and non-rheumatic diseases in association with inflammation and oxidative stress [22-25]. Sertpoyraz et al. [11] recently evaluated IMA in 63 patients with AS and 48 HCs and reported that IMA was higher in those with AS. In addition, IMA was higher in cases of active AS than inactive AS, and there was a positive relationship between IMA, disease activity (BASDAI), and CRP.

Türkon et al. [12] also found that IMA was higher in patients with AS than in HCs, and there was a positive correlation with ASDAS-CRP, BASDAI, and the Bath AS Metrology and Functional Index. Studies on rheumatoid arthritis and Behcet's syndrome have also revealed higher levels of IMA compared to HCs [26, 27]. While some studies have demonstrated an increase in IMA levels in rheumatic diseases, there are also studies with conflicting results. Ermurat et al. [28] reported no difference in IMA levels between SLE patients and HCs in their study.

Similarly, no statistically significant differences were found between IMA levels in HCs and patients with primary Sjögren's syndrome. No correlation was observed between IMA levels and inflammatory markers, clinical parameters, or carotid intima-media thickness [29]. Furthermore, Ahn et al. [30] reported that IMA levels were higher in healthy controls than in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis, which they attributed to differences in the milieu of the affected tissues. In our study, although patients with AS had higher IMA levels than the control group, the difference was not statistically significant.

Th17 T cells and the IL-23/IL-17 axis have been linked to the pathophysiology of AS [31]. IL-17 and IL-23 levels in the sera of patients with AS were shown to be high in numerous studies and to have a correlation with disease activity [32,33]. However, there are contradictory findings where serum levels are similar to those of the healthy group [34]. We examined the oxidative stress marker IMA as well as IL-17 and IL-23, which play a role in pathogenesis. Only IL-23 levels increased among these three parameters in our study. Similarly, Milanez et al. [35] also reported elevated IL-23 levels in patients with active AS, although IL-22 and TNF levels were similar to those of the healthy group.

Proinflammatory cytokines TNF, IL-22, and IL-17 may all be induced in innate immune cells by IL-23. Exposure to IL-23 in vivo is sufficient to trigger extremely targeted entheseal inflammation in the absence of Th17 cells, and it has been shown that IL-23 is elevated locally in affected target organs [36]. This may be due to the increased entheseal inflammation in our sample of patients as a result of the inclusion of patients who had radiographic spondyloarthritis with structural damage.

Limitations

The limitations of our study are the small number of samples and the lack of evaluation of other oxidative stress markers. In addition, patients receiving biologics, which have a significant impact on cytokine balance and inflammation, were excluded from the study to avoid influencing cytokine levels, and the effect of these treatments on IMA levels was not assessed. Although individuals with co-morbidities such as diabetes, a history of cardiovascular disease, and hyperlipidemia were not included in the study, it is difficult to control and eliminate all oxidative stress factors that could influence the results. Additionally, the effect of disease progression on IMA levels was not assessed.

The recruitment of only patients with AS with prominent radiographic damage and the exclusion of patients in earlier phases, such as non-radiographic spondyloarthritis, may have resulted in bias. Furthermore, the presence of metabolic disorders that may impact IMA levels, such as cardiovascular disease hypertension, was excluded based on the patient's history but not by laboratory or imaging. Further studies with a large number of participants and a variety of oxidative stress markers may be useful in better determining the role of IMA in the pathogenesis of AS. Assessing the impact of biologics and other treatments on IMA levels, as well as including tissue-level markers from sites of local inflammation, may offer more comprehensive insight into the relationship between oxidative stress and AS.

Conclusion

In conclusion, our results indicated that IMA levels in patients with AS did not differ from those of healthy individuals. Furthermore, there was no correlation between IMA and other markers such as IL-17, IL-23, CRP, ESR, or indexes of disease activity. While oxidative stress is generally considered a key factor in the disease's pathophysiology, these results suggest that IMA may not be a reliable indicator of inflammation. The lack of higher IMA levels in AS implies a complicated interplay of oxidative stress and inflammation in this disease. Further comprehensive research is needed to further understand the role of IMA and other oxidative stress markers in the diagnosis and pathogenesis of AS.

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Impact of COVID-19 pandemic on acute appendicitis: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Bursa City Hospital Ethics Committee (2022-14/11).
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 probability of infection, especially from hospitals, and fear of contracting a disease caused changes in the clinical courses of many emergency diseases during the pandemic period. This article aimed to compare the histopathological and laboratory investigation results of acute appendicitis cases in a state hospital working as a pandemic hospital before and during the COVID-19 pandemic.

Methods: Patients undergoing appendectomy between March 2019 and March 2021 in the General Surgery Department of our hospital were included in the study. The period between March 2019 and March 2020 and the period between March 2020 and March 2021 were considered as the period before the pandemic and the pandemic period, respectively. Patients in the period before the pandemic were classified as Group A and the ones in the pandemic period as Group B. The patients were randomly selected from the computer system. Data of all patients, including ages, genders, presentation times to the hospital after initiation of pain, laboratory values, and histopathological investigation results were analyzed retrospectively.

Results: A total of 400 patients, including 200 patients in the period before the pandemic and 200 patients during the pandemic period, were included in the study. The mean age of patients who participated in the study before the pandemic was 35.85 (12.40) years, and during the pandemic period was 35.13 (12.30) years (P=0.558). The mean leukocyte values in the period before the pandemic, 13.23 (4.32), and during the pandemic period, 14.67 (4.09), were statistically different (P<0.001). The mean neutrophil value in the period before the pandemic, 10.08 (4.39), was found to be statistically lower than during the pandemic period, 11.26 (4.41) (P=0.007). In the histopathological investigation, one hundred and sixty patients were evaluated to be complicated and 40 patients to be non-complicated in the period before the pandemic. One hundred and ninety-six patients were evaluated to be complicated and 4 patients to be non-complicated during the pandemic period.

Conclusion: The fear of transmission of the virus has caused patients to be admitted to hospitals late. Therefore, the number of complicated appendicitis has increased during the COVID-19 pandemic.

Keywords: appendicitis, COVID-19 pandemic, complicated appendicitis

Introduction

The first case of COVID-19 was explained to be seen in our country on the day the World Health Organization (WHO) announced that COVID-19 disease transited to the pandemic [1–4]. The probability of infection, especially from hospitals, and fear of contracting a disease caused changes in the clinical courses of many emergency diseases during the pandemic period. This article aimed to compare the histopathological and laboratory investigation results of acute appendicitis cases in a state hospital working as a pandemic hospital before and during the COVID-19 pandemic

Materials and methods

Patients undergoing appendectomy between March 2019 and March 2021 in the General Surgery Department of our hospital were included in the study. The period between March 2019 and March 2020 and the period between March 2020 and March 2021 were considered as the period before the pandemic and the pandemic period, respectively. Patients in the period before the pandemic were classified as Group A and the ones in the pandemic period as Group B. The patients were randomly selected from the computer system. Data of all patients, including ages, genders, presentation times to the hospital after initiation of pain, leukocyte counts before the surgery (normal range: 4000–10000 /mm3), neutrophil counts (normal range: 1400–6500 /mm3), lymphocyte counts (normal range: 1000–4000 /mm3), and neutrophil/lymphocyte ratios and postoperative histopathological investigation results were analyzed retrospectively.

In order to determine the number of patients to be included in the study, a pilot study was conducted on 8 patients in each group. As a result of the pilot study, the effect size for leukocyte measurements in groups was 0.28. As a result, it was decided to include at least 200 patients in each group for 80% power and 5% significance level, with an effect size of 0.28.

Ethics committee approval of the study was obtained from the Bursa City Hospital Ethics Committee with the following decision number: 2022-14/11.

Statistical analysis

The Shapiro-Wilk test was used to investigate whether or not the data were normally distributed. Descriptive statistics were indicated as the mean and standard deviation for the quantitative data and the frequency and percentage for the qualitative data. T-test was used for data distributed normally in comparing two independent groups. Pearson's Chi-square and Fisher's exact tests were used to analyze categorical data. Significance was determined to be as α=0.05. Statistical analysis of the data was performed using IBM SPSS 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.) statistic package program.

Results

A total of 400 patients, including 200 patients in the period before the pandemic and 200 patients during the pandemic period, were included in the study. The mean age of patients who participated in the study before the pandemic was 35.85 (12.40) years, and the mean age of patients who participated in the study during the pandemic period was 35.13 (12.30) years (*P*=0.558). Sixty-one (30.5%) of patients who participated in the study before the pandemic were females, 139 (69.5%) of them were males, and 65 (32.5%) of patients who participated in the study during the pandemic were females, and 135 (67.5%) of them were males (*P*=0.667) (Table 1).

Table 1: Characteristics of 2019 and 2020 appendectomies

Appendectomies	Group A (n=200)	Group B (n=200)	*P*-value
Female/ Male	61/139	65/135	0.667
Age	35.85 (12.40)	35.13 (12.30)	0.558

Laboratory data were summarized in Table 2. The mean leukocyte values in the period before the pandemic and during the pandemic period were determined to be 13.23 (4.32) and 13.23 (4.32), respectively (*P*<0.001). The mean neutrophil values in the period before the pandemic and during the pandemic period were found to be 10.08 (4.39) and 11.26 (4.41), respectively (*P*═0.007). The percentages of lymphocytes in the period before the pandemic and during the pandemic period were determined to be 17.19 (11.0) and 15.2 (8.53), respectively (*P*═0.043).

Table 2: Comparison of laboratory values

	Group A	Group B	*P*-value
Wbc	13.23 (4.32)	14.67 (4.09)	<0.001
Baso	0.07 (0.15)	0.08 (0.16)	0.526
Baso %	0.54 (0.82)	0.58 (1.04)	0.647
Lym	2.01 (1.12)	2.05 (0.93)	0.690
Lym %	17.19 (11)	15.2 (8.53)	0.043
Mono	0.96 (1.46)	1.19 (2.23)	0.226
Mono %	6.95 (7.75)	7.86 (12.42)	0.378
Eos	0.11 (0.12)	0.12 (0.15)	0.664
Eos %	1.0 (1.11)	0.87 (1.03)	0.218
Neu	10.08 (4.39)	11.26 (4.41)	0.007
Neu %	74.26 (13.82)	75.5 (14.94)	0.393
Neu Lym	6.58 (5.06)	7.26 (6.15)	0.223
Neu Lym %	6.60 (5.09)	7.28 (6.18)	0.234

In the histopathological investigation, one hundred and sixty patients were evaluated to be complicated and 40 patients to be non-complicated in the period before the pandemic. One hundred and ninety-six patients were evaluated to be complicated and four patients to be non-complicated during the pandemic period.

Histopathological investigation results of 14 patients in the period before the pandemic and 2 patients during the pandemic period were not evaluated to be acute appendicitis.

Discussion

A virus first identified and reported from Wuhan City, China, on December 29th, 2019, was considered to be a pandemic within approximately 1 year and caused a fall on hard times throughout the world [2].

In our country, the first case was announced by the Ministry of Health on March 10, 2020 [3]. With the spread of COVID-19 in Turkey, the hospitals used for the treatment of this disease were announced to be risky areas for infection. With the postponement of elective surgical cases in the state hospitals announced to be pandemic hospitals, a difficult period began for patients [4]. With the fear of risk for viral infection in emergency and elective surgeries, decreases in presenting numbers to state hospitals assigned specifically as pandemic hospitals and delays in presenting periods occurred. Our study observed that patients presented to the hospital on the first day at the earliest beginning from pain in the period before the pandemic and on the third day at the earliest beginning from pain during the pandemic period.

Acute appendicitis is one of the most commonly encountered emergency surgeries in the general surgery department. The incidence is approximately 7%, which is more commonly seen in males [5,6]. Our study, determined no statistically significant difference between the two groups regarding age and gender.

Treatment of acute appendicitis is frequently surgical [7]. Based on the surgeon's decision according to the condition of the patient, medical or surgical treatment can be performed.

Since airway interventions are performed in patients, operative theaters where surgeons spend most of their time are high-risk areas for the spread of respiratory tract infections. This condition caused more difficulty in surgical branches during the pandemic period. It was observed that medical treatment became prominent with the partial change of treatment algorithms in emergency cases in some hospitals, especially during the pandemic period [8–10]. In our hospital, surgical treatment was primarily preferred in cases considered to be acute appendicitis.

The COVID-19 pandemic caused healthcare professionals working in institutions such as hospitals with a high risk of infection to have a more difficult condition. Due to either curfew or possible infection probability in the hospital, delays occurred in the diagnosis of many diseases. During this period, some changes occurred in the course, morbidity, and management of acute appendicitis. Our study determined that the complicated appendicitis rate in Group B was statistically significantly higher than the ratio in Group A.

A hemogram in laboratory investigation almost always takes part as an important component of the diagnosis in patients suspected of acute appendicitis. Leukocyte count is one of the most commonly used laboratory parameters, and while it is generally elevated in acute appendicitis patients, it is not a specific marker [11,12].

Acute appendicitis and leukocytosis were found to be associated with each other in many studies [13,14]. Many studies are reporting that the neutrophil count elevates and the leukocyte count decreases; therefore, the elevated neutrophil/lymphocyte ratio has a higher sensitivity in the diagnosis and shows the severity of acute appendicitis [13,15]. It has been reported that as the degree of inflammation of the vermiform appendix became more serious, this ratio increased significantly [16]. A decrease in lymphocyte counts is expected in complicated appendicitis compared to non-complicated appendicitis conditions [11,17]. In our study, it has been observed that the increased ratio of complicated appendicitis in Group B was reflected in the laboratory values consistent with the literature, and leukocyte and neutrophil counts were found to be statistically higher, but the lymphocyte count to be statistically less compared to the Group A.

Despite physical examination, laboratory findings, and auxiliary radiological methods, negative appendectomies are performed and will continue to be performed. The rate of negative appendectomy in the literature ranges between 2% to 30% [18,19]. In our study, the rate of negative appendectomy in Group A was found to be statistically significantly higher compared to the rate of negative appendectomy in Group B. We attributed this condition to a decrease in non-essential patient visits to the hospital during the pandemic period.

Limitations

The study has a number of possible limitations. Our data contains only cases that refer to the Çekirge State Hospital. Consequently, the need for future studies with prospective and with more patient series is present.

Conclusion

The obscurities in the treatment of the COVID-19 pandemic and higher mortality rates caused anxiety in humans. The fear of virus transmission has caused patients to be admitted to the hospitals late. Therefore, the number of complicated appendicitis has increased during the COVID-19 pandemic.

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Examination of the effect of bupivacaine on brain tissue in rats with induced experimental renal failure

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Ethics Committee Approval
The study was approved by Adıyaman University Animal Experiments Ethics Committee (15.09.2022 and 2022/054).
The present study followed international, national, and/or institutional guidelines for humane animal treatment and complied with relevant legislation from the Animal Ethics Committee.

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Abstract

Background/Aim: Local anesthetics are frequently used and often considered harmless, but they can precipitate local anesthetic systemic toxicity (LAST) when accidentally administered intravascularly or when a toxic dose is rapidly absorbed, which can result in mortality. In cases of renal function impairment, the altered pharmacokinetics of local anesthetics lead to a lowered toxicity threshold. In this study, the aim was to histopathologically investigate the increase in neurotoxicity in the central nervous system due to bupivacaine in experimental renal failure.

Methods: In the study, a total of 28 male Wistar albino rats, aged 8-10 weeks, were evenly divided into four groups: Group C (control group) received intraperitoneal 1 mL/kg saline; Group G (glycerol group) received intramuscular 10 mL/kg glycerol, Group GB (glycerol+bupivacaine group) received intramuscular 10 mL/kg glycerol followed by intraperitoneal 4 mg/kg bupivacaine; and Group B (bupivacaine group) received intraperitoneal 4 mg/kg bupivacaine. All rats were sacrificed after the experimental period. Tissue samples were preserved and stained with hematoxylin-eosin for histopathological analyses. TRPM2 and Reelin levels in brain tissue were measured using immunohistochemical methods.

Results: In the histopathological examination, Group G exhibited higher Reelin and TRPM2 levels compared to all other groups (P<0.001). In Group GB, both Reelin and TRPM2 immunoreactivity were significantly higher compared to Group B (P<0.001).

Conclusion: It can be concluded that renal dysfunction increases neurotoxicity in brain tissue associated with bupivacaine.

Keywords: bupivacaine, neurotoxicity, renal failure

Introduction

Local anesthetics (LA) are pharmacological agents that induce anesthetic effects in the administered area by blocking impulse transmission in neurons responsible for pain and temperature through a temporary Na^+ channel blockade [1]. LA are applied in a wide range of medical procedures, from minor cosmetic interventions to complex surgical procedures, and serve as a cornerstone of multimodal analgesia practices [2,3]. Despite their widespread use, complication rates remain low. While minor and transient side effects are commonly identified, life-threatening systemic toxicity of LA, known as local anesthetic systemic toxicity (LAST), can occur, presenting with central nervous system toxicity and cardiotoxicity manifestations [4,5].

In the context of impaired kidney function, alterations occurring in tissues as well as changes in the pharmacokinetics of local anesthetics lower the toxic dose threshold of the drug, potentially increasing the rate of complications [6]. Glycerol, often employed as a pharmacological agent, profoundly mimics acute kidney injury caused by rhabdomyolysis-induced acute renal damage in humans, manifesting exaggerated myoglobin release, tubular necrosis, and renal vasoconstrictive effects [7].

This study aims to histopathologically examine the increase in neurotoxicity in the central nervous system associated with bupivacaine in rats with experimentally induced renal failure.

Materials and methods

This is an experimental animal study and ARRIVE guidelines were used for this manuscript.

Animal procurement

In our study, a total of 28 male Wistar albino rats, aged 8-10 weeks, weighing from 240 to 260 grams, were systematically allocated into four groups, with each group consisting of seven rats. Throughout the experimental period, the rats were housed in rooms with a light-dark cycle of 12 hours each, at a room temperature ranging from 22 ± 20°C, and with unrestricted access to both food and water.

Ethical approval

Approval for this study was granted by the Adıyaman University Animal Experiments Ethics Committee (15.09.2022-2022/054). Animals were obtained from the Experimental Research Center unit of Adıyaman University, where experimental applications and care were conducted. At the conclusion of the study, rat tissues were processed at the Department of Histology and Embryology, Faculty of Medicine, Adıyaman University, and sera were worked on in the Medical Biology Laboratory of the Faculty of Medicine, Adıyaman University.

Formation of experimental groups

- Group C (Control Group): At the onset of the experiment, injections of 1 mL/kg saline solution were administered intraperitoneally to each subject.

- Group G (Glycerol Group): At the commencement of the experiment, intramuscular injections of 10 mL/kg glycerol solution were administered to each subject.

- Group GB (Glycerol+Bupivacaine Group): At the initiation of the experiment, each subject underwent a dual-phase administration, starting with a single intramuscular injection of 10 ml/kg glycerol, followed by an intraperitoneal injection of 4 mg/kg bupivacaine.

- Group B (Bupivacaine Group): At the outset of the experiment, each subject was administered a single intraperitoneal injection of 4 mg/kg bupivacaine.

At the conclusion of the experimental period, subsequent to intracardiac blood collection while under anesthesia, the rats were humanely euthanized under anesthesia, and tissue and serum samples were carefully preserved under suitable conditions for subsequent histological and biochemical analyses. As per previous literature knowledge, rats were dehydrated by withholding water for 12 hours before glycerol injections [8].

Collection and preservation of tissues

Immunohistochemical assessment was conducted at the Histology Laboratory of Adıyaman University Faculty of Medicine. Tissue samples obtained from euthanized animals underwent standard processing for subsequent light microscopic examination, following a one-week post-fixation period in a 10% formalin solution. Standard histological sections, involving a series of alcohol, xylene, and paraffin treatments, were prepared using the Leica TP1020 automated tissue processor (Leica TP1020, Nussloch, Germany), and 7 μm thick sections were meticulously sliced using the Thermo Shandon Finesse ME microtome (Thermo Fisher Scientific, Cheshire, UK).

Immunohistochemical staining

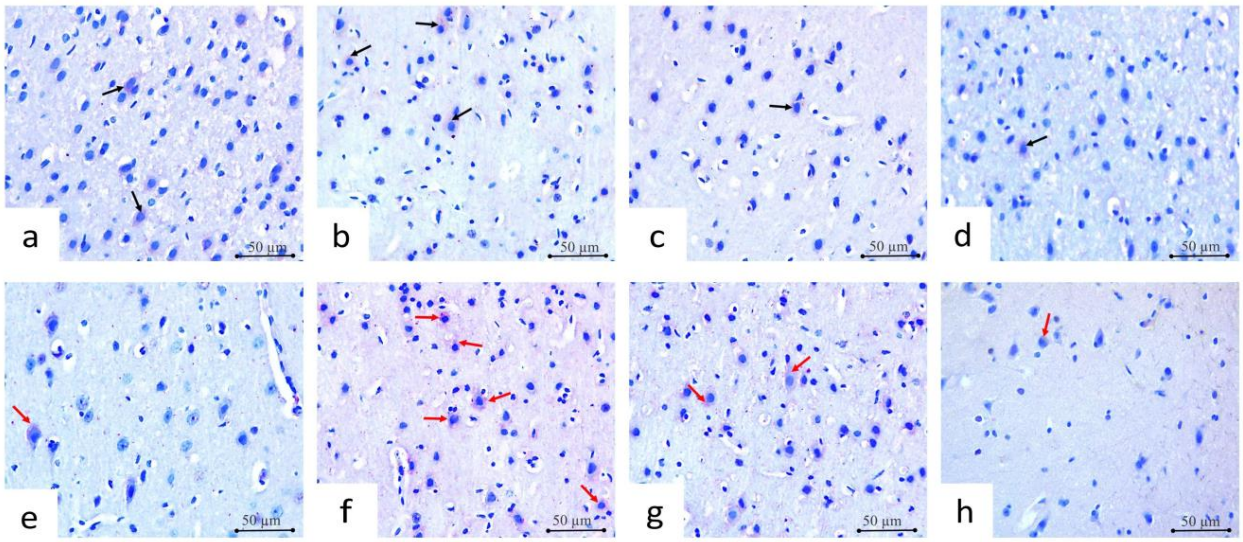
Immunohistochemical staining was conducted using minor adaptations to the avidin-biotin-peroxidase (ABC) complex method [9]. Sections, 7 μm thick, were acquired from paraffin-embedded tissues. Primary antibodies targeting Reelin (Rabbit polyclonal Ig [Reelin E5] Rabbit Polyclonal sc-25346, Santa Cruz Biotechnology, Inc., California, USA) and TRPM2 (anti-TRPM2 Rabbit polyclonal IgG antibody, ab101738 Abcam, London, UK) were appropriately diluted at ratios of 1/50 and 1/200 using the Thermo Scientific™ TP-015-HA commercial kit. Subsequent to AEC chromogen application, the sections were counterstained using Mayer's hematoxylin and subsequently assessed under a light microscope. Prepared slides were scrutinized and captured using the Leica DM500 microscope. The histoscore calculation was based on immunoreactivity prevalence (0.1= <%25, 0.4= %26-50, 0.6= %51-75, 0.9= %76-100) and intensity (0= none, +0.5= very low, +1= low, +2= moderate, +3= intense), with the histoscore being computed as the product of prevalence and intensity (histoscore = prevalence x intensity).

Statistical analysis

To calculate the sample size, we used data from a study that correlated TPRM2 levels with pathologic changes in the hippocampus (respectively, 5.40/1.14 and 8.40/2.07) [10]. Thus, in order to reproduce these findings with a maximum allowable error estimation of 5%, a statistical power of 90%, and an effect size of 1.8, a sample size of seven rats per group was determined sufficient.

