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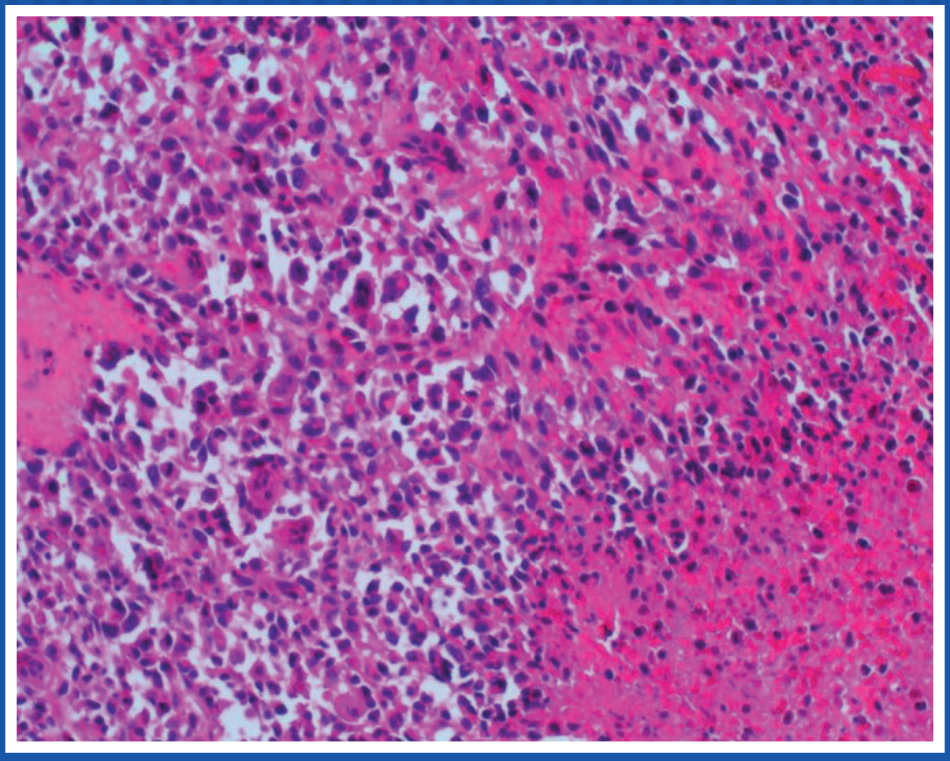

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Northwestern Medical Journal

Editorial Board

Northwestern Medical Journal

Advisory Board

Contents

Editorial

Research Articles

Case Report

Editorial

Dear colleagues