Descriptive statistics encompassed mean, standard deviation, median, minimum, and maximum values for the dataset. The distribution of variables was assessed using the Kolmogorov-Smirnov test. Quantitative independent data were

Figure 1: The light microscope images of brain cortex tissues obtained from the study groups.



subjected to analysis through the Kruskal-Wallis and Mann-Whitney U tests. The statistical analyses were executed utilizing SPSS 28.0 software.

Results

The immunohistochemical staining results for Reelin were examined under light microscopy, revealing Reelin immunoreactivity in the brain tissue (black arrow) (Figure 1). Reelin immunoreactivity in the brain cortex tissue was similar in the control (Figure 1a) and bupivacaine (Figure d) groups (P=0.173). When compared to the control group, it was found that Reelin immunoreactivity significantly increased in the glycerol group (Figure 1b) (P<0.001). Conversely, when compared to the glycerol group, Reelin immunoreactivity was reduced in the glycerol+bupivacaine group (Figure 1c) (P<0.001) (Table 1, Reelin histoscore).

Upon examining the results of immunohistochemical staining for TRPM2 under light microscopy, TRPM2 immunoreactivity was observed in the brain cortex tissue (red arrow) (Figure 1). TRPM2 immunoreactivity in the brain cortex tissue was similar in the control (Figure 1e) and bupivacaine (Figure 1h) groups (P=0.528). It was observed that TRPM2 immunoreactivity significantly increased in the glycerol group (Figure 1f) when compared to the control group (P<0.001). In contrast, TRPM2 immunoreactivity was reduced in the glycerol+bupivacaine group (Figure 1g) compared to the glycerol group (P<0.001) (Table 1, TRPM2 histoscore).

Table 1: Comparison of immunohistoscores among the groups

	Min-Max	Median	Mean (SD)	*P*-value
Reelin				
Group C	0.10 - 0.30	0.20	0.229 (0.076)	**<0.001** [K]
Group G	0.80 - 1.20	0.90	0.914 (0.135)	
Group GB	0.40 - 0.80	0.60	0.571 (0.138)	
Group B	0.10 - 0.30	0.20	0.171 (0.076)	
TPRM2				
Group C	0.10 - 0.30	0.30	0.229 (0.095)	**<0.001** [K]
Group G	0.80 - 1.20	0.90	0.971 (0.160)	
Group GB	0.60 - 0.80	0.60	0.657 (0.098)	
Group B	0.20 - 0.30	0.20	0.214 (0.038)	

[K] Kruskal-Wallis (Mann-Whitney U test)

Discussion

The onset time, potency, and duration of action of LA depends on factors such as pKa, lipid solubility, and protein binding [11]. LA primarily binds to two plasma proteins: α1-acid glycoprotein with high capacity and low affinity, and albumin with low affinity and high capacity. The capacity of albumin to bind LA becomes significant when the concentrations of LA increase. In cases of metabolic acidosis, the levels of free LA unbound to plasma proteins increase, with bupivacaine showing the most prominent effect [12].

Both acute and chronic kidney failure can impact the pharmacokinetics of LA, manifesting in four distinct stages (absorption, distribution, metabolism, and excretion). Due to relative alkalization by LA, absorption is increased. Enhanced blood flow due to hyperdynamic circulation leads to rapid increases in plasma concentrations of LA. In cases of kidney failure, the elimination of LA metabolites through the urinary system will be reduced [13]. Lili et al. [14] demonstrated that renal dysfunction caused by glycerol in rats with acute kidney injury may alter plasma protein binding and vascular permeability, leading to higher plasma drug concentrations. Considering all this pharmacological information, it is recommended to reduce LA doses by 25% in patients with end-stage kidney failure [12].

LAST is a complex and fatal complication that can extend to seizures and cardiac arrest due to the blockade of Na^+ channels in both myocardial cells and thalamocortical neurons [15,16]. LAST initially presents with nonspecific symptoms, like restlessness and agitation, followed by central nervous system (CNS) excitation-inhibition findings and cardiovascular symptoms. While LAST is presented with CNS symptoms in 77% of cases, the most common manifestation is seizures, seen in 53-68% of cases [17,18]. The literature includes numerous case presentations discussing clinical manifestations related to LAST [19-21] as well as studies investigating neurotoxicity on motor neurons due to intrathecal use [22-24]. However, studies investigating the CNS histopathology associated with local anesthetics are limited.

Spitzer et al. [25] reported complications in two patients who experienced CNS toxicity following an interscalene block.

Although initial central nervous system imaging on the day of complications did not reveal any pathology, subsequent control imaging conducted within one to five days indicated the presence of T2/FLAIR hyperintensities accompanied by apparent diffusion coefficient (ADC) restriction in the cortical grey matter and basal ganglia of the left hemisphere.

Reelin is an extracellular matrix protein that controls neuronal migration during the developmental stages of brain tissue. Mice with Reelin deficiency show abnormal neuronal morphology and behavior. Reelin levels have been associated with neuropsychiatric pathologies and brain injuries [26-28]. In our study, the higher Reelin levels observed in the group with experimentally induced kidney failure suggest that renal failure exacerbates CNS damage associated with bupivacaine.

TRPM2 (melastatin-like transient receptor potential 2 channel) is a non-selective calcium channel. When exposed to oxidative stress, it becomes activated, resulting in elevated intracellular free Ca2+ concentrations and subsequent cellular damage. Elevated levels of TRPM2 expression have been linked to brain injury [29]. Similarly, in our study, the higher TRPM2 levels observed in the group with experimentally induced kidney failure suggest that kidney dysfunction exacerbates CNS damage associated with bupivacaine.

Limitations

The limitations of this study include the lack of CNS monitoring, and the inability to demonstrate the physiological effects of kidney failure.

Conclusion

In conclusion, both TPRM2 and Reelin scores, utilized both immunohistochemically and histopathologically, have demonstrated increased neurotoxicity associated with bupivacaine in cases of renal function impairment. In this context, we believe that a reduction in dosage is necessary when using local anesthetics in renal function impairment cases. Furthermore, we anticipate that larger-scale studies involving the monitoring of the central nervous system (such as EEG), and the assessment of acidosis through blood gas analysis will provide additional insights.

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Research article

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Factors affecting the outcome of older adults followed in the intensive care unit according to age stages

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Ethics Committee Approval
The study was approved by Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (November 23, 2021; 2021/252). 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: Increased frailty with age along with an increase in comorbidities heighten mortality in intensive care units. According to the World Health Organization, old age is divided into three stages: 65–74 years, 75–84 years, and 85 years and older. The lengthened human lifespan leads to a growth in the number of elderly patients in intensive care units, and the need to know the factors associated with prognosis in the three stages of old age. We aimed to define factors affecting mortality in these three stages of aging and the factors that can help predict prognoses.

Methods: In this retrospective cohort, data of patients over the age of 65 who were admitted to the intensive care unit of Bolu Izzet Baysal State Hospital between January 2016 and December 2020 were recorded using the hospital's automation system. Demographic data, blood tests, diagnoses and inflammatory biomarkers, such as RDW, NLR, and CAR were recorded. The data were analyzed using SPSS, and $P<0.05$ was considered significant.

Results: In this study, 46.2% of the 1566 patients died. The most common diagnosis for admission to the intensive care unit was sepsis, and the most common comorbidity was hypertension. While neurological impairment ($P<0.001$), malignancy ($P=0.006$), and cardiac disease ($P=0.004$) were associated with mortality in all three stages of old age, chronic obstructive pulmonary disease was associated with mortality in the 85 years and older age group ($P=0.011$) and diabetes in those aged 65–74 years and 75–84 years. The APACHE II score ($P<0.001$) and red cell distribution width ($P<0.001$) were highly effective in predicting prognoses in all three stages of old age.

Conclusion: In examining the factors associated with mortality in older age intensive care unit patients, we found that the APACHE II score and red cell distribution width were effective in establishing prognoses for all age groups.

Keywords: geriatrics, intensive care units, mortality, APACHE II, red cell distribution width

Introduction

Much of the population in intensive care units (ICU) comprises patients of advanced age. Today, patients over the age of 65 are considered older age, and with the recommendation of the World Health Organization, can be divided into three age groups: 65–74,75–84, and 85 years and older. In general, ICUs have high mortality rates. Even if age alone is not a factor, concomitant diseases and age-related systemic disorders can affect mortality [1].

Laboratory follow-ups are carried out daily in critically ill patients to determine the effects of systemic disorders on the body. Scoring systems based on the results of laboratory tests and clinical examinations are used for patient follow-up. The Acute Physiology and Chronic Health Evaluation (APACHE) II is one of the most frequently used scoring systems [2]. With improvements and modifications over the years, it has become a useful and accurate predictor of mortality. There are biomarkers and components of blood tests that are not included in this scoring system but have been proven to play a role in mortality in studies conducted over time. Hospitalization diagnoses, comorbidities, neutrophil count, lymphocyte count, platelet (PLT) count, creatinine level, neutrophil-lymphocyte ratio (NLR), C-Reactive Protein (CRP) albumin ratio (CAR), and red blood cell distribution width (RDW) are among these components [3,4]. Their use became widespread during COVID-19 pandemic [5].

We aimed to determine the conditions affecting mortality and predicting prognosis according to the stages of old age in patients over 65 years of age admitted to the ICU.

Materials and methods

Patient selection

The data of the ICU patients aged 65 years and above were collected after obtaining ethical approval from the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee, dated November 23, 2021 with decision number 2021/252. Based on the classification approved by the WHO, the study population was divided into three subgroups: those aged 65–74, 75–84, and 85 years and older [6]. Inclusion criteria were defined as age >65 years. Exclusion criteria were defined as being under 65 years of age, missing information on patient data, and being diagnosed with COVID-19.

Data collection

This was a retrospective cohort study. Patient data from the hospital database were retrospectively reviewed. The patient's sex, age, diagnosis of intensive care unit admission, ICU length of stay (LoS), current comorbidities, and status of receiving inotropic therapy and renal replacement therapy were examined and recorded. Leukocyte, lymphocyte, PLT, creatinine, RDW, NLR, and CAR levels were recorded. The APACHE II scoring system was used and recorded in the patients' ICU follow-ups.

Statistical analysis

Descriptive statistics are presented as frequency, percentage, mean, standard deviation, median, minimum, maximum, and 25%–75% percentile (Q1–Q3) values. The assumption of normality was checked by examining the histogram, q-q plot, skewness, and kurtosis values using the Shapiro–Wilk test. As the data were not normally distributed, the Mann–Whitney U test was used to analyze the difference between the numerical data of the groups. In examining the relationships between categorical data, the Pearson chi-square test was used when the expected small cell ratio less than 5 was less than 20%, and Fisher's exact test was used when the expected value was greater than 20%. Multivariate binary logistic regression analysis was performed to identify independent risk factors affecting survival. Statistical significance was set at *P*-value <0.05. SPSS software (version 23.0) was used for comparisons, while Medcalc was used for ROC analyses.

Results

In this study, 723 (46.2%) of the 1566 patients died. The mean age of the patients was 78.96 years. Overall, 50.8% of the patients were male. Among the patients, 32.6% were aged 65–74, 38% were 75–84, and 29.4% were 85 years and older. On the basis of the patients' ICU admission diagnoses, the majority were diagnosed with sepsis, pneumonia, and stroke. The most common comorbidities were hypertension (HT) 26.9% and chronic obstructive pulmonary disease (COPD) 23.8% (Table 1).

Table 1: Demographic and clinical characteristics of the study groups

	Total patients (n=1566)
Age (years), Age groups, n (%)	78.9 (65–100)
65–74 years	510 (32.6)
75–84 years	595 (38)
85 years and older	461 (29.4)
Mortality, n (%)	723 (46.2)
Sex, n (%)	
Female	795 (50.8)
Male	771 (49.2)
Diagnosis, n (%)	
Sepsis	633 (40.4)
Pneumonia	287 (18.3)
Stroke	230 (14.7)
Acute kidney injury	85 (5.4)
Pulmonary thromboembolism	74 (4.7)
Intoxication	15 (1)
Urinary tract infection	23 (1.5)
Other	197 (12.6)
Comorbid diseases, n (%)	
Hypertension	422 (26.9)
Diabetes mellitus	289 (18.5)
COPD	373 (23.8)
Malignity	254 (16.2)
Neurologic disorders	287 (18.3)
Cardiac disease	272 (17.4)

COPD: chronic obstructive pulmonary disease

The difference between discharge and exitus status in each of the age groups by numerical variables is presented in Table 2. Age was found to be statistically significant only in the 75–84 years age group (*P*=0.007). No significant differences were observed between the other groups. LoS was higher among patients who died for all age groups (*P*<0.001). The RDW (*P*<0.001), leukocyte count (*P*=0.001), NLR (*P*<0.001), CAR (*P*<0.001), creatinine (*P*<0.001), and APACHE II scores (*P*<0.001) were also higher for those who died in all age groups. Lymphocyte (*P*<0.001) and PLT counts (P<001 in 65-74, *P*=0.026 in >75) were lower among patients who died in all age groups (Table 2).

The analysis of discharged and deceased patients in the three age groups using categorical variables is shown in Table 3. While the rate of diabetes mellitus (DM) was higher in those who died in the 65–74 (*P*=0.05) and 75–84 (*P*=0.02) years age groups than in those who were discharged, this difference was

Table 2: Comparison of old age groups according to mortality predictors

Variables		65–74 years			75–84 years			85 years and older		
		n	m	*P*-value	n	m	*P*-value	n	m	*P*-value
Age(year)	Survived	306	69.4	0.292	346	79.47	0.007	191	88.9	0.647
	Died	204	69.7		249	78.91		270	89.13	
LoS(day)	Survived	306	8.5	<0.001	346	9.82	<0.001	191	9.24	<0.001
	Died	204	12.8		249	14.3		270	15.03	
RDW	Survived	306	15.6	<0.001	346	15.83	<0.001	191	15.91	<0.001
	Died	204	18.3		249	1775		270	17.67	
Leukocyte (10^3/µL)	Survived	306	11.6	<0.001	346	11.74	<0.001	191	10.52	<0.001
	Died	204	14.8		249	14.31		270	13.23	
Lymphocyte (10^3/µL)	Survived	306	1.2	<0.001	346	1.16	0.003	191	1.39	<0.001
	Died	204	0.96		249	0.97		270	0.93	
Platelet (10^3/µL)	Survived	306	228	<0.001	346	220.03	0.292	191	216.19	0.026
	Died	204	200		249	208.91		270	197.63	
NLR	Survived	306	12.88	<0.001	346	13.31	<0.001	191	11.46	<0.001
	Died	204	22.42		249	20.09		270	20.3	
CAR	Survived	306	21.29	<0.001	346	25.7	<0.001	191	26.17	<0.001
	Died	204	38.22		249	28.22		270	38.89	
Creatinine (mg/dL)	Survived	306	1.53	<0.001	346	1.58	<0.001	191	1.52	0.007
	Died	204	2.16		249	1.91		270	1.77	
APACHE ll	Survived	306	17.73	<0.001	346	19.45	<0.001	191	21.93	<0.001
	Died	204	26.73		249	28.22		270	28.49	

APACHE: Acute Physiology and Chronic Health Evaluation, CAR: CRP to albumin ratio, NLR: neutrophil to lymphocyte ratio, RDW: red cell distribution width, LoS: Length of Stay

Table 3: Patient characteristics affecting mortality according to older age groups

		65–74 years old			75–84 years old			85 years and older		
Prognosis		**Survived**	**Died**		**Survived**	**Died**		**Survived**	**Died**	
Variables		**n (%)**	**n (%)**	***P*-value**	**n (%)**	**n (%)**	***P*-value**	**n (%)**	**n (%)**	***P*-value**
Sex	Female	136 (44.4)	76 (37.3)	0.107	178 (51.4)	128 (51.4)	0.992	117 (61.3)	160 (59.3)	0.666
	Male	170 (55.6)	128 (62.7)		168 (48.6)	121 (48.6)		74 (38.7)	110 (40.7)	
Diagnosis	Pneumonia	54 (17.6)	36 (17.6)		66 (19.1)	52 (20.9)		34 (17.8)	45 (16.7)	
	Stroke	50 (16.3)	21 (10.3)		57 (16.5)	43 (17.3)		23 (12.0)	36 (13.3)	
	Sepsis	91 (29.7)	104 (51.0)		123 (35.5)	112 (45.0)		72 (37.7)	131 (48.5)	
	Acute kidney injury	19 (6.2)	9 (4.4)		11 (3.2)	9 (3.6)		15 (7.9)	22 (8.1)	
	Pulmonary thrombo-embolism	20 (6.5)	7 (3.4)		23 (6.6)	13 (5.2)		7 (3.7)	4 (1.5)	
	Trauma	10 (3.3)	2 (1.0)		6 (1.7)	0 (0.0)		3 (1.6)	1 (0.4)	
	Intoxication	7 (2.3)	2 (1.0)		3 (0.9)	1 (0.4)		1 (0.5)	1 (0.4)	
	Urinary tract infection	2 (0.7)	2 (1.0)		2 (0.6)	3 (1.2)		7 (3.7)	7 (2.6)	
	Other	53 (17.3)	21 (10.3)		55 (15.9)	16 (6.4)		29 (15.2)	23 (8.5)	
Comorbidity	HT	76 (24.8)	50 (24.5)	0.933	88 (25.4)	81 (32.5)	0.058	51 (26.7)	76 (28.1)	0.732
	DM	48 (15.7)	46 (22.5)	0.05	64 (18.5)	66 (26.5)	0.02	24 (12.6)	41 (15.2)	0.426
	COPD	70 (22.9)	37 (18.1)	0.198	96 (27.7)	82 (32.9)	0.173	47 (24.6)	41 (15.2)	0.011
	Malignancy	39 (12.7)	58 (28.4)	<0.001	45 (13.0)	61 (24.5)	<0.001	12 (6.3)	39 (14.4)	0.006
	Neurologic disorder	29 (9.5)	30 (14.7)	0.07	55 (15.9)	73 (29.3)	<0.001	24 (12.6)	76 (28.1)	<0.001
	Cardiac disease	43 (14.1)	23 (11.3)	0.036	60 (17.3)	64 (25.7)	0.013	26 (13.6)	56 (20.7)	0.004

COPD: chronic obstructive pulmonary disease, HT: hypertension, DM: diabetes mellitus

Table 4: Univariate logistic regression analysis of the variables for the development of mortality

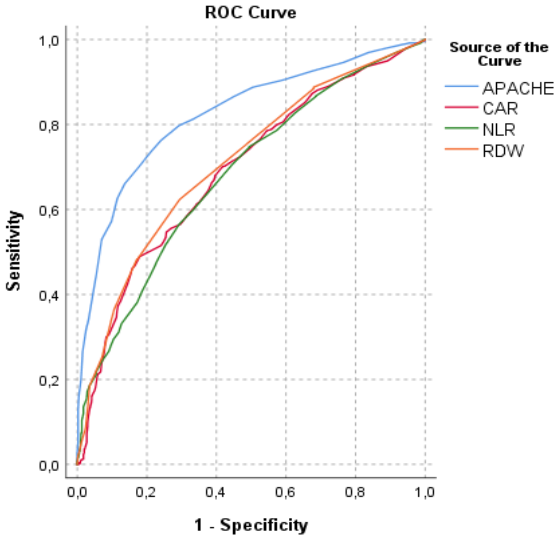
	65–74 years old		75–84 years old		85 years and older	
	OR [95%CI]	***P*-value**	**OR [95%CI]**	***P*-value**	**OR [95%CI]**	***P*-value**
Age	0.975 [0.891–1.067]	0.584	0.842[0.766–0.925]	<0.001	1.009[0.932–1.092]	0.833
RDW	1.298 [1.18–1.428]	<0.001	1.174[1.076–1.281]	<0.001	1.25[1.143–1.368]	<0.001
Leukocyte (10^3/µL)	1.055[1.002–1.11]	0.04	1.007[0.961–1.054]	0.776	1.06[1.001–1.122]	0.04
Lymphocyte(10^3/µL)	0.883[0.574–1.357]	0.57	0.913[0.557–1.495]	0.716	0.74[0.513–1.069]	0.1
Platelet (10^3/µL)	0.995[0.992–0.998]	<0.001	0.999[0.996–1.014]	0.333	0.997[0.994–1.0]	0.02
NLR	1.023[0.995–1.051]	0.11	1.031[1.0–1.062]	0.05	1.035[1.003–1.068]	0.033
CAR	1.014[1.002–1.026]	0.02	1.005[0.996–1.014]	0.274	1.004[0.995–1.014]	0.371
Creatinine(mg/dL)	1.101[0.891–1.36]	0.374	0.838[0.687–1.022]	0.08	1.054[0.813–1.367]	0.69
APACHE II	1.219[1.162–1.278]	<0.001	1.238[1.188–1.29]	<0.001	1.129[1.088–1.171]	<0.001

not significant in the 85 years and older age group. The incidence of COPD was higher among those who were discharged in the 85 years and older age group than in those who died (*P*=0.011). The malignancy ratio was higher in patients who died in all age groups (*P*<0.001). While neurological impairment (*P*<0.001) and heart disease (*P*=0.013) were higher in those who died in the 75–84 and 85 years and older age groups, there were no differences in the 65–74 years age group.

The results of the logistic regression analysis presented in Table 4 were evaluated to determine whether the variables examined in the three age groups were independent risk factors affecting mortality. Accordingly, RDW (*P*<0.001), leukocyte count (*P*=0.04), PLT (*P*<0.001) (negative effect), CAR (*P*=0.02), and APACHE II (*P*<0.001) were determined to be effective independent risk factors in patients who died in the 65–74 years group. In the 75–84 years age group, the RDW (*P*<0.001) and APACHE II (*P*<0.001) variables were found to be effective independent risk factors for death. In the 85 years and older age group, RDW (*P*<0.001), leukocyte count (*P*=0.04), PLT (negative effect) (*P*=0.02), NLR (*P*=0.03), and APACHE II (*P*<0.001) scores were effective independent risk factors in patients who died.

When all older adult patients were evaluated regardless of age, the mortality prediction sensitivity of the APACHE II score was 76.2%, with a specificity of 76%. The cut-off APACHE II score was 23. The RDW sensitivity was 62.2%, with a specificity of 70.6%. The cutoff value for RDW was 17. The ROC curves showing the power of APACHE II, RDW, NLR, and CAR are shown in Figure 1.

Figure 1: ROC curves of APACHE II, RDW, NLR and CAR for predicting mortality



Discussion

In our study examining 1566 patients admitted to the ICU, the most common diagnosis was sepsis. The presence of COPD did not increase mortality in any age group. The presence of DM increased mortality in the 65–74 and 75–84 age groups, while neurological impairment and heart disease increased mortality in the two older age groups. Malignancy was associated with increased mortality in all age groups. The increase in the ICU LoS, RDW, leukocyte count, CAR, and APACHE II scores, and the decrease in PLT affected mortality. In the 75–84 age group, as the variables of ICU LoS, RDW, and APACHE II score increased, so did mortality. In the oldest age group, the increase in ICU LoS, RDW, leukocyte count, NLR, APACHE II score, and decrease in PLT were consistent with mortality.

As a result of health care developments, the older adult population is increasing in Turkey and worldwide. According to data provided by the Turkish Statistical Institute, the older adult population has increased by 24% in the last five years, reaching 8,245,124 people in 2021; The ratio of older adults to the total population has increased to 9.7% [7]. A decrease in physiological reserves caused by aging and chronic diseases can lead to increased susceptibility or death in many diseases [8]. In this advanced age period, when frailty increases, sepsis develops very easily and progresses with high mortality [9]. Additionally, in the older adult population, acute exacerbations or complications of chronic diseases, new-onset catastrophic diseases, and indoor and outdoor accidents are among the most common reasons for admission to the ICU [10]. The most common diagnoses and causes of treatment in our ICU were sepsis and organ failure associated with sepsis.

In the ICU follow-up, the search for guidelines to assist the clinician in terms of the patient's response to treatment continues. APACHE is of great importance in these guidelines and is frequently used [2]. In our study, the accuracy of APACHE scoring in predicting mortality in all older age groups in our ICU was evaluated.

NLR and CAR, which are ratios derived based on laboratory tests, are used by many clinicians in ICU follow-ups. In a study screening 4717 patients followed up in the ICU, RDW, NLR, and platelet-lymphocyte ratio (PLR) were examined. If the RDW ratio was 14.1 and above, atrial fibrillation (AF) rhythm disorder was common, and this may increase mortality. It was found that the NLR and PLR values did not affect AF [11]. In a study conducted in the palliative care unit, the effects of CRP, CAR, NLR, and the Glasgow scoring system on 90-day mortality were examined. The cut-off value for these parameters was indicated as CRP ≥6.7mg/L, CAR ≥2.0, leukocytes ≥9300/µL, neutrophils ≥7426/µL, and NLR ≥6.0. It has been reported that all these biomarkers (especially CAR) are below these threshold values and are indicators of a good prognosis [12].

These ratios are widely used in Turkey to predict mortality. In one study, 2147 patients in the ICU were screened retrospectively and these ratios were reported to be the best predictor of mortality in patients in the ICU. It was stated that among the laboratory rates, RDW, CAR, and NLR accurately determined mortality estimation. The mean age of the patients was 72.1 (15.8) years. In the patient group with exitus, this number increased to 75.3 (13.4) years, which was statistically significant. However, the patients were not divided into age groups, and the course of these values in the three older age subgroups was not examined [13].

In a study conducted on patients with acute ischemic stroke and intracerebral hemorrhage admitted to the neurology ICU, the effects of laboratory values used in the follow-up and their rates on mortality were examined. The calculated NLR, lymphocyte-monocyte ratio (LMR), PLR, and CAR were examined to determine the factors affecting 30-day and 90-day mortality. While NLR, and CAR were found to be significant predictors of 30-day mortality, only a high NLR has been reported as a valuable indicator of 90-day mortality [14].

The importance of these markers has been further elucidated, particularly during the COVID-19 pandemic. In a study in which independent risk factors predicting the severity of COVID-19 were determined, using logistic regression analysis, age, and CAR elevation were identified as independent risk factors. In the ROC curve analysis, the CAR threshold value was 0.9 in COVID-19 cases, and in cases with a higher value, the mortality rate was higher [15]. In a study examining the relationship between NLR and CAR ratio and mortality in geriatric patients diagnosed with COVID-19, creatinine, NLR, CRP, and CAR values were high in patients who died. Threshold values were determined as 4.02 for NLR, 23 for CAR, and 81.4 for CRP [16]. In the examination of 613 patients who were admitted to the emergency department due to COVID-19, it was found that acute-phase reactants were high in deceased patients. It was also emphasized that CAR, NLR, fibrinogen albumin ratio (FAR), and urea albumin ratio (UAR), which are the ratios obtained from these laboratory values, also affected mortality. Threshold values were determined as 2.1561 for CAR, 1.5622 for UAR, 7.7321 for NLR, and 11.1078 for FAR [17].

These rates are widely used to predict mortality not only in ICUs but also in emergency services. In a study in which patients with dyspnea who visited the emergency room were screened, the relationship between RDW and NLR and mortality was determined using ROC analysis. A low NLR has been previously reported to increase the chance of survival, but it is not an independent risk factor. There was no relationship with

RDW [18]. In another study conducted in Turkey, researchers examined emergency room applications. They reported that an increase in NLR and CAR increased mortality in the emergency room. It was determined that the risk of in-hospital mortality was 9.87 times higher in patients with high NLR and CAR values simultaneously (CAR >12.3, NLR >7.1). These values (NLR 7.21, CAR 12.65) were significantly higher among patients who were admitted to the ICU from the emergency room than in those who were discharged (NLR, 3.64; CAR, 2.88) [19].

Factors affecting resuscitation success were examined in a publication examining the issues affecting mortality in out-of-hospital cardiac arrests. Spontaneous circulation was restored in 91 of the 191 patients. It was determined that the first 24-hour mortality was affected by the neutrophil count, NLR, and lactate level at the time of admission, and if the NLR value was below 3.05, the first 24-hour mortality was low [20].

Surgeons also use these ratios to predict postoperative mortality. In a study examining patients aged >80 years who had undergone laparotomy, NLR and CAR values were high in patients with sepsis. It was found that the preoperative NLR increased the 30-day and 90-day mortality in patients with visceral perforation, while the CAR value did not affect mortality. It was emphasized that if the preoperative NLR value was 8 or above, mortality increased significantly [21].

Limitations

Our study was conducted with ICU patients at a single center. Only the NLR and CAR were calculated to evaluate their effects on mortality inpatients divided into age groups. Although these ratios have been shown to affect mortality, no threshold value was provided. Additionally, other ratios such as the LMR and PLR used in intensive care follow-up were not examined. New publications with a larger patient group and multicenter participation are needed to evaluate more ratios and determine threshold values to alert the attending physician.

Conclusions

In our study examining the factors affecting mortality in the ICU of three older age groups, we found that the LoS in the ICU, APACHE II score, and RDW were associated with mortality. Although CAR is an indicator of mortality in the 65–74 years age group, NLR has gained importance in the 85 years and older age group. We believe that follow-up on the APACHE II scores, laboratory values, and combinations of various laboratory parameters, considering the age of the patients, is meaningful in predicting mortality and in the follow-up of the clinical course. We are of the opinion that more randomized controlled studies are needed to support our findings.

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Demographic characteristics of patients with anosmia consulting to the COVID-19 outpatient clinic

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Ethics Committee Approval
The study was approved by the Ministry of Health and the Ethics Committee at Kartal Dr Lütfi Kırdar City Hospital (date: June 11, 2020, number: 2020/514/179/8).
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: Coronavirus disease 2019 (COVID-19) cases first emerged in Turkey in March 2020, spreading rapidly and peaking in April and May. This study aimed to assess individuals with loss of taste and smell who were admitted to our hospital with a COVID-19 diagnosis.
Methods: Between March and June 2020, we retrospectively assessed 6966 patients who visited Kartal Dr. Lütfi Krdar City Hospital's Infectious Diseases and Clinical Microbiology COVID-19 outpatient clinics; 137 patients with loss of taste and smell were included in the study. We enrolled 18-year-old patients who were admitted to the infection emergency outpatient clinics.
Results: Out of the 6966 patients hospitalized with a pre-diagnosis of COVID-19 infection, 137 (0.19%) complained of poor taste and smell. Among these, 69 (50.4%) were female, and 68 (49.6%) were male. Of the 137 patients, 100 (73%) reported a loss of smell, while 94 (68.6%) reported a loss of taste. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR (reverse transcriptase-polymerase chain reaction) was positive in approximately one-third (n=2672, 38.4%) of the 6966 patients and roughly half (n=62, 48.4%) of the patients with loss of taste and smell. The most common symptoms observed in patients with anosmia were fever (n=123, 91%), cough (n=102, 75%), shortness of breath (n=411, 30%), sore throat (n=12, 9%), malaise (n=12, 9%), myalgia (n=11, 8%), nausea/vomiting (n=6, 5%), diarrhea (n=4, 3%), loss of smell (n=2, 2%), and loss of taste (n=2, 2%). Comorbidities included hypertension (n=4, 3%), diabetes mellitus (n=4, 2%), chronic obstructive pulmonary disease (n=2, 2%), and coronary artery disease (n=1, 1%).
Conclusion: Patients admitted to our hospital during the initial wave of the pandemic experienced typical and prevalent symptoms such as fever, cough, shortness of breath, sore throat, and loss of taste and smell. Further large cohort studies are required to address the "tasteless" COVID-19 more fully.

Keywords: COVID-19, inability to smell, inability to taste

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Introduction

Late in 2019, the coronavirus disease (COVID-19) first emerged in Wuhan, China, and subsequently spread rapidly [1]. Recently, the World Health Organization (WHO) classified COVID-19 as a public health emergency of global concern. Coronaviruses (CoV) are responsible for 5-10% of all acute respiratory infections. The causative agent of the COVID-19 pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an enveloped, RNA-stranded beta coronavirus. The infection can present with various clinical manifestations, from asymptomatic cases to multi-organ dysfunction [2-4].

In addition to the common symptoms of COVID-19 disease, such as fever, dry cough, fatigue, shortness of breath, sore throat, headache, chest pain, diarrhea, nausea/vomiting, conjunctival congestion, and nasal congestion, individuals may also experience olfactory and taste dysfunction [4,5].

SARS-CoV-2 primarily infects the respiratory epithelium, similar to many other respiratory viruses. Both symptomatic and asymptomatic patients show higher viral loads in the nasal cavity than the pharynx, indicating that the nasal cavity is the primary point of infection.

The taste buds, located in various types of taste papillae on the tongue, palate, throat, and larynx, are innervated by the third cranial nerve. Olfactory chemoreceptor cells, which are bipolar nerve cells, reside in the olfactory mucosa, a unique area in the nasopharynx. SARS-CoV-2 affects the olfactory neuroepithelium through its binding to the respiratory epithelium. The virus enters the respiratory epithelium via airborne droplets, and there are also possibilities of transmission through the fecal-oral route and direct contact with bodily fluids [4,6].

The primary host cell receptor for SARS-CoV-2 is angiotensin-converting enzyme-2 (ACE-2), which is crucial in virus entry and infection. ACE-2 is expressed in the oral mucosa, and the tongue's epithelial cells contain high levels of this receptor [7-9]. This study aimed to assess patients with COVID-19 disease who presented with olfactory and gustatory impairment.

Materials and methods

A retrospective evaluation was conducted on 6966 individuals over the age of 18 who had been assessed with a pre-diagnosis of COVID-19 infection in the emergency outpatient clinic of our hospital. Among them, 137 individuals who reported a loss of taste and smell were included in the study. The inclusion criteria comprised patients above the age of 18 who were admitted to the infection emergency outpatient clinics. Data on age, gender, underlying illnesses, symptoms, and PCR positivity status of the study patients were retrospectively obtained from the hospital's automated system. The severity of COVID-19 was visually assessed for each of the five lung lobes on a scale from 0 to 5, based on the following definitions: 0 for no involvement, 1 for 5%, 2 for 5–25%, 3 for 26–49%, 4 for 50–75%, and 5 for >75% involvement [10]. Patients were contacted by phone to collect information about their general condition and symptoms. The study received approval from the Ministry of Health and the Ethics Committee at Kartal Dr Lütfi Kırdar City Hospital before its commencement (date: June 11, 2020, number: 2020/514/179/8).

Statistical analysis

Statistical analyses were conducted using IBM SPSS 18.0 (SPSS Inc., Chicago, USA). The significance level for this study was set at *P*-value <0.05. Descriptive statistical methods were employed to examine the research data, including counts, percentages, means, medians, and standard deviations.

Results

There were 137 patients, comprising 69 females (50.4%) and 68 males (49.6%). The mean age was 35.3 (ranging from 18 to 60) in females and 33.3 (ranging from 19 to 55) in males. There was no statistically significant difference in age between males and females (*P*=0.325). Taste complaints were reported by 100 patients (73%), while 94 (68.6%) experienced gustatory impairment and 53 (38.7%) had olfactory impairment (this percentage refers to the percentage of the whole sample and not just the women). SARS-CoV-2 RT-PCR was positive in 62 patients (48.4%). Other respiratory pathogens were not screened in these patients; hence, additional illnesses were not ruled out.

When the patients were contacted by phone and questioned about the duration of their loss of sense of smell and taste, it was found that the average period for smell loss was 18.5 days and for taste loss was 18.4 days.

The most common symptoms observed in patients with anosmia were fever (n=123, 91%), cough (n=102, 75%), shortness of breath (n=41, 30%), sore throat (n=12, 9%), malaise (n=12, 9%), myalgia (n=11, 8%), nausea/vomiting (n=6, 5%), diarrhea (n=4, 3%), loss of smell (n=2, 2%), and loss of taste (n=2, 2%). Among the comorbidities, hypertension was present in four patients (3%), diabetes mellitus in four patients (2%), chronic obstructive pulmonary disease in two patients (2%), and coronary artery disease in one patient (1%).

A radiologist thoroughly reviewed thorax computed tomography (CT) scans, and CT scores [10] were calculated. Common CT findings such as ground-glass areas, consolidations, the connection between ground-glass areas and consolidations, and vascular dilatation were identified. Atypical CT findings included septal thickening, air bronchogram, pleural effusion, inverted halo, fibrosis nodules, and mediastinal lymphadenopathy (LAP) findings [10]. Among the 5484 patients who underwent thoracic CT, 4113 (75.2%) showed radiological involvement. SARS-CoV-2 RT-PCR positivity resulted in 3315 (80.6%) positive tests and 798 (19.4%) negative tests. Laboratory values were as follows: white blood cell count: 7242 × 10^3/μL, lymphocyte count: 2158 × 10^3/μL, hemoglobin: 13.8 mg/dL, platelet count: 255,000 mg/dL, CRP (C-reactive protein): 10 mg/dL, creatinine: 0.9 mg/dL, AST (aspartate aminotransferase): 32 U/L, ALT (alanine aminotransferase): 39 U/L, and troponin I: 0.002 ng/mL (Table 1).

Table 1: Laboratory values of patients with anosmia symptom

Parameters	Mean (n=137)	Min-Max
White blood cell (10^3/μL)	7242	4500-7700
Lymphocyte (×10^3/μL)	2158	510-3500
Hb (mg/dL)	13.8	12.8-17.8
Platelets (mg/dL)	255,000	166,000-455,000
CRP (mg/dL)	10	3-8
AST (U/L)	32	11-159
ALT (U/L)	39	7-236
Creatinine (mg/dL)	0.9	0.03-6.2
Troponin I (ng/mL)	0.003	0.001-0.09

Discussion

Olfactory dysfunction has emerged as a new symptom of COVID-19, particularly with the spread of the European pandemic. Interestingly, this symptom was not frequently reported in most of the early studies conducted in China and still remains highly prevalent in COVID-19 patients in China, occurring only in 5% of all patients [10,11]. In March 2020, the American Society of Otolaryngology-Head and Neck Surgery stated that COVID-19-positive patients frequently describe symptoms of anosmia and dysgeusia and should be included in the screening criteria for COVID-19 [12].

According to Zayet et al. [13], patients with a positive SARS-CoV-2 RT-PCR test showed a 77% prevalence of anosmia, and 83% had both anosmia and taste disorder. Some patients who test negative for COVID-19 but experience anosmia and taste abnormalities might still have a COVID-19 infection, and this possibility should not be ruled out. Smell and taste abnormalities are increasingly common in COVID-19-positive patients. In various case series, the reported prevalence of olfactory dysfunction ranges from 5.14% to 98.33%, while the reported prevalence of taste dysfunction ranges from 5.61% to 92.65% [14].

Anosmia and ageusia were observed in 5.1% and 5.6% of the COVID-19-positive individuals included in the study, respectively [15]. In a case series focusing on the senses of taste and smell, dysfunction of at least one sense was observed in 19.38% of the cases, which is consistent with our findings [16]. However, Bénézit et al. [17] reported higher percentages, with 75% experiencing olfactory abnormalities and 92.65% reporting taste abnormalities.

The highly varying numbers can be attributed to several factors, such as the presence of taste and smell impairment, the evolving pathogenicity of different SARS-CoV-2 strains in the nasal cavity, and the diversity of strains across different countries. Smell and taste disturbances have emerged as important symptoms of COVID-19, affecting approximately 40% of outpatients. These symptoms serve as crucial markers of infection. During the early stages of the pandemic, our study did not extensively inquire about these symptoms, resulting in their underreporting. However, their prevalence increased as we proactively questioned patients [18,19].

In a retrospective investigation by Klopfenstein et al., it was found that 54 (47%) out of 114 confirmed COVID-19 patients experienced anosmia. The study also revealed that patients developed anosmia on average 4.4 days after the onset of SARS-CoV-2 infection, which typically lasted for 8.96 days, with 98% of patients recovering within 28 days [6].

In our research, COVID-19 PCR was positive in 62 (48.4%) out of 137 patients with anosmia. We contacted each patient individually to inquire about the duration of their smell and taste loss, which was reported to have an average duration of 18.5 days and 18.4 days, respectively. Additionally, several investigations have consistently shown that the incidence of smell problems in COVID-19-positive cases is higher in female patients than male patients [19-21]. In our study, out of the 137 anosmia patients, 69 (50.4%) were female, and 68 (49.6%) were male. There was no significant difference in age between men and women.

Conclusion

During the initial wave of the pandemic, patients admitted to our hospital exhibited typical and commonly prevalent symptoms, including fever, cough, shortness of breath, sore throat, and loss of taste and smell. However, further investigation using large cohort studies is necessary to comprehensively understand the phenomenon of “tasteless” COVID-19.

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The etiological, demographic, and seasonal characteristics of patients with dizziness and vertigo

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Ethics Committee Approval
The study was approved by the Kastamonu University Clinical Research Ethical Committee (Decision no: 2020-KAEK-143-115, Date: October 6, 2021).
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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No conflict of interest was declared by the authors.

Financial Disclosure
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Abstract

Background/Aim: Vestibular disorders are common and can negatively affect quality of life and result in workforce losses; they can also be life-threatening diseases. As a result, studies of their etiology and treatment approaches are of particular importance. The aim of this study was to analyze the etiological, demographic, and seasonal characteristics of patients presenting to the Kastamonu Training and Research Hospital Ear, Nose, and Throat (ENT) clinic in Kastamonu, Turkey complaining of vertigo/dizziness.
Methods: In this retrospective cohort study, the files of 1033 patients who presented at the clinic with a report of vertigo/dizziness between September 2020 and September 2021 were examined. The patients' demographic characteristics, presentation dates, and diagnoses were recorded.
Results: Six hundred and fifty-one patients (63%) were female, and the mean age of the patient cohort was 50.3 years (standard deviation: 16.0 years). Six hundred and twenty-seven patients (60.7%) were identified with chronic subjective dizziness, 302 (29.2%) were identified with benign paroxysmal positional vertigo, 18 (1.7%) were identified with vestibular migraine, 7 (0.7%) were identified with bilateral vestibulopathy, 41 (4.0%) were identified with unilateral vestibulopathy, 16 (1.5%) were identified with vestibular neuritis, 6 (0.6%) were identified with Meniere's disease, 10 (1.0%) were identified with central vertigo/dizziness, 3 (0.3%) were identified with labyrinthitis and 3 (0.3%) were identified with another form of vertigo/dizziness. An increase in the number of cases was observed in the spring, and the number of patients presenting with vertigo/dizziness decreased thereafter and reached a minimum in the fall (P<0.001).
Conclusion: The most common vestibular disorder was chronic subjective dizziness. Vestibular disorders are more common in women and in the spring season. Although ENT specialists generally focus on pathologies of the ear, vertigo/dizziness are symptoms that may involve several etiologies. Meticulous clinical examinations should be performed; the etiological cause and clinical diagnosis in these cases will dictate additional tests to be requested and therapeutic strategies. Due to the broad diagnostic spectrum of these cases, a multidisciplinary approach is also critical.

Keywords: subjective dizziness, benign paroxysmal positional vertigo, seasonal characteristics, quality of life

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Introduction

Vestibular symptoms, including vertigo and dizziness, affect 20–30% of the population and are a common cause of presentations to health institutions [1,2]. Several central and peripheral factors, cardiovascular causes, or psychiatric, hematological, and endocrinological disorders may be involved in the etiology of vestibular symptoms, and multidisciplinary approaches may occasionally be required because of the complicated etiology [3].

Obtaining a detailed patient history and conducting a physical examination are critical aspects when evaluating patients complaining of vertigo/dizziness. Vestibular tests represent another important component of diagnostic evaluation. Laboratory tests and imaging methods may also be required for diagnosis [1]. The detection of central pathologies in particular is critically important in terms of morbidity and mortality. Computed tomography (CT) or magnetic resonance imaging (MRI) should be employed when a central cause is suspected or in persistent cases [4].

Because vestibular disorders are common, can be potentially life-threatening, and can result in workforce losses and adverse effects on quality of life, studies of their etiology and treatment approaches are of particular importance. The aim of this study was to analyze the etiological, demographic, and seasonal characteristics of patients presenting to the Kastamonu Training and Research Hospital Ear, Nose, and Throat (ENT) clinic in Kastamonu, Turkey with vertigo/dizziness and to discuss our results in the light of the current literature.

Materials and methods

Approval was granted by the Kastamonu University Clinical Research Ethics Committee before the study commenced (Decision no: 2020-KAEK-143-115, Date: October 6, 2021). In this retrospective cohort study, the files of 1033 patients with vertigo/dizziness who visited the clinic between September 2020 and September 2021 were examined. The patients' demographic characteristics, presentation dates, and diagnoses were recorded. Patients under the age of 18 and individuals who could not be diagnosed because their tests were not completed were excluded from the study.

The patients were divided into subgroups who suffered from chronic subjective dizziness, benign paroxysmal positional vertigo (BPPV), vestibular migraines, bilateral vestibulopathy, unilateral vestibulopathy, vestibular neuritis, Meniere's disease, central vertigo, labyrinthitis and other forms of vertigo/dizziness according to the diagnoses they received based on their examination and vestibular test results.

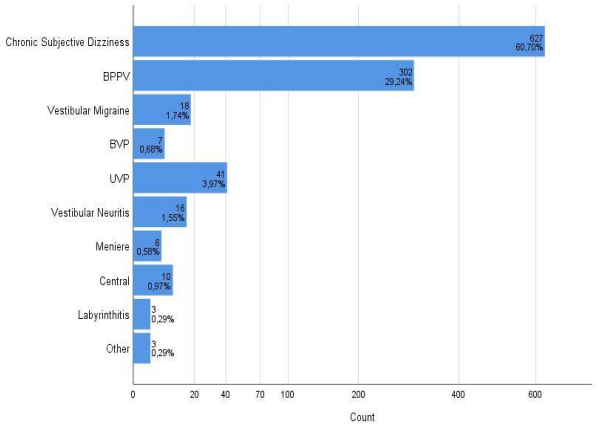
Statistical analysis

The data are described as frequencies (percentages) for categorical data and means (standard deviations) for numerical variables. The equality of the seasonal distribution of vertigo/dizziness and BPPV types were assessed using a chi-squared goodness of fit test. Categories with case numbers less than 1.5% were collapsed into a single category and were labeled as "other" when comparing the sex and age distributions; a comparison of the distributions between the groups for these two variables were made using a chi-squared test and the Kruskal-Wallis test, respectively. A Bonferroni correction was implemented to control the type I error rate for the pairwise comparisons. Two-sided p-values less than 0.05 were considered to be statistically significant. All of the statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, Version 21.0, Armonk, NY: IBM Corp.).

Results

A total of 1033 patients with vertigo/dizziness were included in the study; 651 (63%) were female. The mean age of the patients was 50.3 years (standard deviation: 16.0 years). Six hundred and twenty-seven patients (60.7%) were identified with chronic subjective dizziness, 302 (29.2%) were identified with BPPV, 18 (1.7%) were identified with vestibular migraine, 7 (0.7%) were identified with bilateral vestibulopathy (BVP), 41 (4.0%) were identified with unilateral vestibulopathy (UVP), 16 (1.5%) were identified with vestibular neuritis, 6 (0.6%) were identified with Meniere's disease, 10 (1.0%) were identified with central vertigo/dizziness, 3 (0.3%) were identified with labyrinthitis, and 3 (0.3%) were identified with other forms of vertigo/dizziness (Figure 1).

Figure 1: Distribution of diagnoses

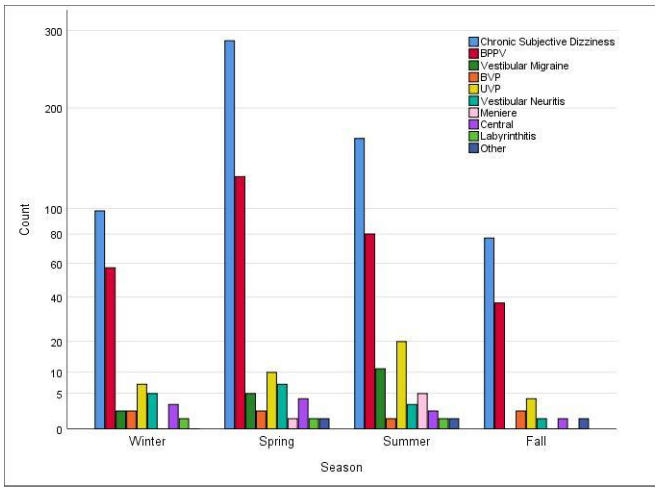


The age distribution of the patients revealed a statistically significant difference between the groups; the median age for the BPPV group was 56 years (range: 18–86 years) was significantly higher than that of patients with chronic subjective dizziness (48 years; range: 18–88 years) and patients with vestibular migraines (42 years; range: 24–64 years) (P<0.001). The percentage of females also differed between the groups (P<0.001); the vestibular migraine was composed of a higher percentage of females (17; 94.4%) than the BPPV group (175; 57.9%), the vestibular neuritis group (6; 37.5%), and the other vertigo/dizziness group (12; 41.4%).

An increase in the number of cases was observed in the spring; the caseload gradually declined over the following two seasons and attained a minimum in the fall (P<0.001). Cases of chronic subjective dizziness also exhibited an increase in the spring and dropped in the fall (P<0.001). The number of BPPV cases peaked in the spring and was followed by a decline in summer and a minimum in the fall (P<0.001). Vestibular migraine cases displayed a linear increase from the winter to the summer, and no cases were observed in the fall (P=0.030). The number of UVP cases displayed a gradual increase from the winter to the summer and then a sudden drop in the fall (P=0.003). There were no statistically significant differences in the distribution of case numbers over time among the remaining groups, most likely due

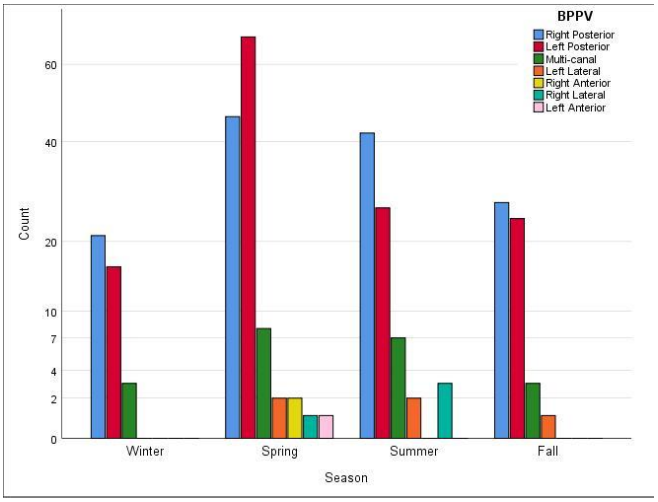
to their small sample sizes. The number of patients diagnosed as a function of season is shown in Figure 2.

Figure 2: The number of patients diagnosed as a function of season



One hundred and thirty-six BPPV cases (44.9%) were identified as right posterior, 134 (44.2%) were identified as left posterior, 21 (6.9%) were identified as multi-canal, 5 (1.7%) were identified as left lateral, 2 (0.7%), were identified as right anterior, 4 (1.3%) were identified as right lateral, and 1 (0.3%) was identified as left anterior. The number of cases with right posterior canal BPPV was the lowest in winter and the highest in spring; there was a gradual drop in both the summer and fall (P=0.006). The seasonal distribution of left posterior canal BPPV cases was similar (P<0.001). There were no statistically significant trends observed for the remaining BPPV cases, most likely because of the low case numbers. The numbers of patients with each type of BPPV as a function of season are shown in Figure 3.

Figure 3: Number of BPPV cases as a function of season



Discussion

Specialists of ENT conditions generally focus on inner ear pathologies in cases of vertigo/dizziness. However, neurological, cardiological, and psychiatric pathologies must also be kept in mind during the diagnostic process [5]. Vertigo/dizziness is observed across n all age groups. However, it is most common between the ages of 40 and 50, and women constitute 60–70% of patients [6]. The mean age of the patients in our study was 50.3 years and, in agreement with the literature, 63% were women.

Chronic subjective dizziness is a common vestibular disorder. It is defined as a persistent feeling of dizziness with subjective instability and chronic hypersensitivity to movement in the absence of any physical neurological disease, medical condition, or medication use capable of causing dizziness [7]. Anxiety is a potent predisposing factor. One study reported a chronic subjective dizziness rate of 10.6% in a population of Lausanne, Switzerland [8]. However, the incidence of chronic subjective dizziness has increased in line with increases in the stress of daily life, particularly in recent years [9]. Furthermore, it is twice as common in women compared with men [8]. In the present study, 60.7% of patients presenting to our clinic with vertigo/dizziness were evaluated as having subjective dizziness; this group encompassed the largest number of cases.

The most frequent cause of peripheral vertigo is BPPV, followed by unilateral/bilateral vestibulopathy, vestibular neuronitis, and Meniere's disease. Labyrinthitis and acoustic neurinoma are other, less common, etiological factors [1]. Benign paroxysmal positional vertigo was detected in 29.2% of cases in our study; consistent with the literature, we found that BPPV was the most frequent cause of peripheral vertigo. History and physical examinations occupy important roles in the diagnosis of BPPV. Detecting BPPV is therefore important in terms of preventing unnecessary tests, minimizing costs to patients, and determining appropriate treatments [10].

Vestibular neuronitis was detected in 16 cases (1.5%) in our study. Due to the acute and severe symptoms of vestibular neuritis, patients generally present to the emergency service rather than to an ENT clinic. This situation can lead to diagnostic difficulties and the incidence of vestibular neuronitis being underestimated. Similarly, although vestibular migraines are frequently observed in the general population, patients cannot always be identified due to diagnostic difficulties [1]. Vestibular migraines were detected at a rate of 1.7% in our study and, in agreement with the literature, they were more common in women.

Other studies have investigated the seasonal distributions of vestibular disorders. Whitman et al. [11] reported a higher incidence of BPPV in Boston, Massachusetts in the early months of spring (March, April, and May). Similarly, Pereira et al. [12] reported that vertigo in Brazil was more common at the end of winter and in the spring. Cao et al. [13] reported that more cases of BPPV were observed in months characterized by low temperatures, low levels of rainfall, and high atmospheric pressure. Consistent with our findings, those authors also noted that the number of cases of BPPV was highest in the spring. A decrease then occurred in the summer, and the smallest numbers of cases were observed in the fall. Lower exposure to sunlight and low vitamin D levels in cold weather and more sedentary lifestyles during that time of the year might all contribute to the seasonality of BPPV cases [14,15]. Increased upper airway infections and allergies in winter and spring are also believed to be associated with the observed frequency of BPPV [16].

The retrospective nature of our study is its primary limitation because the treatment responses and follow-up results of the patients were not considered. Future prospective studies will be important for complementing our results.

Conclusion

We found that the most common vestibular disorder was chronic subjective dizziness. Vestibular disorders were more common in women and in the spring. Although ENT specialists

generally focus on pathologies of the ear, vertigo/dizziness are symptoms that may involve several etiologies. Meticulous clinical examinations should be performed given that etiological cause and clinical diagnoses dictate future tests and therapeutic strategies. Due to the broad diagnostic spectrum of these cases, a multidisciplinary approach is also critical.

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Research article

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Kite excision in complicated pilonidal sinuses: A retrospective cohort study of a tissue-sparing technique

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Ethics Committee Approval
The study was approved by the Haydarpaşa Numune Training and Research Hospital Education Planning Commission (EPC) (August 25, 2023 - 223052508). Written consent was obtained from the patients to use images of their likenesses.
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: Pilonidal sinus (PS) is a benign chronic condition that primarily affects young people and can have a significant impact on their social life and work. Treatment options range from minimally invasive methods to surgical interventions involving wide excision. This study evaluates the outcomes of Kite excision, which aims to preserve healthy tissues, in cases of complicated PS extending along the natal cleft line.

Methods: This retrospective cohort study included cases of complicated PS extending along the intergluteal sulcus. Patients with minimally extended PS, sinus openings extending laterally, or patients in whom the defect area was closed using other methods (e.g., rotation flap or Limberg flap) were excluded. Patient data were obtained from medical records and the hospital information system: patient age, gender, body mass index (BMI), length of hospital stay, duration of drainage, follow-up period, presence of flap necrosis or flap edema, wound dehiscence, and presence of seroma, hematoma, or surgical-site infections.

Results: A total of 41 patients were included in the study; five (12%) were female. Twenty-three patients (56%) had recurrent PS; 18 patients (44%) underwent surgery for the first time. The mean age of the cohort was 28.5 years (standard deviation: 5.1 years). The mean BMI of the group was 30.2 kg/m^2 (standard deviation: 2.9 kg/m^2), and the mean hospital stay was 1.3 days (standard deviation: 0.6 days). Wound dehiscence was observed in two patients (4.9%), and hematoma beneath the flap was observed in one patient (2.4%). Seroma was detected in one patient (2.4%). A surgical-site infection was identified in two patients (4.9%). The overall postoperative complication rate was 14.6%, and recurrence was observed in one patient (2.4%).

Conclusion: Kite excision performed along the natal cleft line in cases of complicated PS is a safe, effective, and minimally invasive procedure that preserves healthy tissues. It is a recommended surgical treatment option in cases of complicated PS with vertical extension, and it will reduce the incidence of recurrence and increase patient comfort.

Keywords: pilonidal sinus, complication, natal cleft, recurrence, surgery

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Introduction

Pilonidal sinus (PS) is a condition that primarily affects young adults and is characterized by intergluteal discharge. Pilonidal sinus can significantly impact people's social lives and overall comfort; severe cases may require individuals to take time off from work. Minimally invasive methods have been used to treatment the disease [1,2]. However, the prevalence of PS, its recurrence rate, and changes in skin quality in the intergluteal region due to procedures can pose challenges. Undesirable outcomes such as skin deformities, scar tissue expansion due to tissue tension, and further thinning of the skin can occur after PS surgeries in the intergluteal region [3]. The positive effects of minimizing tissue tension during PS surgery are frequently emphasized in the literature [3-5]. In cases of recurrent PS and in patients with widespread disease in the intergluteal area, it is crucial to plan surgical interventions that minimize tissue tension. High tissue tension can lead to the development of complications in the surgical area. Flap techniques, which involve closing the tissue defect that occurs after excision without tension, are used to treatment PS. Flap techniques vary depending on the surgeon's experience and the extent of the disease [4].

Kite incision has proven efficacy in complicated cases in the intergluteal region [6,7]. In this study, the results of surgery using the Kite incision technique in recurrent and complicated PS cases extending along the intergluteal line were evaluated.

Materials and methods

We considered cases of recurrent and widespread PS in the intergluteal region that were treated between March 2018 and December 2022. Care was taken to include all cases of vertically extending recurrence or complicated PS in which the Kite incision method was used. The study protocol was approved by the Haydarpaşa Numune Training and Research Hospital Education Planning Commission (EPC) (August 25, 2023 - 223052508). Written consent was obtained from the patients to use their likenesses. The age, gender, body mass index (BMI), length of hospital stay, duration of drain removal, follow-up period, incidence of flap necrosis or flap edema, wound dehiscence, and the presence of seroma, hematoma, or surgical-site infections were evaluated. Two patients received general anesthesia due to previous lumbar disc herniation surgery; another patients received spinal anesthesia. All patients received a prophylactic dose of 1 gram of cefazolin sodium prior to surgery. Methylene blue was injected into the sinus tracts of all patients to make the sinus tracts more visible. Kite excision was planned and performed (Figures 1, 2). The Kite incision model, developed by the author based on many years of PS surgery experience, has become a routine surgical practice in cases of complicated or recurrent PS with vertical extension [6,7]. When the procedure involves descending below the coccyx, the electrocautery power is reduced to minimize thermal damage. Care is also taken to leave a full-thickness layer of tissue under the flap, with the muscle fibers of the gluteus maximus visible. The lower lateral part of the flap is also released and mobilized to reduce tissue tension and create a well-vascularized flap (Figures 3, 4). In all of the patients in this study, 2/0 polyglactin and 2/0 polypropylene sutures were used to close the defect (Figure 5). The surgical specimen resembles the shape of a kite (Figure 6).

Figure 1: Recurrent PS and Kite excision line drawing along the natal cleft line.

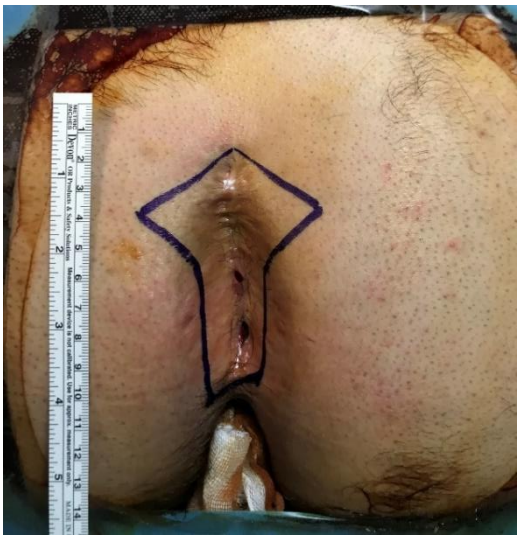


Figure 2: Appearance of retracted specimen after Kite excision in a case of recurrent PS with good traction.

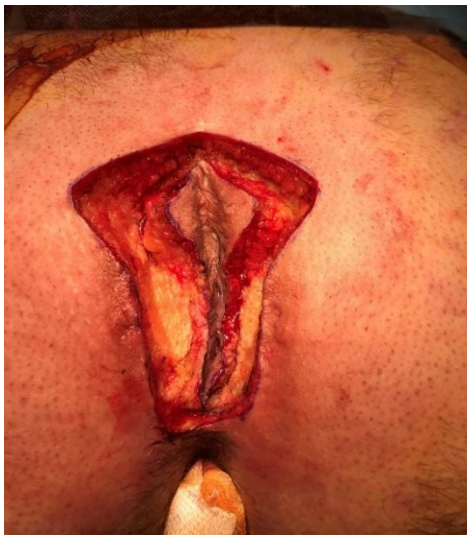


Figure 3: Defect area formed after excision.

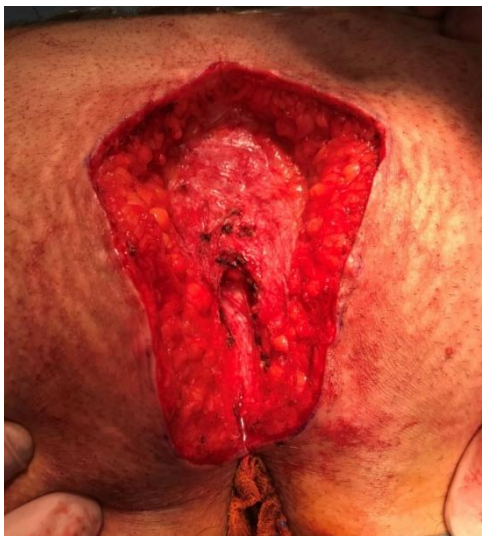


Figure 4: The flap in which the inferolateral of the pedicle is released by separating over the gluteus maximus muscle to close the defect area.

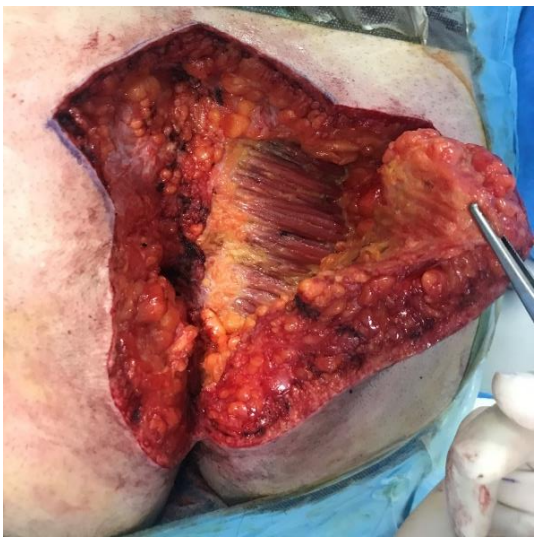


Figure 5: Covering the defect area with 2/0 polypropylene.

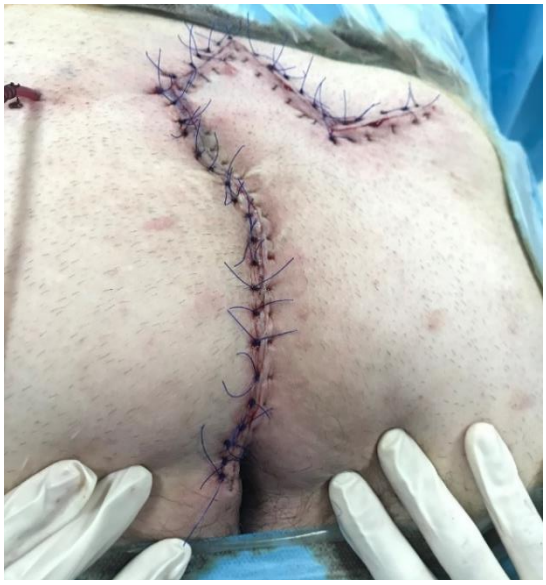
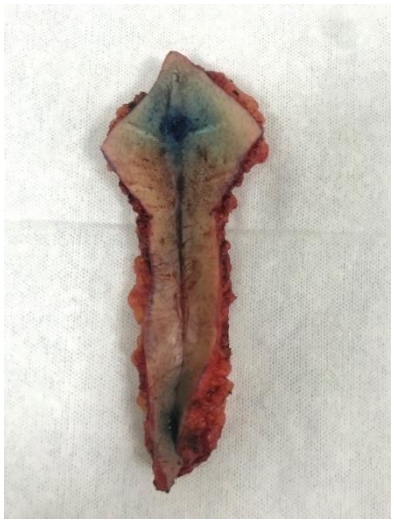


Figure 6: View of the surgical specimen. The view of a recurrent case of methylene blue extending from the superior sinus mouth to the inferior sinus mouth.



Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS; version 22; IBM SPSS, Istanbul, Turkey) for the statistical analyses. We adopted descriptive statistics, including means and standard deviations for numerical variables and numbers and percentage values for categorical variables. The Pearson correlation coefficient was used to test relations between numerical variables.

Results

Twenty-three (56%) of the patients had recurrent PS, and 18 (44%) were undergoing surgery for the first time. Five patients (12.2%) were female and 36 (87.8%) were male. The data of the patients are presented in table 1. No flap necrosis or flap edema was observed in any of the patients. Wound dehiscence was observed in two patients (4.9%); hematoma was observed under the flap in one patient (2.4%). Seroma was detected in one patient (2.4%). Surgical-site infections occurred in two patients (4.9%). The overall postoperative complication rate was 14.6%. One patient had a combination of wound dehiscence, hematoma, and a surgical-site infection. This patient presented on the 8th postoperative day with complaints of bleeding and swelling at the surgical site, without any history of trauma. Antibiotic therapy was administered to treat the infection. One patient (2.4%) experienced recurrence five months after surgery (Figure 7). Excision was performed on this patient, and the defect area was closed (Figure 8).

Table 1: Patients' demographics results

	Mean (Standard deviation)
Age	30.2 (2.9) year
BMI	30.2 (2.9) kg/m^2
Hospital stay	1.3 (0.6) day
Follow-up	23.7 (9.2) month
Duration of drain removal	2.7 (0.7) day

BMI: body mass index

Figure 7: Recurrence in the patient who had excision of the Kite.

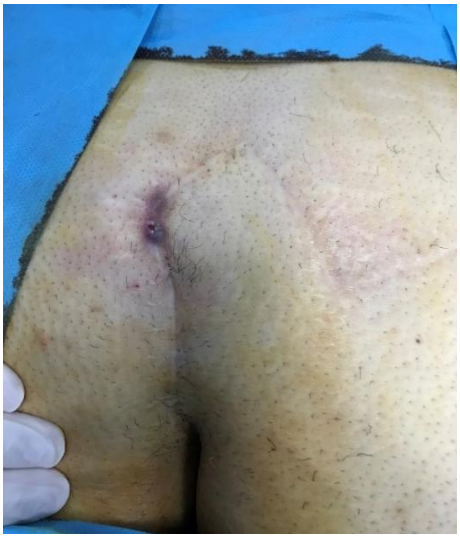
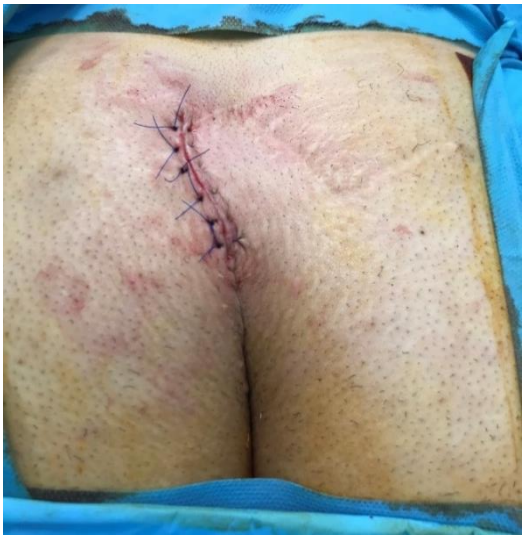


Figure 8: Postoperative view of recurrence. Primary repair after excision.



Discussion

While PS surgery is considered to be relatively straightforward, it requires care and good planning in cases of recurrence and when a large area is affected. Excessive removal of healthy tissues may cause difficulties in closing the defect in cases requiring wide excision. Attention to tissues is even more important in wide excisions. The flap method used with the patients in this study aims to preserve healthy tissues to the maximum extent possible.

Complicated PS is frequently seen in the natal cleft line. Furthermore, the remaining natal cleft after PS surgery can result in PS recurrence [8,9]. In cases where the natal cleft is deep and the disease extends towards the anus, there may be concerns about damaging the anal sphincters. However, the complete excision of the sinus tracts identified with methylene blue will reduce the risk of recurrence and the possibility of repeated surgical interventions [6,7]. Such complete excision is particularly important in cases of complicated PS disease. After an excision, the defect area in the sacral region, where tension is high, is often enlarged while the excision material appears contracted [6]. We suggest determining the size of the flap to be taken from the gluteal region—where the flap will be used to close the defect—in order to minimize volume loss. Closing the defect with a flap method reduces tissue tension, which allows patients to move more comfortably during the healing period [10,11]. The flap should be selected to close the defect smoothly, without tension, and with a well-vascularized pedicle. Such a choice, together with Kite incision, yields a tension-free closure in the subcutaneous tissue with 2/0 polyglactin sutures. n this study, the good blood supply of the flap emphasizes that the flap pedicles provide good vascularization. Furthermore, we believe that surgical-site infections were the causes of the two cases of wound dehiscence. However, wound dehiscence due to thermal damage caused by electrocautery has also be observed in cases in which the skin is not completely incised with a scalpel and the skin incision is made with electrocautery [12].

In the Kite excision, tension-free repair is achieved by removing less tissue than one would take away in cases that extend along the vertical axis. It is emphasized in the literature that flap repairs provide better results than primary repairs [13,14]. It is believed that fixing the base of the flap to the posterior fascial tissue of the sacrum increases postoperative pain. In this study, the base of the flap was not fixed to the postsacral fascia, which has been linked to increased patient comfort.

Excision of the midline and lateral displacement of the suture line can be effectively achieved with Kite excision. The displacement of the midline is important in the surgical treatment of PS and also one of the primary goals in the surgical treatment models of Baskom and Karydakis [8,9]. The total complication rate in our study was 14.6%, which is lower than the rate reported in the literature [15-17].

Limitations

There are limitations to this study. It is retrospective, the sample size was relatively small, and we did not make a direct comparison with a similar technique.

Conclusion

Treatment of PS can be challenging when a case is complicated. However, safe and effective treatment is more likely be achieved in centers where complicated cases are frequently treated. The Kite incision model, developed as a result of experience, is the right option for many patients.

Natal cleft excision with the Kite excision method and closure of the resulting defect with a safe and easy flap method is a procedure with low complication rates. This method allows for better cosmetic results with minimal tissue excision in complicated PS cases that extend vertically. The Kite incision model can contribute to effective treatment and patient satisfaction with only one surgical procedure in complicated PS cases. The success of PS surgery is possible with low wound tension and effective excision of the sinus tracts. The Kite incision model stands out as a superior treatment model that yields wide excision and low wound tension.

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Research article

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The effect of quercetin, a flavonoid, on lung injury caused by sepsis

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Ethics Committee Approval
This study was carried out at Adıyaman University Experimental Animals Application and Production Center with the permission of Adıyaman University Animal Experiments Local Ethics Committee (ADYÜ-HADYEK) (2019/045).
The present study followed international, national, and/or institutional guidelines for humane animal treatment and complied with relevant legislation from the Animal Ethics Committee.

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

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Abstract

Background/Aim: Lung injury is frequently observed in cases with sepsis, which can lead to conditions that progress to acute respiratory distress syndrome (ARDS) causing mortality. There is no specific treatment for sepsis or sepsis-induced lung injury. Antioxidant therapy has been one of the most prominent options for treatment, according to pathophysiological studies. The aim of this study was to investigate the effects of quercetin, a powerful antioxidant, on sepsis and sepsis-related lung injury.
Methods: Thirty-two adult male Sprague Dawley rats were divided into five groups. The control group (CNRL) received 1.5 ml saline via the intragastric route. The quercetin group (QUER [n=5]) underwent no sepsis procedure and received 20 mg/kg quercetin via the intragastric route starting 15 days before the procedure. The sham group (SHAM [n=6]) underwent a surgical incision and received 1.5 ml intragastric olive oil (quercetin dissolves in oil). The sepsis group (SEPS [n=7]) underwent the sepsis procedure. The sepsis and quercetin group (SEPS+QUER [n=7]) underwent the sepsis procedure and received 20 mg/kg quercetin via the intragastric route for 15 days before the procedure. Cecal ligation and puncture methods were used to induce sepsis. While ALT, AST, LDH, GGT and CRP values were analyzed from rat blood, MDA and GSH levels were analyzed from lung tissue.
Results: The results showed that quercetin reduced neutrophil infiltration (TLIS 3.5 [0.26] in the SEPS group vs TLIS 2.75 [0.29] in the SEPS+QUER group [*P*=0.01]), intra-alveolar macrophage count (SEPS vs SEPS+QUER [*P*=0.01]) and cell proliferation (SEPS vs SEPS+QUER [*P*=0.01]), and that it helped to preserve lung anatomy during sepsis. It was observed that MDA levels in the lung tissue decreased with the treatment of quercetin to septic rats (SEPS vs SEPS+QUER [*P*=0.046]).
Conclusion: These findings suggest that quercetin may be a potential treatment option for sepsis. However, more studies are needed to determine whether quercetin is a viable option as a therapeutic strategy in patients.

Keywords: sepsis, quercetin, acute respiratory distress syndrome, lung

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Introduction

Sepsis is a life-threatening response to infection, which typically starts in an organ and results in a dysregulated host response [1]. Sepsis can manifest as hypoxemia, inflammatory changes, tissue damage, or hypotension [2]. Acute lung injury (ALI) is a critical condition involving rapid-onset respiratory failure associated with intra- and extra-pulmonary causes. ALI is characterized by non-cardiogenic edema, severe systemic hypoxia, alveolar hemorrhage, pulmonary infiltration, and alveolar membrane changes. It particularly develops due to sepsis, shock, aspiration, and blood transfusion. The mortality rate for ALI is 18.0-54.7% [3].

The addition of lipopolysaccharides (LPS) stimulates the rat airways and causes the release of proinflammatory cytokines, which can result in apoptosis in epithelial and endothelial cells. This produces damage to the alveolar-capillary barrier, which causes an increase in permeability. This sequence of events instigates the migration of polymorphonuclear (PMN) cells to the lung. Tissue damage occurs through oxidative stress because activated PMN cells respond to infectious pathogens. Oxidative substances include superoxide anion, toxic metabolites, such as H_2O_2, hydroxyl radicals, and hypochlorous acid. Antioxidative enzymes work to protect the lung against the onslaught of oxidative damage [3,4]. Humans consume anti-inflammatory and antioxidant compounds such as flavonoids, which are naturally occurring and exhibit a wide range of biological effects through diet. Quercetin is a flavonoid widely found in nature, and it produces a wide anti-inflammatory, anti-proliferative, and antioxidant effect. Recent evidence suggests that quercetin can protect the lung against oxidative damage in different models of pulmonary injury [5,6]. The aim of this study was to investigate the efficacy of quercetin in sepsis-related lung injury and its protective and therapeutic effects on lung damage in sepsis.

Materials and methods

This study was carried out at Adıyaman University Experimental Animals Application and Production Center with the permission of Adıyaman University Animal Experiments Local Ethics Committee (Adyü-Hadyek) (2019/045). Thirty-two adult male Sprague Dawley rats weighing 280-300 grams were used. The sample size was identical to those in similar studies [4]. The animals were randomly divided into groups. The control group (CNRL) received 1.5 ml saline via the intragastric route. The quercetin group (QUER [n=5]) underwent no sepsis procedure and received 20 mg/kg quercetin via the intragastric route starting 15 days before the procedure. The sham group (SHAM [n=6]) underwent a surgical incision and received 1.5 ml intragastric olive oil (quercetin dissolves in oil). The sepsis group (SEPS [n=7]) underwent the sepsis procedure. The sepsis and quercetin group (SEPS+QUER [n=7]) underwent the sepsis procedure and received 20 mg/kg quercetin via the intragastric route for 15 days before the procedure. Cecal ligation and puncture methods were used to induce sepsis.

The rats in each group were kept in separate cages and housed at 22 ± 2°C with ad libitum access to food and water in a 12-hour light-dark cycle. Anesthesia was induced with the intramuscular administration of xylazine hydrochloride (20 mg/kg Rompun; Bayer Türk İlaç Ltd. Şti., Turkey) and ketamine hydrochloride (70 mg/kg Ketalar; Eczacıbaşı, Istanbul, Turkey) under veterinary supervision.

Euthanasia

The rats were euthanized 24 hours after the sepsis procedure. Prior to euthanasia, the rats were anesthetized using intraperitoneally xylazine hydrochloride at a dose of 20 mg/kg and ketamine hydrochloride at a dose of 70 mg/kg. Transcardiac perfusion using 0.9% sodium chloride was performed for the euthanasia. Intracardiac blood samples were taken after the induction of deep anesthesia for the biochemical analysis. The lung was rapidly removed following the euthanasia.

Administer of quercetin

20 mg/kg of quercetin was administered with olive oil and oral gavage (for 15 days) [7].

Sepsis model with cecal ligation

This model was described by Wichterman et al. [8] in 1980. Following induction of general anesthesia, the rat was placed in a supine position and fixed on the operating table. The skin was prepared and disinfected, and the cecum was exposed using a 2-cm abdominal incision from the front of the genital protrusion to the cranial region. The ileocecal valve was ligated distally and punctured twice with an 18 G needle from the anti-mesenteric edge. All layers were then sutured. The animals received subcutaneous fluid replacement.

Anesthesia

On the 16th day of the study, all rats scheduled for surgery were anesthetized by an intraperitoneal administration using 20 mg/kg xylazine hydrochloride (20 mg/kg Rompun; Bayer Türk İlaç Ltd. Şti., Turkey) and 70 mg/kg ketamine hydrochloride (70 mg/kg Ketalar; Eczacıbaşı, Istanbul, Turkey) under aseptic conditions.

Research parameters

Oxidant-antioxidant analysis was carried out on lung tissue samples. Blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP), and gamma-glutamyl transferase (GGT) levels were measured.

Tissue homogenates

Lung tissues were washed with 0.9% NaCl at 4°C. They were then cut into small sections according to cold chain principles and placed into Eppendorf pipettes. The tissues were homogenized with cold 1.15% KCl for MDA analysis [9].

Malondialdehyde analysis

Tissue MDA concentration is a lipid peroxidation marker. Tissue MDA was analyzed using the thiobarbituric acid reaction (TBARS) method [10-12]. After the homogenates were homogenized in 10% trichloroacetic acid, they were centrifuged. After the superficial liquid part was mixed with 0.67% thio-butyric acid in equal volumes, it was incubated in boiling water at 90°C for 15 minutes followed by cooling and centrifugation. Tissue MDA levels were measured for absorbance at 532 nm and expressed in units of nmol/g tissue.

Glutathione analysis

GSH analysis was performed according to Ellman's analysis [13]. The glutathione in the tube reacted with 5.5'-dithiobis 2-nitrobenzoic acid, producing a yellow-greenish color.

The light intensity of this color was read in the spectrophotometer at a wavelength of 410 nm. Reduced glutathione was measured.

Histopathological preparation

Lung tissues were fixed in 10% formaldehyde, embedded in paraffin, and subjected to histopathological examination. Sections 5 µm in thickness were taken from the blocks, stained with hematoxylin and eosin, and evaluated under an Olympus BX53 microscope.

The items descriptive for acute lung injury, namely interstitial edema, alveolar wall thickness, congestion, neutrophil infiltration, hemorrhage, intra-alveolar debris, and intra-alveolar macrophage and cell proliferation, were scored semi-quantitatively. Each finding was scored 0=none, 1=0-25%, 2=25-50%, 3=50-75%, or 4=75-100%. In addition, the total lung injury score (TLIS) was calculated as the average of the scores for each group divided by the number of rats in it.

Statistical analysis

The one-sample Kolmogorov-Smirnov test was used to determine whether the data were distributed normally. Statistical comparisons were performed using one-way ANOVA or the Kruskal Wallis H test. The groups found to be significant in these tests were compared using the pairwise Mann Whitney U test or Tukey's multiple range test. Results were reported as mean, standard deviation (SD) or median (min-max). A p value less than 0.05 was considered significant. All analyses were performed using IBM SPSS Statistics 15.0 for Windows (New York; USA).

Results

One member of the quercetin group (QUER) died during the study period and was excluded from the experimental protocol.

Histopathological findings

The alveolar structure was normal in the CNRL group. Mild neutrophil infiltration, mild interstitial edema, congestion, hemorrhage, and intra-alveolar macrophages were observed in only one rat. The total lung injury score (TLIS) was 3. Very mild interstitial edema was observed in the QUER group, while the other structures were normal. No neutrophil infiltration was observed in any members of that group. The TLIS was 1.8. Slightly more interstitial edema, congestion, hemorrhage, and intra-alveolar macrophages were observed in the SHAM group compared to the CNRL and QUER groups. No neutrophil infiltration was observed. The TLIS was 5.8.

Very intense neutrophil infiltration and a significant increase in all other findings were observed in the sepsis group. The TLIS was 23.16 in the sepsis group. Decreases were determined in all findings in the SEPS+QUER group compared to the SEPS group. The TLIS was 18.5 in the SEPS+QUER group. TLIS was lower in the SEPS+QUER group than in the SEPS group. A detailed analysis of total lung scores between the SEPS and SEPS+QUER groups with the relevant p values is given in Table 1. Images reflecting the histopathological features of the groups are shown in Figure 1.

Table 1: The detailed scoring and p-values between the SEPS and SEPS+QUER groups total lung damage score

	SEPS (n=7) Mean (SD)	SEPS+QUER (n=7) Mean (SD)	*P*-value
Interstitial edema	3.33 (0.39)	2.75 (0.66)	0.19
Alveolar wall thickness	3.0 (0.43)	2.37 (0.42)	0.22
Congestion	3.16 (0.31)	2.62 (0.34)	0.24
Neutrophil infiltration	3.5 (0.26)	2.75 (0.29)	0.01
Hemorrhage	3.0 (0.27)	2.87 (0.34)	0.35
Intraalveolar debris	2.3 (0.24)	1.75 (0.25)	0.36
Intraalveolar macrophages	2.3 (0.19)	1.62 (0.17)	0.01
Cell proliferation	2.5 (0.21)	1.75 (0.18)	0.01

SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Lung oxidative stress and anti-oxidative response

Lipid peroxidation in lung homogenates was evaluated in terms of MDA levels. These increased significantly in the septic rats (CNRL vs SEPS [*P*=0.012]). Tissue MDA levels decreased significantly with the addition of quercetin to the sepsis group (SEPS vs. SEPS+QUER [*P*=0.046]).

Antioxidant activity was determined by levels of GSH in the lung tissues. GSH levels were significantly lower in the lung homogenates from septic mice (CNRL vs. SEPS [*P*=0.001]). Although the GSH levels in lung homogenates increased in the SEPS+QUER group, this was not statistically significant (SEPS compared to SEPS+QUER [*P*=0.35]).

Comparisons between the groups' tissue MDA and GSH levels are shown in Tables 2 and 3 and Figure 2.

Figure 1: Histopathological images from the study groups a- CNRL: An 40xH&E image of normal alveolar structures with mild edema. b- QUER: A 40xH&E image showing mild interstitial edema, and no neutrophils. c- SHAM: A 40xH&E image showing interstitial edema and intra-alveolar macrophages. d- SEPS: A 40xH&E image showing intense edema, neutrophilic infiltration, and intra-alveolar macrophages. e- SEPS: A 100xH&E image showing diffuse neutrophils in alveolar walls and erythrocytes in alveolar spaces. f- SEPS+QUER: A 40xH&E image showing diffuse neutrophils and edema in alveolar walls, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

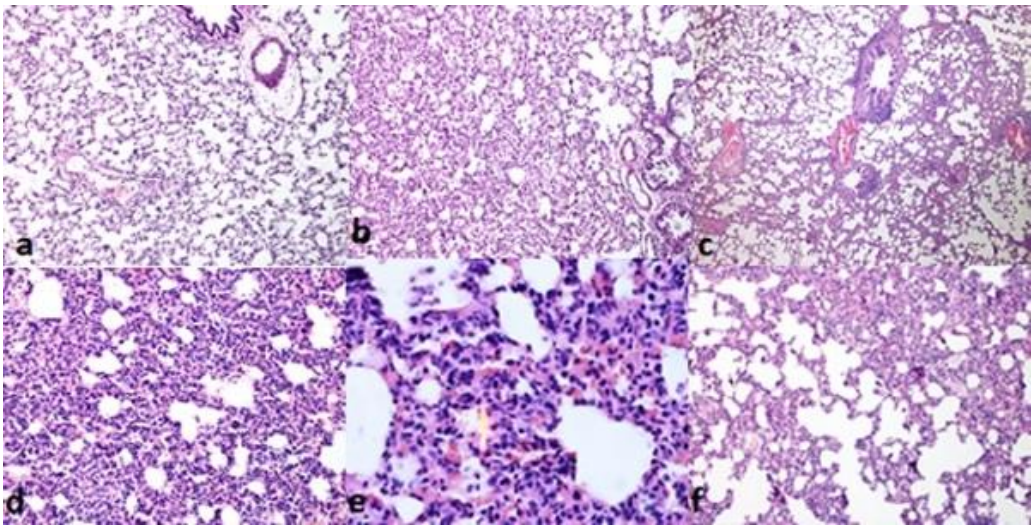
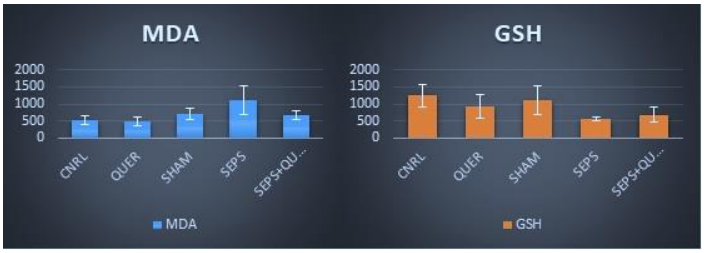


Figure 2: Tissue MDA and GSH levels in the study groups



MDA: malondialdehyde, GSH: Glutathione, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

ALT, AST, GGT, LDH, and CRP values

ALT values differed significantly between the control group and all groups except the SHAM and QUER groups. There was no significant difference between the SEPS, SEPS+QUER, CNRL, and QUER groups regarding AST values, but a significant difference was found between the other groups. The increase in LDH values in the SHAM, SEPS and SEPS+QUER groups was statistically different compared to all the other groups. No difference was observed between the SHAM, SEPS, and SEPS+QUER groups' LDH values. No difference between groups was determined in GGT or CRP values. Blood biochemistry values, intergroup comparisons, and p values are given in Tables 3 and 4.

Table 2: Comparison of MDA and GSH values between groups

	CNRL /SHAM	CNRL/SEPS	CNRL/SEPS+QUER	CNRL/QUER	SHAM/SEPS	SHAM/SEPS+QUER	SHAM/QUER	SEPS/SEPS+QUER	SEPS/QUER	SEPS+QUER/QUER
MDA	0.942	0.012	0.377	0.473	0.016	0.735	0.046	0.046	0.013	0.238
GSH	0.557	0.001	0.004	0.152	0.011	0.011	0.457	0.219	0.033	0.172

MDA: malondialdehyde, GSH: Glutathione, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Table 3: Comparison of ALT, AST, LDH, GGT, CRP, MDH and GSH values between groups

	Group (n)	Mean (SD)	*P*-value*
ALT (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	41 (15) 44 (13) 42 (11) 149 (97) 86 (21)	0.001
AST (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	121 (19) 107 (21) 170 (27) 740 (299) 672 (196)	0.001
LDH (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	713 (100) 768 (197) 1525 (495) 2243 (424) 1963 (1203)	0.001
GGT (U/L)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	8 (4) 6 (1) 6 (1) 8 (5) 5 (1)	0.38
CRP (mg/dL)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	0.15 (0.07) 0.13 (0.03) 0.13 (0.03) 0.15 (0.06) 0.18 (0.07)	0.45
MDA (nmol/g)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	524 (103) 716 (173) 1110 (420) 670 (121) 500 (121)	0.002
GSH (nmol/g)	CNRL (6) QUER (5) SHAM (6) SEPS (7) SEPS+QUER (7)	1244 (324) 1112 (423) 571 (50) 690 (217) 928 (345)	0.003

* One Way Anova, ALT: alanine amino transferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, GGT: gamma-glutamyl transferase, CRP: c-reactive protein, MDA: malondialdehyde, GSH: Glutathione, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Table 4: Comparison of ALT, AST and LDH between groups and *P*

	CNRT/QUER	CNTR/SHAM	CNTR/SEPS	CNRT/SEPS+QUER	QUER/SEPS	QUER/ SEPS+QUER	SHAM/QUER	SHAM/SEPS	SHAM/SEPS+QUER	SEPS/SEPS+QUER
ALT	1.00	0.818	0.001	0.001	0.003	0.005	0.931	0.001	0.002	0.097
AST	0.107	0.015	0.001	0.001	0.003	0.003	0.004	0.001	0.001	1.000
LDH	0.792	0.002	0.001	0.001	0.005	0.003	0.004	0.366	0.022	0.053

ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate Dehydrogenase, CNRL: control group, QUER: quercetin group, SHAM: sham group, SEPS: sepsis group, SEPS+QUER: sepsis and quercetin group

Discussion

ALI is a sepsis-related pathological process [14]. Sepsis is one of the causes of apoptosis in the lung epithelium. Quercetin is a powerful anti-inflammatory and antioxidant [5,15]. The results of this study show that quercetin reduces the negative effects of sepsis on the lungs by lowering inflammation and oxidative stress.

ALI can occur directly as a result of lung pathologies or indirectly as a result of extrapulmonary pathologies. Sepsis, a common cause of ALI, is the leading in-hospital cause of mortality, resulting in some five million deaths per year. Sepsis increases vascular permeability and damages heart function and metabolic balance, thus leading to multiple organ failure and mortality [16,17].

LPS found in gram-negative bacteria occupies a significant place in the pathogenesis of sepsis [18-20]. Based on the current evidence, it appears that the development of sepsis is related to oxidative stress and reactive oxygen species (ROS). ROS causes cellular damage and is involved in the pathogenesis of sepsis [4]. Studies have shown that flavonoids can protect experimental animals against LPS-induced tissue damage or septic shock. Research has also shown that quercetin reduces TNF alpha and IL-1 levels and improves inflammatory responses. Studies have further reported that quercetin inhibits IL-8 production, TNF-α, and macrophages. Blockades of mitogen activated protein kinase and activation of nuclear factor-kappa B have been reported to not only protect mice from tissue damage, but also to reduce the production of proinflammatory cytokines. In addition, quercetin can inhibit nitric oxide (NO) formation, which is stimulated by activation of macrophages and microglia [16].

A previous study of the distribution of quercetin showed that it accumulates mostly in lung tissue. One study reported that quercetin blocks microglia activation and also protects neurons from inflammatory damage [21]. Yılmaz et al. [22] described that quercetin was effective against lung damage caused by aspiration. Sang et al. [23] showed that quercetin alleviated sepsis-induced ALI by suppressing oxidative-mediated ER stress by activation of SIRT1/AMPK pathways in rats with sepsis induced by the CLP method. Wang et al. [24] reported that lung injury in LPS-induced sepsis was alleviated by quercetin. Quercetin not only prevents sepsis-related lung injury but also reduces pulmonary fibrosis caused by silica dust [25], reduces oxidative damage caused by paraquat, a widely used herbicide [26], and has been shown to have the potential for use as a therapeutic agent in the treatment of *Pseudomonas aeruginosa*-induced inflammation by regulating IL-1β production in macrophages infected with the bacterium [27].

In the present study, quercetin suppressed inflammation in rats with sepsis and reduced the damage caused by ALI. Histological examination showed that quercetin reduced neutrophil infiltration, intra-alveolar macrophage numbers, and cell proliferation in rats with sepsis. Quercetin significantly reduced MDA levels in lung tissue and also lowered lipid peroxidation. However, it did not exhibit a comparable effect on GSH levels. However, an increase of GSH level, which indicates an anti-oxidative effect was observed in the present study, but there was no statistical difference. We believe that it may be depend on the quercetin dosage.

The functions of different organ systems are compromised when the severity of infection exceeds the body's ability to cope with it. Sepsis can lead to dysfunction in many organs and even death. The lungs are usually the first organ to be affected, while the organs most commonly affected by sepsis are the lungs, liver, and kidneys. There is a close relationship between the number of dysfunctional organs and mortality. Studies generally suggest that sepsis increases the levels of the enzymes described in this study [28,29]. The present study investigated the amount of quercetin, an antioxidant capable of reversing lung damage in sepsis. However, we also examined AST, ALT, and LDH values as indicators of liver damage, a common finding in sepsis. These three values were significantly higher in septic rats compared to the control group. Decreases were also observed in ALT, AST, and LDH values in rats with sepsis receiving supplementary quercetin, although these were not statistically significant.

Limitations

One possible limitation of our study might be the use of a lower dose of quercetin as compared to previous trials in the literature, which have employed much higher doses.

Conclusion

No antioxidant therapy, including quercetin use, has been approved for treating ALI caused by sepsis. However, the result of this study shows that a powerful antioxidant such as quercetin may have a place in the treatment of ALI. Therefore, further studies on quercetin use in patients with ALI are needed.

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The prevalence and impact of sarcopenia in myeloproliferative neoplasms

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

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

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Abstract

Background/Aim: Rapid identification of patients with myeloproliferative neoplasms (MPNs) is crucial for clinical decision-making and healthcare management. Sarcopenia is characterized by muscle loss and increases the risks for adverse outcomes; there is limited information in the literature regarding possible links between sarcopenia and MPNs. This study evaluated the frequency of sarcopenia in patients with MPNs and investigated whether biochemical or clinical features were associated with the development of sarcopenia.

Methods: Fifty-six BCR-ABL1-negative patients were included in this randomized prospective cohort research study. Muscle strength was measured using a handgrip dynamometer. Muscle mass was evaluated using a bioelectrical-impedance analyzer, and physical performance was evaluated via gait speed in a 6-minute walking test.

Results: The mean handgrip strength of the cohort was 27.7 kg, and 13 patients (23.2%) tested positive for low muscle strength. Mean muscle mass was found to be 7.58 (1.17) kg/m^2, and seven patients (12.5%) exhibited low muscle mass. Three patients (5.4%) had low muscle quality. Nine patients (16.1%) were diagnosed with probable sarcopenia, and four patients (7.1%) were diagnosed with severe sarcopenia. There was no difference between the groups in terms of clinical features (P>0.05), nutritional assessment (macro and micronutrients) (P=0.959), comorbidities (P=0.476), or laboratory measurements (P>0.05).

Conclusion: There was a high prevalence of sarcopenia among patients with MPNs, which indicates that periodic measurements of muscle strength, body composition and physical performance may contribute to the management of MPNs.

Keywords: sarcopenia, prevalence, myeloproliferative neoplasms, muscle strength, muscle mass

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Introduction

The term "myeloproliferative neoplasms" (MPNs) refers to a class of clonal malignancies formed from hematological stem cells that are distinguished by clonal proliferation of myeloid, erythroid, and megakaryocytic lineages in bone marrow [1]. There are various MPN subtypes that have been classified by the World Health Organization (WHO); the most important include primary myelofibrosis (PMF), secondary myelofibrosis (SMF), essential thrombocythemia (ET), and polycythemia vera (PV) [2]. Myeloproliferative neoplasms are considered diseases of older age and share a common pathophysiology with clonal hematopoiesis and chronic systemic inflammation. They have been linked to a four-fold greater risk of vascular events, a higher incidence of non-MPN solid cancers, and a shorter lifespan [3].

Muscle loss is a symptom of the disorder known as sarcopenia, which frequently develops as people age [4]. In addition to an elevated risk of unfavorable outcomes such as declines in both function and appearance, poor quality of life, socioeconomic burden, and death, sarcopenia is characterized by a generalized and progressive loss of muscle strength and function [5]. While primary sarcopenia is a common occurrence of aging, secondary sarcopenia may be associated with chronic diseases, inflammation, physical inactivity, malnutrition, and cancers. These factors have also been reported to be common in MPNs [6]. However, there is a dearth of information in the literature pertaining to the frequency of sarcopenia and risk factors in patients with MPNs.

This study focused on identifying the incidence of sarcopenia in individuals with MPNs and determining whether biochemical or clinical characteristics were linked to its development.

Materials and methods

The investigation was conducted at Kartal Lutfi Kirdar City Hospital in Istanbul, Turkey between January 2022 and March 2022. It was designed as a randomized prospective cohort research study. We included 56 individuals with BCR-ABL1-negative MPNs according to the WHO classification [2].

Patient selection and study design

We included patients aged 18 years and older. The study excluded participants with a history of pregnancy, rheumatological conditions, severe kidney illness, and other types of cancers besides MPNs. Patients with acute diseases, such as acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), and patients who had received an allogeneic stem cell transplant were also excluded from the study. The ethics committee of the Dr. Lütfi Kırdar State Hospital approved the study. The subjects furthermore provided verbal and written consent to participate in the study.

Diagnoses

A diagnosis of PV was made according to four criteria [7]: (1) a hemoglobin value above 16.5 g/dL in men or 16.0 g/dL in women or a hematocrit value above 49% in men or 48% in women or an expanded red cell mass; (2) hypercellularity in a bone marrow biopsy examination with pan-lineage growth with erythroid, granulocytic, and megakaryocytic proliferation; (3) the existence of JAK2 mutations (V617F or exon 12); and (4) a low serum erythropoietin (EPO) level. A diagnosis was made of when criteria (1), (2), and (3) were satisfied or when criteria (1), (2), and (4) were satisfied.

A diagnosis of ET was made according to five criteria [2]: (1) a platelet count above 450 x 109/L, (2) a bone marrow biopsy demonstrating proliferation largely of the megakaryocyte lineage with elevated numbers of enlarged hyper lobulated mature megakaryocytes, (3) a non-detection of other myeloid neoplasms or MPNs according to WHO criteria, (4) the presence of JAK2 or CALR or MPL mutations, and (5) the absence of evidence for reactive thrombocytosis. A diagnosis is made when criteria (1), (2), (3), and (4) were satisfied or when criteria (1), (2), (3), and (5) were satisfied. Primary and secondary myelofibrosis were also diagnosed according to the 2016 WHO criteria [2].

Data collection

Clinical and demographic characteristics were obtained from the patients' files. To evaluate the nutritional status of the patients, a mini-nutritional assessment (MNA) was performed. A total MNA score less than 8, between 8 and 11, and above 11 defined malnutrition, a risk of malnutrition, and the absence of malnutrition, respectively [8]. Sarcopenia was assessed in all cases. In 2018, the revised European consensus recommended three primary characteristics for the diagnosis of sarcopenia: low muscular strength, weak muscle quantity or quality, and subpar physical performance [4]. A digital hand grip dynamometer (Takei TKK 5401 model, Takei Scientific Instruments Co. Ltd, Tokyo, Japan) was used to quantitatively measure muscle strength. Values below 16 kg for females and 27 kg for males were considered to correspond to low muscle strength. We assessed physical performance using the typical gait speed for a 6-minute walk; a gait speed below 0.8 m/s was considered to indicate low muscle function. Appendicular skeletal muscle mass (ASMM) was estimated using a bioelectrical impedance analyzer (Tanita Body Composition Analyzer TBF-300 model, Tanita Co., Tokyo, Japan) using the Sergi equation, which was modified by the patient's body surface area to yield the ASMM index [4]. Low muscle mass was defined as an ASMM index below 5.5 kg/m^2 for women and below 7.5 kg/m^2 for men. Only when low muscle strength was found was sarcopenia considered likely. When reduced muscle strength, weak muscle quantity/quality, and subpar physical performance were observed, sarcopenia was deemed to be severe. The same doctor performed each measurement and evaluation, and strict guidelines were followed to guarantee the accuracy of the results.

Biochemical evaluation

After the patients fasted for 24 hours, blood was taken from the antecubital vein. Complete blood counts, including white blood count (WBC), platelet count, mean corpuscular volume (MCV), hemoglobin, and hematocrit, were analyzed using a Mindray BC-6800 autoanalyzer (Mindray Electronics Co. Ltd., Shenzhen, China). Creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total protein, albumin, and C-reactive protein (CRP) were studied using photometric methods with an Abbott Architect c8000 analyzer (Abbott Laboratories, Abbott Park, IL, USA). A chemiluminescent enzyme immunoassay was conducted using a UniCelDxI 800 (Beckman Coulter Inc., Brea,

CA, USA) to examine vitamin B12 and vitamin D levels. Real-time polymerase chain reaction and mutation studies of JAK2, CALR, JAK2 EXON12, and MPL were carried out at genetic laboratories. All of the blood samples were evaluated within an hour of being collected.

Statistical analysis

SPSS Statistics for Windows (version 26.0; IBM Corp., Armonk, NY, USA) was used to conduct the analyses. The Kolmogorov-Smirnov test was used to verify the normality of the data. Normally distributed data are presented as means and standard deviations; continuous variables are presented as medians (and minimum-maximum ranges). Categorical variables are presented as frequencies (%). We used the chi-square test to assess categorical variables. Depending on the number of groups, an independent samples t-test or one-way analysis of variance (ANOVA) were used to evaluate the normally distributed variables. Depending on the number of groups, non-normally distributed variables were evaluated using the Mann-Whitney U test or the Kruskal-Wallis test. The statistical significance threshold was set at 0.05.

Results

Table 1 lists the demographic information and clinical features of the patients. Thirty-three patients (58.9%) were male, and the mean age of the cohort was 54.0 years (standard deviation: 15.4 years). The average body mass index (BMI) of the patients was 26.9 kg/m^2 (standard deviation: 4.6 kg/m^2). Twenty-eight patients (50.0%) were diagnosed with ET, 18 patients (32.1%) were diagnosed with PV, 8 patients (14.3%) were diagnosed with primary MF, and 2 patients (3.6%) were diagnosed secondary (postpolycythemia) myelofibrosis. We noted JAK2 mutations in 26 patients (46.4%), and we noted CALR mutations in 3 patients (8.1%). Twenty patients (35.7%) were treated with acetylsalicylic acid, 29 patients (51.8%) were treated with acetylsalicylic acid+hydroxyurea, three patients (5.4%) were treated with hydroxyurea+anagrelide, and four patients (7.2%) were treated with ruxolinitib. The median MNA score was 14. Forty-nine participants walked for physical activity, and 11 patients (19.6%) were smokers. The most common comorbidities of the participants included diabetes (26.8%) and hypertension (33.9%).

The mean skeletal muscle index of the patients was 16.8 kg/m^2 (standard deviation: 3.1 kg/m^2). There was 16 participants (28.6%) in the low skeletal muscle index group. The mean handgrip strength of the cohort was 27.7 kg, and 13 patients (23.2%) exhibited low muscle strength. Muscle mass was calculated as ASMM/height^2 and the mean value was found to be 7.58 (1.17) kg/m^2. Seven patients (12.5%) exhibited low muscle mass. Muscle function was evaluated using a 6-minute walking time, and the mean value was found to be 447.1 seconds (standard deviation: 93.0 seconds). Three patients (5.4%) were assessed as having low muscle function. As a result, nine patients (16.1%) were diagnosed with probable sarcopenia, and four patients (7.1%) were diagnosed with severe sarcopenia. Table 2 lists the data related to the sarcopenia diagnoses.

Based on a diagnosis of sarcopenia, the study population was divided into groups (Table 1). Age (*P*=0.109), age at MPN diagnosis (*P*=0.080), BMI (*P*=0.396), cytogenetic

Table 1: Demographical and clinical characteristics of participants

Variables	Total	Probable-Confirmed Sarcopenia (n=13)	Non-Sarcopenia (n=43)	*P*-value
Age, years	54.0 (15.4)	61 (25-81)	53 (25-77)	0.109
Age of MPNs diagnosis, years	50.4 (15.3) (22-80)	59 (22-80)	49 (24-74)	0.080
Sex				
Male (n,%)	33 (58.9)	8 (61.5)	25 (58.1)	0.827
Female (n,%)	23 (41.1)	5 (38.5)	18 (41.9)	
BMI, kg/m^2	26.9 (4.6) (19.5-43)	26.6 (20.5-43)	26.9(19.5-40.6)	0.396
JAK2				
Negative, (n,%)	30 (53.6)	8 (61.5)	22 (51.2)	0.511
Positive, (n,%)	26 (46.4)	5 (38.5)	21 (48.8)	
CALR				
Negative, (n,%)	34 (91.9)	3 (75)	31 (93.9)	0.298
Positive, (n,%)	3 (8.1)	1 (25)	2 (6.1)	
Diagnosis				
Polycythemia vera (n,%)	18 (32.1)	8 (61.5)	10 (23.3)	0.071
E.Thrombocythemia (n,%)	28 (50.0)	4 (30.8)	24 (55.8)	
Primary MF, (n,%)	8 (14.3)	0 (0.0)	8 (18.6)	
Secondary MF, (n,%)	2 (3.6)	1 (7.7)	1 (2.3)	
Treatment				
Acetylsalicylic acid, (n,%)	20 (35.7)	3 (23.1)	17 (39.5)	0.491
Acetylsalicylic acid+ Hydroxyurea (n,%)	29 (51.8)	10 (76.9)	19 (44.2)	
Hydroxyurea + Anagrelide (n,%)	3 (5.4)	0 (0.0)	3 (7.0)	
Ruxolinitib (n,%)	4 (7.2)	0 (0.0)	4 (9.3)	
Mini-nutritional assessment				
10, (n,%)	1 (1.8)	0 (0.0)	1 (2.3)	0.959
11, (n,%)	1 (1.8)	0 (0.0)	1 (2.3)	
12, (n,%)	4 (7.1)	1 (7.7)	3 (7.0)	
13, (n,%)	7 (7.1)	2 (15.4)	5 (11.6)	
14, (n,%)	43 (76.8)	10 (76.9)	33 (76.7)	
Physical Activity				
Low physical activity / home-office, (n,%)	1 (1.8)	1 (7.7)	0 (0.0)	0.095
Walking, (n,%)	49 (87.5)	12 (92.3)	37 (86.0)	
Doing sport, (n,%)	6 (10.7)	0 (0.0)	6 (14.0)	
Smoking, (n,%)	11 (19.6)	1 (7.7)	10 (23.3)	0.426
Thrombosis/Emboli (n,%)	5 (8.9)	0 (0.0)	5 (11.6)	0.580
Co-morbidities				
Ischemic heart failure, n (%)	11 (19.6)	2 (15.4)	9 (20.9)	0.476
Hypertension, n (%)	19 (33.9)	6 (46.2)	13 (30.2)	
Diabetes mellitus, n (%)	15 (26.8)	5 (38.5)	10 (23.3)	
PAH, n (%)	3 (5.4)	0 (0.0)	3 (7.0)	
Hypothyroidism, n (%)	8 (14.3)	3 (23.1)	5 (11.6)	
HM, n (%)	13 (23.2)	3 (23.1)	10 (23.3)	

MPNs: Myeloproliferative neoplasms, BMI: Body mass index, MF: Myelofibrosis, E. Thrombocythemia: Essential Thrombocythemia, PAH: Pulmonary arterial hypertension, HM: Hepatomegaly, JAK2: Janus kinase 2, CALR: Calreticulin. Data are given as mean (standard deviation) or median (minimum - maximum) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables

profile for *JAK2V617F (P*=0.511), cytogenetic profile for *CALR* (*P*=0.298), current medications (*P*=0.491), MNA score (*P*=0.959, smoking status (*P*=0.426), and the presence of comorbidities (*P*=0.476) did not significantly differ between the groups.

Table 2: Results of Sarcopenia Criteria based on revised European consensus of participants

	Values
Skeletal Muscle Index (kg/m^2)	16.8 (3.1)
Positive (n,%)	16 (28.6)
Negative (n,%)	40 (71.4)
Hand Grip strength, kg	27.7 (10.2)
Positive, (n,%)	13 (23,2)
Negative (n, %)	43 (76,8)
ASM	21.2 (4.7)
ASM/height^2	7.58 (1.17)
Positive, (n,%)	7 (12.5)
Negative, (n,%)	49 (87.5)
6-m walking time (s)	447.1 (93.0)
Positive, (n,%)	3 (5.4)
Negative, (n,%)	53 (94.6)
Diagnosis of sarcopenia	
Probable, (n,%)	9 (16.1)
Confirmed, (n,%)	4 (7.1)

ASM: Appendicular Skeletal Muscle Mass. Data are given as mean (standard deviation) or median (minimum - maximum) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables

Data pertaining to the biochemical analyses of the participants are listed in Table 3. The mean results of the biochemical tests were within the normal physiological reference value for age and sex. Biochemical results such as vitamin D (*P*=0.528), vitamin B12 (*P*=0.489), creatinine (*P*=0.278), AST (*P*=0.465), ALT (*P*=0.156), LDH (*P*=0.756), total protein (*P*=0.281), albumin (*P*=0.167), CRP (*P*=0.426), WBC (*P*=0.318), hemoglobin value (*P*=0.826), platelet count (*P*=0.313), hematocrit ratio (*P*=0.930), and MCV (*P*=0.793) were similar between the groups in terms of probable/confirmed sarcopenia.

Table 3: Biochemical analysis of participants according to sarcopenia diagnosis

	Total	Probable-Confirmed Sarcopenia (n=13)	Non-Sarcopenia (n=43)	*P*-value
Vitamin D (ng/mL)	20.9 (13.0)	14.95 (8.9-39.6)	20.1 (5.8-59.7)	0.528
Vitamin B12 (pg/mL)	327.1 (111.2)	362 (205-471)	338 (108-595)	0.489
Creatinine (mg/dL)	0.83 (0.26)	0.87 (0.53-2.14)	0.79 (0.45-1.14)	0.278
AST (U/L)	19.5 (6.4)	18 (13-31)	20 (10-54)	0.465
ALT (U/L)	19.8 (11.1)	14 (9-29)	19 (5-78)	0.156
LDH (U/L)	269.1 (133.5)	221 (131-447)	231 (134-722)	0.756
Total protein (g/dL)	7.03 (0.47)	6.8 (5.9-7.6)	7 (5.8-7.9)	0.281
Albumin (mg/dL)	4.62 (0.25)	4.6 (4.2-4.9)	4.7 (4.1-5.2)	0.167
CRP (mg/L)	1.34 (0.92)	1 (0.32-3.56)	1.26 (0.11-3.29)	0.426
WBC (x10^6/L)	9014.8 (3616.2)	7420 (4440-17330)	8420 (3300-21200)	0.318
HGB (g/dL)	13.7 (1.6)	13.9 (11.9-15.9)	13.5 (10.5-17.1)	0.826
HCT (%)	43.1 (5.4)	42.9 (35.9-51)	43.2 (31.4-58.7)	0.930
MCV (fL)	92.7 (13.4)	86 (77.8-118.4)	90.4 (64.9-126.9)	0.793
PLT(x10^9/L)	503.5 (270.6)	426 (208-786)	450 (123-1285)	0.313

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, WBC: White blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet. Data are given as mean (standard deviation) or median (minimum - maximum) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables

Discussion

The purpose of the study was to evaluate the incidence of sarcopenia in individuals with various MPN subtypes and to ascertain whether biochemical or clinical traits had an effect on the onset of the disease. The importance of identifying sarcopenia has been identified for treating aging patients and individuals with chronic illnesses [6]. In this study, sarcopenia was identified as being probable in 16.1% of patients with MPNs and severe in 7.1% of patients with MPNs. While 13 patients presented with low muscle strength, seven patients had weak muscle mass, and three patients exhibited weak muscle function. We found similar biochemical and clinical characteristics between the groups with and without sarcopenia.

Sarcopenia is a multifactorial disorder resulting from changes in endocrine function, suboptimal protein intake, activation of inflammatory response, reductions in physical activity, and reductions in the number of alpha motor units in the spinal cord [9]. The determinants leading to sarcopenia in cancer patients are primarily attributable to decreased food intake, side effects of medications, anorexia, and muscle disuse; previous reports have suggested complex interactions between glucose utilization, immune response, inflammation, energy metabolism, and body muscle mass in oncological patients [6,10]. Sarcopenia can also lead to an inability to tolerate optimal cancer managements, resulting in postoperative complications and high chemotherapy toxicity [11]. Furthermore, anticancer therapy seriously influences body composition by causing muscle wasting, cachexia, and loss of bone mass and adipose tissue [12]. Among the elderly, the prevalence of sarcopenia has been reported to be 10% [13]. In hospitalized patients the prevalence is 14.7%, in nursing home residents the prevalence is 59%, in community residents the prevalence ranges from 12.9–40.4%, and in cancer patients the prevalence is 38.6% [13]. The prevalence of sarcopenia was found to be 11.8% among elderly Turkish individuals living in rural areas; it was 21.6% in among Turkish individuals living in urban areas [14]. A meta-analysis of 1578 patients with different hematological malignancies revealed that 39.1% of patients with lower overall survival were sarcopenic [15]. Burkat et al. [16] studied 109 patients with aggressive B cell lymphoma and found that male patients with sarcopenia, unlike female patients, had decreased progression-free survival and overall survival. That finding suggests a role of cachexia in sex-specific prognostic use. The same authors also found that 65 of patients (60%) were identified as sarcopenic; there was furthermore a relationship between cachexia and low serum marker levels of in-glucose utilization (as insulin-like growth factor-binding protein 6), inflammation (as lymphotoxin-like inducible protein), and energy metabolism (as leptin).

A meta-analysis of 1752 patients with hematological malignancies who were in remission showed that sarcopenia was linked to a lower overall survival rate among individuals who had undergone hematopoietic stem cell transplant [17]. Kamiya et al. [18] reported that the prevalence of sarcopenia based on the low mass strength, weak muscle function, and decreased muscle mass was 36% in women and 24% in men among 56 elderly patients with hematological malignancies. In this study, we consistently demonstrated high sarcopenia frequencies: 16.1% of patients had probable sarcopenia, and 7.1% of patients had severe sarcopenia. This finding may be related with the fact that patients with MPNs often suffer from low appetite and weight loss from immunosuppressive drugs, inactivity due to fatigue, and tumor-related inflammation resulting in catabolism and high protein consumption. Our results support the hypothesis that sarcopenia contributes to clinical adverse outcomes of MPNs by reducing quality of life and limiting functionality. Periodic measurements of body composition, muscle strength and performance may contribute to the primary prevention and management of the disease in patients with MPNs.

Sarcopenia is a common disease worldwide, and it is especially prevalent in elderly populations [11,14]. It is also associated with sex, disease status and comorbidities, and the

type and duration of treatment (e.g., high-dose chemotherapy and steroids) [17]. Kurose et al. [19] showed that age, obesity, hypertension, the frequency of daily conversation, and malnutrition were independent predictors of sarcopenia. Wu et al. [20] showed that risk factors for sarcopenia included age, sex, smoking status, and BMI. However, we could not find a relationship between sarcopenia and clinical and biochemical features in patients diagnosed with MPN. This is likely due to the heterogeneity of MPN subtypes with small sample size. Variations in the clinical manifestations of MPNs and heterogeneity in drug use may have also contributed to the disparate results. To clarify the specific association between clinical variables and sarcopenia and to support our findings, additional large-scale prospective investigations that consider various patient clinical statuses and MPN subtypes are required.

Limitation

The study has a number of limitations. First off, it was conducted at a single institution with a cross-sectional design. The range of MPN subtypes considered was furthermore small, and only a limited number of patients were enrolled in the study. Finally, there was an absence of information about sarcopenia or changes in body composition prior to the development of MPNs.

Conclusion

We found that among individuals with MPNs there was a pronounced rate of sarcopenia. This finding suggests that sarcopenia may be important for clinical outcomes and management of MPNs. Our findings highlight the importance of patient-specific strategies in order to reduce symptoms, increase overall survival rates, and enhance quality of life.

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Research article

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Renal implications of off-pump coronary artery bypass grafting: A retrospective cohort study analyzing postoperative creatinine levels

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Ethics Committee Approval
The study was approved by Koç University Ethical Committee (2019. 353.IRB2.113). 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: Coronary artery disease is a significant health concern worldwide. While coronary artery bypass grafting is a gold standard of treatment, acute kidney injury (AKI) is a possible postoperative complication of concern. Off-pump coronary artery bypass grafting (OPCABG) aims to curtail perioperative complications; however, its impact on postoperative AKI is debated. This retrospective study aims to inform patient care by identifying potential effects of OPCABG on AKI utilizing postoperative creatinine alterations.

Methods: This retrospective study was conducted at Koç University Hospital in Istanbul, Turkey. We reviewed the records of patients who underwent OPCABG between June 2018 and June 2019. Patients with incomplete records or individuals who had undergone renal replacement therapy prior to surgery were excluded. The primary metric was serum creatinine levels, which were assessed preoperatively and up to 7 days postoperatively. Preoperative creatinine levels were compared with postoperative levels using the Wilcoxon signed-rank test. Acute kidney injury was defined using Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Results: Seventy-two patients satisfied the inclusionary criteria. A significant increase in creatinine was observed on postoperative Day 1 (P<0.001); creatinine levels fell below baseline by postoperative Day 4 and 5. We note that the incidence of AKI was low; there were no instances of Stage 2 or higher AKI during the observation period.

Conclusion: Our data suggest that OPCABG may result in a transient increase in creatinine post-surgery. Creatinine levels normalize over time, implicating the renal safety of OPCABG. Despite these promising findings, additional comprehensive studies are essential to validate these observations and assess long-term renal outcomes after OPCABG.

Keywords: coronary artery bypass, off-pump, coronary artery disease, kidney, creatinine

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Introduction

Coronary artery disease (CAD) remains a leading cause of morbidity and mortality worldwide [1]. Coronary artery bypass grafting (CABG) has been established as a gold standard for the treatment of multivessel CAD, and it has significantly improved outcomes in a significant number of patients. Coronary artery bypass grafting is traditionally performed using cardiopulmonary bypass (CPB). However, off-pump coronary artery bypass grafting (OPCABG), which avoids the use of CPB, has gained popularity in recent decades due to its ability to reduce perioperative complications [2,3].

Acute kidney injury (AKI) is a well-recognized and often devastating complication after cardiac surgery [4-6]. The pathogenesis of postoperative AKI is multifactorial, with factors such as systemic inflammation, oxidative stress, and hemodynamic instability playing pivotal roles [7,8]. Off-pump coronary artery bypass grafting, by potentially mitigating some of these factors, particularly the systemic inflammatory response associated with CPB, has been hypothesized to reduce the incidence or severity of AKI postoperatively [9,10].

However, the actual impact of OPCABG on postoperative AKI remains a topic of ongoing debate: while some studies have suggested a reduced risk of AKI with off-pump techniques, others have found no significant differences [9-13]. A better understanding of this relationship is crucial given that AKI is associated with prolonged hospitalization stays, increased healthcare costs, and elevated long-term morbidity and mortality rates [14-17].

This retrospective study aims to contribute to this discourse by analyzing creatinine levels before and after OPCABG surgery to determine the potential effects of this technique on postoperative AKI. By assessing the incidence and severity of AKI following OPCABG, we aim to provide clinicians with further insights into patient management and the potential renal implications of choosing an off-pump technique.

Materials and methods

Study design and patient selection

This retrospective study was conducted at Koç University Hospital in Istanbul, Turkey. After obtaining approval from the Koç University Committee on Human Research (Approval No: 2019. 353.IRB2.113 and approval date: 26.11.2019), we reviewed the medical records of patients who underwent OPCABG surgery between June 2018 and June 2019. Patients with incomplete records or who had undergone renal replacement therapy prior to the surgery were excluded. Demographic information, relevant comorbidities, medications, and perioperative variables were extracted from the patients' electronic health records. The primary data of interest included serum creatinine levels recorded preoperatively and on postoperative days up to Day 7.

Definition of AKI

Acute kidney injury was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [16]. According to the KDIGO guidelines, AKI is present when there is:

- An increase in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) within 48 hours or an increase in serum creatinine of 1.5–1.9-fold above baseline within the last 7 days (Stage 1)
- An increase in serum creatinine of 2.0–2.9-fold above baseline (Stage 2)
- An increase in serum creatinine at least 3.0-fold above baseline OR a value exceeding 4.0 mg/dL (353.6 µmol/L) (Stage 3)

Statistical analysis

Changes in serum creatinine levels between the preoperative and postoperative periods were analyzed using the Wilcoxon signed-rank test, which is a non-parametric test suitable for paired, non-normally distributed data. The normality of the data was assessed using the Kolmogorov-Smirnov test. A *P*-value less than 0.05 was considered to indicate statistical significance. All of the statistical analyses were performed using the Statistical Package for Social Sciences for Windows version 24.0 program (SPSS, Chicago, IL).

Results

Of the 98 patients who underwent OPCABG and had recorded preoperative creatinine levels, 26 exhibited creatinine levels above 1.1 mg/dL. That level surpassed our laboratory's threshold for normal creatinine. Those patients were subsequently excluded from further analysis, and the final study cohort therefore consisted of 72 patients.

Postoperative creatinine monitoring

As time progressed postoperatively, the number of patients with recorded creatinine levels decreased. On postoperative Day 1, creatinine levels were available for 64 patients. This number successively decreased to 58, 57, 48, 27, 12, and 10 patients for postoperative Days 2, 3, 4, 5, 6, and 7, respectively. This trend was due to patients either being discharged from the hospital or, unfortunately, mortality. Figure 1 shows the postoperative creatinine levels of the patients.

Incidence of acute kidney injury

Throughout the postoperative monitoring period, none of the patients developed AKI at Stage 2 or above. However, the incidence of Stage 1 AKI varied over the 7-day postoperative period. Specifically, the number of patients who developed Stage 1 AKI on postoperative Days 1–7 were 11, 8, 4, 5, 1, 1, and 1, respectively. Figure 2 shows the number of patients with and without AKI over the course of the study.

Figure 1: Postoperative creatinine levels

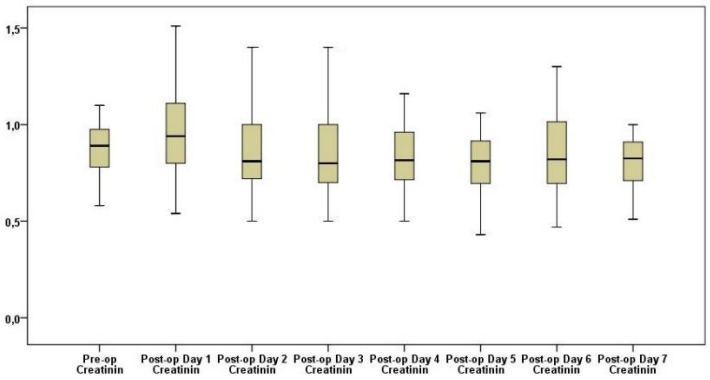
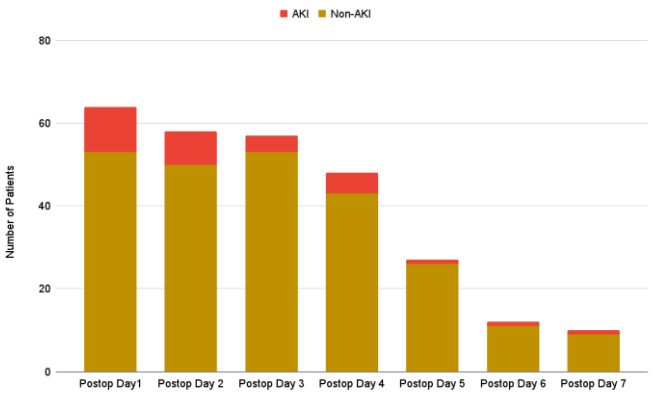


Figure 2: AKI trends of patients



Comparison of creatinine levels

The Wilcoxon signed-rank test was used to assess changes in postoperative creatinine levels from Day 1 to Day 7.

A substantial increase in creatinine levels on postoperative Day 1 was observed relative to baseline (Z value: -4.151; P<0.001). On the other hand, creatinine levels on postoperative Days 4 and 5 were statistically lower than baseline levels (P=0.042 and 0.029, respectively; Table 1). And while changes in creatinine levels on Days 2, 3, 6, and 7 were observed, those changes were not statistically significant.

Table 1: Test statistics.

	Z	*P*-value
Pre-op vs Post-op Day 1	-4.151	<0.001
Pre-op vs Post-op Day 2	-0.254	0.799
Pre-op vs Post-op Day 3	-1.271	0.204
Pre-op vs Post-op Day 4	-2.038	0.042
Pre-op vs Post-op Day 5	-2.187	0.029
Pre-op vs Post-op Day 6	-0.314	0.754
Pre-op vs Post-op Day 7	-0.663	0.507

P<0.05: statistically significant

Discussion

Coronary artery bypass grafting is as a critical intervention for managing CAD [1-3]. Off-pump coronary artery bypass grafting, which eschews CPB, holds promise for minimizing perioperative complications [9,10]. One of the most notable complications that arises post-cardiac surgery is AKI, which has profound implications on patient outcomes and healthcare costs [14-17]. Given the multi-faceted nature of the pathogenesis of AKI, OPCABG might be a potential mitigating solution given that it can possibly counteract certain instigating factors such as systemic inflammation [9,10]. However, the literature is replete with divergent findings on the impact of OPCABG on AKI [12,13].

This retrospective study investigated this complex relationship and explored creatinine levels as a surrogate for kidney function in the context of OPCABG. We specifically gauged whether OPCABG might exert a protective effect against AKI, potentially reflecting decreased renal insult compared with traditional CABG.

An integral finding was a discernible spike in creatinine levels on the first postoperative day. This observation hinted at either initial kidney stress or reduced glomerular filtration. This elevation, which was statistically significant, is consistent with previous research that found immediate postoperative renal alterations [14,15]. The etiology of this increase might encompass factors such as intraoperative hemodynamic changes, inflammation, or other transient insults. Interestingly, by postoperative Day 4 or 5, creatinine levels dipped below baseline. This finding possibly signifies renal recovery or adaptation, which is in accordance with a number of studies that claim AKI may be temporary and suggests that the initial damage may be transient and repairable [18,19].

While our study did record fluctuations in creatinine levels on postoperative Days 2, 3, 6, and 7, these changes did not attain statistical significance. This finding underscores the importance of not just noting clinical changes but also evaluating their statistical and therefore potential clinical significance.

Furthermore, our study observed that the incidence of AKI, as classified by KDIGO criteria, was relatively low; no cases exceeded Stage 1 during the observed postoperative period. This finding is encouraging and hints at the potential renal safety of OPCAB, at least during the immediate postoperative period.

Limitations

There are several limitations to this study. Retrospective studies are beneficial for cost-efficiently investigating uncommon diseases, but they suffer from drawbacks. For instance, these types of studies depend on information that was gathered for clinical uses and not for research purposes. Because the data were not collected using a predesigned proforma in accordance with the unique criteria of the study, some data are almost always going to be missing. Additionally, it is impossible to document all of the parameters that might possibly influence the results. Second, while serum creatinine is a widely accepted marker for renal function, it is not without limitations: factors such as muscle mass, hydration status, and medications can influence creatinine levels, and it might not be the most sensitive indicator of early renal injury [20].

Conclusion

In conclusion, our study reveals the renal implications of OPCABG and highlights transient postoperative increases in creatinine levels. (Those levels appear to normalize from postoperative Day 2 onwards.) While our findings are promising in terms of the potential renal safety of OPCABG, more extensive prospective studies are warranted to corroborate our observations and to better understand long-term renal outcomes post-OPCABG. Our hope is that such insights can guide clinical decision-making, ensuring optimal patient outcomes for individuals battling CAD.

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Research article

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The protective effect of hydroxytyrosol on the heart in rats fed corn syrup: The role of spexin, pentraxin-3

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Ethics Committee Approval
The study was approved by Adıyaman University Experimental Animal Ethics Committee (Protocol No: 2023/008).
The present study followed international, national, and/or institutional guidelines for humane animal treatment and complied with relevant legislation from the Animal Ethics Committee.

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

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Abstract

Background/Aim: Increased consumption of corn syrup has been linked to various metabolic diseases. The Mediterranean diet, one of the healthiest known diets, is renowned for its cardioprotective effects. We investigated the possible roles of new molecules such as spexin (SPX) and pentraxin-3 (PTX-3) in the protective effect of hydroxytyrosol (HT), one of the primary main components of olive oil, in rats fed corn syrup.
Methods: The animals were divided into four groups of n=6 rats each: Group I (Control), Group II (HT), Group III (Corn Syrup), and Group IV (Corn Syrup+HT). The rats were given 30% corn syrup with drinking water for 6 weeks. Liquid containing HT (4 ml/kg/day) was applied by oral gavage alone and together with corn syrup for 6 weeks. SPX and PTX-3 were examined histopathologically in the animals' heart tissue after the rats were sacrificed, and histoscores were created for SPX and PTX-3 immunoreactivity. The data were analyzed using both one-way ANOVA and Tukey's HSD test.
Results: We detected a decrease in SPX (P<0.001) and an increase in PTX-3 (P=0.013) in the Corn Syrup group compared with the Control group. After HT treatment, an increase in SPX (P=0.025) and a decrease in PTX-3 (P<0.001) were detected. There were no differences between the HT and Control groups.
Conclusion: The protective effects of HT against heart damage might be conferred via SPX and PTX-3. These molecules are considered to be important target molecules involved in the diagnosis and treatment of metabolic diseases.

Keywords: corn syrup, hydroxytyrosol, spexin, pentraxin-3

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Introduction

Consumption of fructose—used as a sweetener in carbonated beverages—has increased significantly in recent years; it is commonly ingested in the form of high fructose corn syrup or sucrose [1-3]. Corn syrup is added as a sweetener in a wide range of products because it is both cheap and creates a feeling of fullness [4]. However, extensive use of corn syrup has been linked to many metabolic disorders such as fatty liver, excess weight, high blood pressure, Type 2 Diabetes Mellitus and Metabolic Syndrome (MetS) [5]. Furthermore, there is evidence that the consumption of high fructose corn syrup increases the rate of cardiovascular disease (CVD) by triggering hypertension, dyslipidemia, inflammation and coronary heart disease [6]. Although an increased risk of CVD risk be partly related to fructose-related obesity or insulin resistance, cardiac-specific fructose toxicity is also possible [7].

The Mediterranean diet (MD) is one of the healthiest diets known, and it has demonstrated cardioprotective effects [8]. In Mediterranean populations, this diet is associated with the prevention of obesity, MetS, and related disorders [8–10]. A key feature of the MD is its use of olive oil, which contains many phenol compounds characterized by antioxidant and anti-inflammatory properties [9]. One of these compounds, hydroxytyrosol (3,4 dihydroxyphenylethanol, HT), is a bioactive phenyl ethanol and has a catechol moiety in olive products. Hydroxytyrosol has antioxidant, anti-inflammatory, and antimicrobial properties [10]. Furthermore, HT is believed to have cardioprotective, neuroprotective, and anticancer properties and a wide variety of positive endocrine-related effects [11]. Although HT has been investigated extensively, the precise molecular mechanisms underlying many of its effects have not been fully elucidated.

Spexin (SPX), a novel 14-amino acid neuropeptide, is also called Neuropeptide Q. This peptide is encoded by the C12orf29 gene on chromosome 12 of the human genome. Spexin is mainly released by human white adipose tissue [12,13]; however, it is also produced by other tissues and organs (e.g., the brain, heart, lungs, liver, thyroid, adrenal gland, muscles, ovaries, testis, pancreas, stomach, and the gastrointestinal (GI) tract) [12,14,15]. The functions of SPX are still not fully known, but it may be effective at weight and metabolism control, appetite and satiety control, glucose and lipid metabolism, fatty acid consumption, cardiovascular/kidney function, GI function, endocrine metabolism, and reproduction [16]. Recent findings have also speculated that SPX is a candidate biomarker for evaluating cardio-metabolic risk [17].

Pentraxin-3 (PTX-3), which belongs to the Pentraxin family, is a peptide that functions as an important biomarker of pro-inflammatory states in innate immunity [18,19]. PTX-3 is produced by immune cells such as monocytes/macrophages and neutrophils [20]. At the same time, PTX-3 is released by vascular cells (e.g., endothelial cells and smooth muscle cells) in response to inflammatory members such as Tumor Necrosis Factor-Alpha (TNF-α), interleukin-1β (IL-1β), and lipopolysaccharides [20,21]. It has been reported that PTX-3 expression is stimulated by TNF-α in adipocytes [22]. Recent studies have shown that there may be a relationship between high PTX-3 levels and the formation and progression of MetS. It has been shown that PTX-3 levels are elevated in people who are obese and suffer from MetS; increased PTX-3 levels are associated with low HDL cholesterol as well as high triglycerides [23]. In conclusion, PTX-3 may be a valuable and novel biomarker for MetS prediction.

In this study, we investigated the role of SPX and PTX-3 in the mechanisms underlying the effect of HT.

Materials and methods

Animals and experimental design

Study approval was granted by the Adıyaman University Experimental Animal Ethics Committee (Protocol No: 2023/008). Twenty-four male Sprague-Dawley rats between the ages of 8–10 weeks and weighing 200–250 grams born at the Adıyaman University Experimental Research Center were used. The animals were fed water and food ad libitum. The rats were divided into four groups of n=6 rats each: Group I (Control), Group II (HT), Group III (Corn Syrup), and Group IV (Corn Syrup+HT). The Control Group did not receive any treatments. Hydroxytyrosol was obtained in liquid form from Kale Natural Herbal Products Company in Turkey, and 4 ml/kg of this liquid that contained HT was administered orally to the rats in Groups II and IV each day for 6 weeks. The rats in Groups III and IV were given 30% corn syrup mixed into their drinking water for 6 weeks [24]. At the end of 6 weeks, IP Ketamine (75 mg/kg) and Xylazine (10 mg/kg) was given to the rats to anesthetize the animals prior to sacrifice. The experiment was terminated by taking blood samples from the hearts of the rats in all of the groups. The heart tissues were fixed in 10% formaldehyde for histopathological examination.

Immunohistochemical examination

The heart tissues of the rats were embedded in paraffin blocks and examined histopathologically. Immunohistochemical procedures were adopted as previously described in the literature [25]. Immunohistochemistry (IHC) was performed using 3 μm-thick histological tissue microarray slides. The following antibodies were used: Spexin primary antibodies (A04088-1, Booster Biological Technology, Pleasanton, CA, USA) and PTX-3 antibodies (PA5-36156, Thermo Fisher Scientific, İnvitrogen, Waltham, MA, USA). The slides were evaluated and photographed using a Zeiss Axio Scope A1 microscope (Carl Zeiss Microscopy GmB H 07745 Jena, Germany). Finally, histoscores were established for SPX and PTX-3.

Values were determined based on microscopic evaluations of the staining intensity: 0 for negatively stained areas, 0.1 for <25% stained areas, 0.4 for 26–50% stained areas, 0.6 for 51–75% stained areas, and 0.9 for 76–100% stained areas. The final histoscore was calculated using the following formula: Histoscore = Distribution × Density [25].

Power analysis

We used the G*power 3.1.9.7v program (Company, Location) and ANOVA with fixed effects to calculate the appropriate sample sizes of the groups. For an effect size of 0.90, a statistical power (1 - β) of 0.90, and significance level 0.05 as bidirectional, the actual power was determined to be 0.90 and six animals for each group. Given that we analyzed four groups, that yielded a total of 24 animals.

Statistical analysis

Statistical analyses were performed using SPSS 22 (IBM Corporation, Chicago, IL, USA). The one-way ANOVA test was used, and Tukey's HSD test was used for post-hoc multiple comparisons. The study data are expressed as means and standard deviations (SDs). *P*-values less than 0.05 were considered to be statistically significant.

Results

Immunohistochemical findings

SPX immunoreactivity was found to be lower in the Corn Syrup group compared with the Control and HT Groups ($P<0.001$). SPX immunoreactivity was elevated in the Corn Syrup+HT group relative to the Corn Syrup group ($P=0.025$) (Table 1). The SPX immunoreactivity histoscores of the four groups are shown in Figure 1.

PTX-3 immunoreactivity was found to be elevated in the Corn Syrup group compared with the Control and HT Groups ($P=0.013$ and $P=0.045$, respectively). PTX-3 immunoreactivity was lower in the Corn Syrup+HT group compared with the Corn Syrup group ($P<0.001$) (Table 2). The PTX-3 immunoreactivity histoscores of the four groups are shown in Figure 2.

Table 1: Immunohistochemical findings for SPX in heart tissues

Groups	Control	HT	Corn Syrup	Corn Syrup+HT
SPX	1 (0.15)	1.1 (0.16)	0.43 (0.06) [ab]	0.7 (0.15) [abc]

The values are expressed as mean (SD), a. $P<0.05$ compared to the control, b. $P<0.05$ compared to the HT, c. $P<0.05$ compared to the Corn Syrup.

Table 2: Immunohistochemical findings for PTX-3 in heart tissues

Groups	Control	HT	Corn Syrup	Corn Syrup+HT
PTX-3	0.8 (0.15)	0.85 (0.12)	1.1 (0.15) [ab]	0.65 (0.12) [c]

The values are expressed as mean (SD), a. $P<0.05$ compared to the control, b. $P<0.05$ compared to the HT, c. $P<0.05$ compared to the Corn Syrup.

Discussion

The prevalence of MetS has gradually increased over time, and so have cardio-metabolic and cardiovascular risks [26]. We have demonstrated for the first time the protective effects of HT, which has cardioprotective characteristics, against corn syrup-induced heart damage; we hypothesize that such effects might be mediated by SPX and PTX-3.

SPX is a newly discovered peptide that is believed to play a role in the formation and progression of metabolic diseases [16]. Low levels of blood-borne SPX have been observed in various diseases such as diabetes, obesity, MetS, CVD, kidney diseases, Non-Alcoholic Fatty Liver Disease (NAFLD) and Polycystic Ovary Syndrome (PCOS) [17]. SPX treatment has been observed to have positive effects on appetite suppression, fat mass, lipid accumulation and inflammation; administration of SPX has also been shown to improve insulin sensitivity, energy expenditure, and organ functioning in fish and rodents [17]. A study of patients with MetS exhibited an inverse relationship between SPX and glucose, blood pressure, and blood lipids (triglycerides and High-Density Lipoprotein [HDL]) [27]. Additionally, SPX treatment has been shown to reduce fatty acid uptake by hepatocytes [28]. Subcutaneous injection of SPX reduced appetite and decreased calorie intake by approximately 32% in rats [29]. However, a negative relationship between SPX levels and dietary fat intake has been observed in overweight children. SPX is believed to play a potential regulatory role in metabolic status [30].

In this study, we determined that SPX levels decreased in the Corn Syrup group compared with the Control group and increased after HT treatment. Based on this finding, we speculate that SPX may also be involved in the effects of HT. The antioxidant properties of HT are likely responsible for its protective effects on cardiac functions [31]. Hydroxytyrosol treatment (2 and 5 mg/kg/day for 1 week) has been shown to reduce heart weight and heart weight/body weight ratio in mice with CVD [32]. At the same time, a decrease in systolic and diastolic blood pressure and increases in arterial blood pressure, heart rate, and ST segment elevation were observed. The same

Figure 1: Immunohistochemical findings for SPX in heart tissues (A. Control, B. HT, C. Corn Syrup, D. Corn Syrup+HT)

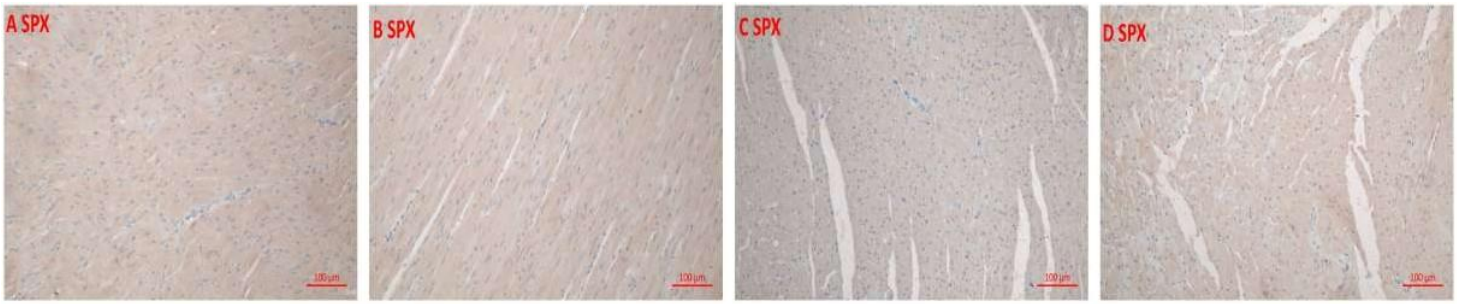
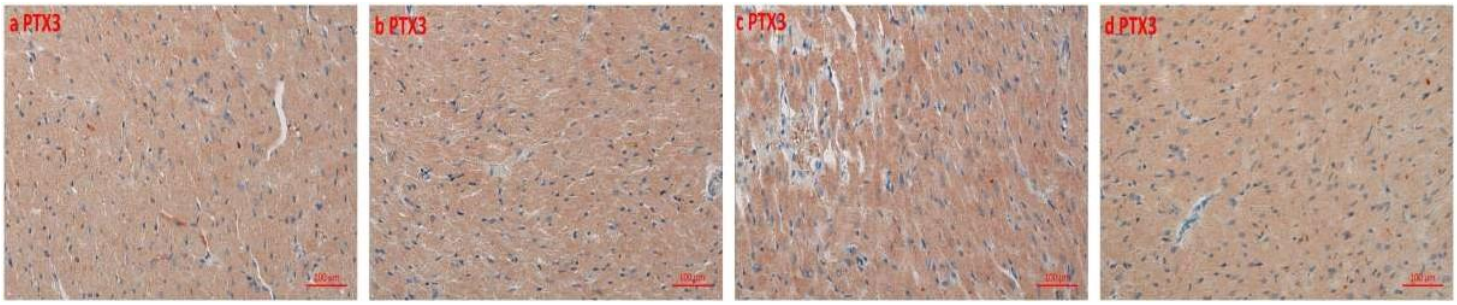


Figure 2: Immunohistochemical findings for PTX-3 in heart tissues (A. Control, B. HT, C. Corn Syrup, D. Corn Syrup+HT)



authors also reported increased protein levels of lactate dehydrogenase and Creatine kinase, possibly indicating an increase in glucose consumption via elevated ATP. Other studies have shown that HT confers protective effects (i) by preventing Low-Density Lipoprotein (LDL) oxidation, (ii) inhibiting platelet aggregation, (iii) attenuating mitochondrial abnormalities and preventing MetS caused by high fructose consumption [33], and (iv) producing anti-inflammatory effects in conjunction with decreased activity of cyclooxygenase 1 (COX1) and COX2 enzymes [34]. SPX may also be involved in the protective effects of HT on glucose, blood pressure, and blood lipids. Based on these recent findings, we can conclude that SPX may be a novel and interesting target for the development of new pharmacological strategies to ameliorate metabolic diseases. However, many open questions remain. For example, which cellular mechanism coordinates the action of SPX? Additional studies are necessary to understand the effects of SPX on tissue function and cell signaling in animal models.

Pentraxin-3 is a marker of immune response that is released in local and general inflammation. PTX-3 is released by immune cells in response to endotoxins, IL-1β, bacterial agents, and TNF-α. Since PTX-3 is an acute-phase protein, it has very low serum levels under normal conditions [35]. However, in case of inflammation, PTX-3 levels rise rapidly [35-37]. PTX-3 is released by a variety of cells (e.g., adipocytes, macrophages, dendritic cells, neutrophils, fibroblasts, vascular endothelial cells) and is produced by known cardiovascular risk factors, including inflammatory stimuli and oxidized LDL [20,21]; therefore, it is believed to reflect the local inflammatory state in tissues [38]. PTX-3 levels have been associated with lower HDL cholesterol levels as well as elevated triglycerides [23]. Likewise, it has been reported that there is a relationship between low HDL cholesterol levels and PTX-3 and high PTX-3 levels in patients with MetS and subclinical atherosclerosis [39]. Furthermore, a recent study reported that the severity of MetS was correlated with PTX-3 and also correlated with glucose levels, HDL cholesterol levels, and waist circumference [40]. In our study, we found that PTX-3 levels increased in the Corn Syrup group compared with the Control group; PTX-3 levels also decreased after HT treatment. The fact that PTX-3, which increases during inflammation and metabolic conditions, was found to be elevated in the Corn Syrup group highlights that our findings are consistent with literature data. Additionally, the observed decrease in PTX-3 in the HT group lends credence to the idea that PTX-3 may be involved in the protective mechanisms of this antioxidant, anti-inflammatory, and hypolipidemic agent. For this reason, PTX-3 may be a novel candidate immunoinflammatory marker because it is associated with cardiometabolic risk factors.

Limitations

One of the important limitations of this study is the fact that our findings are not supported by biochemical or genetic studies. Additional studies that include larger numbers of animals will be important for better understanding the molecular mechanisms behind HT. Finally, we believe that supporting our findings with further clinical studies will make significant positive impacts on scientific progress in the field of HT.

Conclusion

In conclusion, novel molecules such as SPX and PTX-3 might mediate the effects of HT against corn syrup-induced cardiac damage. These molecules might also represent therapeutic targets for cardiometabolic diseases.

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A retrospective cohort study of human papillomavirus (HPV) genotypes in women with abnormal Pap smear cytology in Turkey

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Ethics Committee Approval
The study was approved by the Istanbul University, Istanbul Faculty of Medicine Ethics Committee (reference number: 2018/881/11). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
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Abstract

Background/Aim: The most common genotypes of human papillomavirus (HPV) in patients with cervical cancer worldwide are HPV16 and HPV18. The persistence of these genotypes is associated with cervical cancer and detection, and HPV genotyping, particularly in women with abnormal Pap smears, has become a crucial tool for cervical cancer screening, diagnosis and management. We evaluated the overall prevalence of HPV in women with abnormal Pap smear cytology and also investigated age-specific HPV prevalence and HPV genotype distribution.

Methods: We analyzed 716 cervical smear specimens in this retrospective cohort study. Cytological diagnoses of typical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSILs), and high-grade squamous intraepithelial lesions (HSILs) were made utilizing the Bethesda System. The Papanicolaou method was used for the staining of the Pap smears. The specimens were pre-screened for HPV DNA positivity using an HC2 assay (Qiagen, USA). After the pre-screening, a Cobas 4800 HPV test system (Roche Diagnostics GmBH, Germany) was used to genotype the HPV-positive samples.

Results: Of the 716 cervical smear samples, 520 (72.6%) were found to be HPV-negative. Among the HPV-positive samples, 106 (23.2%), 57 (28.8%) and 33 (53.2%) were identified from 456 ASCUS, 198 LSIL and 62 HSIL cases, respectively. These findings revealed a gradual decrease in HPV prevalence with increased cytological grade (P<0.05). For high-risk, low-risk and high-risk/low-risk HPV types, 76 (38.8%), 78 (39.8%) and 42 (21.4) were positive according to the HC2 assay, respectively (P<0.05) Only 117 of the 196 HPV-positive samples were found to be HPV-positive with the Cobas 4800 HPV test system. HPV16 was the most prevalent type detected by the Cobas 4800 HPV test: 55 out of 117 HPV-positive smear samples across all age groups (47%). HPV16 was significantly more frequently detected in the HSIL samples than HPV18 (P<0.05). The prevalence of HPV was the highest in women with ages between 29 and 38 (71/196, 36.22%) and declined with age.

Conclusion: We found that HPV16 and HPV18 were the most prevalent genotypes of HPV in a cohort of Turkish women; HPV16 was most frequently detected in HSIL samples from women with ages between 29 and 38. We conclude that investigating the incidence of HPV16 and HPV18 genotypes will be important for implementing new programs and protocols to reduce the incidence of cervical cancer. These data may contribute to the development of preventive strategies to reduce the cervical cancer burden in Turkey.

Keywords: human papillomavirus genotypes, cervical cancer, HPV16, HPV18

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Introduction

Cervical cancer, the fourth most frequent malignancy in women worldwide, is believed to be responsible for more than 342,000 deaths annually in low- and middle-income nations [1]. Ninety percent of human papillomavirus (HPV) infections are typically resolved within two years [2], and the majority of HPV infections are transitory. However, high-grade squamous intraepithelial lesions (HSILs) and cervical cancer development are linked to the persistence of high-risk HPV strains [2]. Human papillomavirus genotyping is a very useful tool for diagnosing, screening, and treating cervical cancers [3,4]. There are currently at least 200 known HPV genotypes [3]. In humans, 25 of these genotypes are known to be carcinogenic, with HPV16 and HPV18 being the most common genotypes in cervical cancer patients globally [5,6]. The average probability of developing cervical cancer increases with a person's age, their number of sexual partners, whether they smoked during young adulthood and whether they engaged in unprotected sexual activity in a young age [7,8]. We evaluated the overall prevalence of HPV, the age-specific prevalence of HPV and HPV genotype distribution in a cohort of Turkish patients with cervical Pap smears indicating atypical cells.

Materials and methods

Study population

We analyzed retrospectively 716 cervical smear specimens with atypical cells indicated on a Pap test. The specimens were collected from the Gynecology and Obstetrics Clinics of Istanbul Faculty of Medicine between 2008 and 2018. All of the eligible specimens derived from women who had a history of sexual activity, either current or previous, with were not pregnant at the time of the sample collection. All patients gave their consent to undergo HPV genotyping and cervical histopathology evaluation. Patients with acute genital inflammation, clinically suspected immunodeficiency, cervical or total uterus resection, or a previous cervical, vulval, or vaginal cancer diagnosis or treatment were excluded from the study. Atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) were the three cytological diagnoses that were made utilizing the Bethesda System [9]. The Istanbul University, Istanbul Faculty of Medicine Ethics Committee approved this study (reference number: 2018/881/11).

HPV DNA analysis

The Hybrid Capture Cervical Sampler Qiagen GmbH, Hilden, Germany) and the Hybrid Capture 2 (HC2) DNA Collection Device (Qiagen GmbH, Hilden, Germany) were used to collect the smear specimens. The modified Papanicolaou procedure was used to stain Pap smears. The residual material was stored at -80°C until the specimens were pre-screened for HPV DNA positivity with a HC2 assay (Qiagen, Maryland, USA). The HC2 assay (*in-vitro* nucleic acid hybridization assay) was used to identify DNA from five low-risk genotypes (HPV6, 11, 42, 43 and 44) and 13 high-risk HPV genotypes (genotypes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [10]. After pre-screening the Pap smear samples with the HC2 assay, the HPV-positive samples were genotyped using a Cobas 4800 HPV system (Roche Diagnostics GmBH, Germany). The Cobas 4800 HPV test is a qualitative multiplex assay that detects 12 high-risk HPV types (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) while providing specific genotyping information for HPV16 and HPV18. The results were interpreted automatically by the Cobas 4800 HPV system software (Roche Diagnostics GmBH, Germany) as "Target Not Detected," "HPV16," "HPV18," "other high-risk HPV" or any combination of the latter three. Samples that yielded invalid results were retested.

Statistical analysis

We used SPSS software (version 21) (IBM, New York, USA) to analyze the data. Categorical data were presented as numbers and percentages. To evaluate the categorical data, we used the chi-square method. The chi-square test was also used to assess HPV prevalence with cytological grade and HPV infection prevalence predictions with age to evaluate trends. A *P*-value less than 0.05 was considered to indicate statistical significance.

Results

Of the 716 cervical smear samples, 520 (72.6%) were found to be HPV-negative via pre-screening with the HC2 assay. Among the HPV-positive samples, 106 (23.2%), 57 (28.8%) and 33 (53.2%) were identified from 456 ASCUS, 198 LSIL and 62 HSIL cases, respectively. These numbers indicate a gradual decrease in HPV prevalence with increasing cytological grade ($P<0.05$). The proportion of HPV positivity was highest in the HSIL group (Table 1).

For high-risk, low-risk and high-risk/low-risk HPV types, 76 (38.8%), 78 (39.8%) and 42 (21.4) were positive according to the HC2 assay, respectively ($P<0.05$) (Table 2).

After pre-screening the atypical Pap smear samples with the HC2 assay, only 117 of the 196 HPV-positive samples were detected to be HPV-positive according to the Cobas 4800 HPV test. The most common genotype discovered by the Cobas 4800 HPV test was HPV16: 55 out of 117 HPV-positive smear samples across all age groups (47%). HPV16 was significantly more frequently detected in the HSIL samples than HPV18; 13 versus 3 samples were HPV DNA positive. The next most prevalent genotype was HPV18, which was detected in 20 of the samples (17.1%) (Table 3).

HPV16 was most commonly detected in smears from women with ages between 29 and 38 (54.8%). However, the detection frequency of HPV16 was slightly higher in women aged 18–28 than in those aged 29–38 (17.5% versus 16.6%). Other high-risk HPV genotypes (HPV31, 33, 35, 39, 45, 51, 54, 56, 58, 59, 66 and 68) were detected in 27.4% of HPV-positive samples across all age groups (Table 4). However, a type-specific genotype was not available.

Table 1: HPV prevalence in pap smears.

Cytology	ASCUS n=456 n (%, 95 CI)	LSIL n=198 n (%, 95 CI)	HSIL n=62 n (%, 95 CI)	Total
HPV DNA-	350 (76.8, 72.38-81.22)	141 (71.2, 63.73-78.67)	29 (46.8, 28.64-64.96)	520 (72.6, 68.77-76.43)
HPV DNA+	106 (23.2, 15.16-31.24)	57 (28.8, 17.04-40.56)	33 (53.2, 36.18-70.22)	196 (27.4, 21.16-33.64)

ASCUS: atypical squamous cells of undetermined significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, CI: confidence interval

Table 2. HPV positivity prevalence distribution in different age groups.

Age	*HR HPV n=76 (%, 95% CI)	*LR HPV n=78 (%, 95% CI)	HR/LR HPV n=42 (%, 95% CI)	HPV (-) n=520 (%, 95% CI)
18-28	25 (32.9%, 14.4-51.3)	24 (30.8%, 12.3-49.2)	15 (35.7%, 11.4-59.9)	114 (22%, 14.4-29.6)
29-38	27 (35.5%, 17.4-53.5)	28 (35.9%, 18.1-53.6)	16 (38%, 14.2-61.7)	186 (35.8%, 28.9-42.6)
39-48	16 (21%, 1-40.9)	17 (21.8%, 2.1-41.4)	9 (21.4%, 5.3-48.1)	143 (27.5%, 20.1-34.8)
49<	8 (10.5%, 10.7-31.7)	9 (11.5%, 9.3-32.3)	2 (4.7, 3.9-13.3)	77 (14.8%, 6.8-22.7)

HR: high risk, LR: low risk, CI: confidence interval

Table 3: HPV status versus cervical cytology.

Cytology	ASCUS n=58 (%, 95% CI)	LSIL n=34 (%, 95% CI)	HSIL n=25 (%, 95% CI)	Total n=117 (%, 95% CI)
HPV16	31 (53.4%, 35.8-70.9)	11 (32.3%, 4.6-59.9)	13 (52%, 24.8-79.1)	55 (47%, 33.8-60.1)
HPV18	10 (17.2%, 6.1-40.5)	7 (20.6%, 9.3-50.5)	3 (12%, 24.7-48.7)	20 (17.1%, 0.6-33.6)
OHR types*	14 (24.1%, 1.7-46.5)	13 (38.2%, 11.7-64.6)	5 (20%, 15-55)	32 (27.4%, 11.9-42.8)
HPV16/ OHR types	1 (1.7%, 23.6-27)	2 (5.9%, 26.7-38.56)	3 (12%, 24.7-48.7)	6 (5.1%, 12.5-22.7)
HPV18/ OHR types	2 (3.4%, 21.7-28.5)	1 (2.9%, 29.9-35.7)	1 (4%, 34.4-42.4)	4 (3.4%, 14.3-21.6)

ASCUS: atypical squamous cells of undetermined significance, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, CI: confidence interval, *Other high-risk (OHR) HPV types: 31, 33, 35, 39, 45, 51, 54, 56, 58, 59, 66, 68

Table 4: The age distribution of patients by HPV type.

Age range	HPV 16 n, (%, 95% CI)	HPV 18 n, (%, 95% CI)	Other High Risk HPV* (OHR) n, (%, 95% CI)	HPV16/OHR n, (%, 95% CI)	HPV 18/OHR n, (%, 95% CI)
18-28 (n=40)	18 (45%, 22.02-67.9)	7 (17.5%, 10.6-45.6)	12 (28%, 30.4-55.9)	2 (5%, 25.1-35.2)	1 (2.5%, 28.1-33.1)
29-38 (n=42)	23 (54.8%, 41.4-68.2)	7 (16.6%, 10.9-44.1)	10 (23.8%, 2.5-50.1)	1 (2.4%, 27.6-32.4)	1 (2.4%, 27.6-32.4)
39-48 (n=25)	10 (40%, 9.6-70.3)	2 (8%, 29.6-45.6)	10 (40%, 9.6-70.3)	2 (8%, 29.6-45.6)	1 (4%, 4.4-42.4)
49< (n=10)	4 (40%, 8-88)	4 (40%, 8-88)	0	1 (10% , 48.8-68.8)	1 (10%, 48.8-68.8)
Total (n=117)	55 (47%, 33.8-60.1)	20 (17%, 0.5-33.4)	32 (27.4%, 11.9-42.8)	6 (5.1%, 12.5-22.7)	4 (3.4%, 14.3-21.1)

* Other high-risk (OHR) HPV types: 31, 33, 35, 39, 45, 51, 54, 56, 58, 59, 66, 68; CI: confidence interval

Table 5: Prevalence rates of HPV in women with abnormal cytology tested in Istanbul and Ankara (included are studies with more than 400 tested samples).

Region	Study	Number of samples tested	HPV DNA (+)(%)	HPV16 (+)(%)	HPV18 (+)(%)	OHR (+)(%)
Turkey, multicenter	[ref #17]	6170	25.0	32.0	8.0	23.4
Istanbul	This study	716	27.4	47	17	27.1
Istanbul	[ref #18]	500	16.5	34.0	n.d.	n.d.
Istanbul	[ref #19]	420	20.2	n.d.	n.d.	n.d.
Ankara	[ref #16]	403	23.0	36.0	13.0	8.8
Ankara	[ref #20]	1797	22.4	25.5	2.5	41.8
Ankara	[ref #21]	530	17.9	3.6	0.4	5.8
Ankara	[ref #22]	501	4.2 (hr)	n.d.	n.d.	n.d.
Ankara	[ref #23]	890	25.7	46.3	4.4	61.9

n.d.: not determined, hr: high-risk

Discussion

In Turkey, cervical cancer is the eighth most common malignancy overall among women and the 12th most common among women aged 15–44 [1]. According to estimates, 4.2% of women in the general Turkish population have a cervical HPV16/18 infection at any given time, and invasive cervical malignancies caused by HPV16 or HPV18 account for 67.6% of cases [11]. Because more than 96% of cervical malignancies test positive for high-risk HPV types, it is well-documented that HPV16 and HPV18 are the primary causes of cervical cancer [12]. It has been shown that there are significant regional and global differences in the prevalence of HPV and the distribution of HPV genotypes [13]. The prevalence of HPV has been reported to be higher in the United States and Africa for women with ages between 35 and 50 but lower in European, Asian and Middle Eastern countries [4,14-15]. Dursun et al. [16] retrospectively evaluated data from 6388 patients from Turkey collected between 2006 and 2010 and found that 25% of cervical samples were positive for HPV DNA. Other studies from Turkey have reported HPV prevalence rates varying from 17–25% (Table 5) [16-22].

The slightly lower prevalence of HPV in Turkey in the Dursun et al. [16] results may be explained by the inclusion of HPV genotypes detected in women who had negative cytology results. In our study, on the other hand, we included only women who had abnormal cytology results. The HPV DNA positivity

prevalence in our study on cervical smear samples with atypical Pap smear test results is similar to the numbers reported worldwide.

The most common genotype that we detected across all age groups was HPV16. This genotype is also the most prevalent genotype worldwide regardless of cytological status [18,23-25]. Another commonly found genotype was HPV18 (17%); however, other HPV genotypes that indicated a high risk of cancer were not differentiated the Cobas 4800 HPV test. Therefore, we suggest that the HPV18 genotype was the second most commonly detected genotype in this study. The high prevalence of HPV18, unlike that noted in other limited studies in Turkey, is consistent with the findings of other studies [13,14,24,26].

HPV16- and HPV18-related cancer cases have been reported to be the highest in Africa (94.2%) [26]. The prevalence of such cases has been noted to be 89.2% and 68.0% in North America and Asia, respectively [26]. Dursun et al. [17] identified HPV16 and HPV18 as the most common HPV genotypes (32% and 8%, respectively). However, those authors found a slightly lower prevalence than we did (47% and 17%, respectively). High-grade squamous intraepithelial lesions were significantly associated with HPV16 across all age groups in our investigation. Interestingly, higher rates of HPV16 and HPV18 infections were found in women older than. We note, however, that the sample size of that older cohort (10) was too small to draw robust conclusions.

A review of the literature published about HPV screening in cervical samples with abnormal cytology from Istanbul and Ankara revealed no significant difference in HPV prevalence in those two cities [11]. Turkey is the first Islamic country to recently implement a centralized national cervical cancer screening program. Preliminary results of this centralized HPV testing revealed a prevalence rate of 3.8% for high-risk HPV, which is low compared to European and Western countries [27]. Vaccinations can help prevent HPV infections. However, because the HPV vaccination is not included in Turkey's immunization program, it is administered solely based on a medical recommendation [28]. Given that Turkey has not yet introduced a publicly funded national HPV vaccination program [12,29], we expect that our work will inform decisions about the development of such a program.

Limitations

We considered data from a relatively small cohort of women, and our results were restricted to a single center. Therefore, it is difficult to draw comprehensive conclusions from our investigation. Another limitation is the retrospective nature of this study; we did not include prognostic variables. An incorrect diagnosis could result from an HPV DNA test administered without a colposcopic examination. To more accurately estimate the prevalence and distribution of the HPV genotypes with aberrant and normal cytology, more population-based research is required.

Conclusions

The HPV genotypes that are most frequently observed in women with abnormal Pap smears are HPV16 and HPV18. In our work, the HPV16 genotype was more frequently detected in HSIL samples of women with ages between 29 and 38. The HPV DNA positivity rates that we found are similar to those reported in other studies worldwide. Moreover, the high prevalence of HPV18 that we noted is consistent with other investigations but higher than that reported by other Turkish studies. We suggest that investigating the incidence of HPV16 and HPV18 genotypes will be important for implementing new programs to curb the incidence of cervical cancer. These data may contribute to the development of preventive strategies to reduce the cervical cancer burden in Turkey.

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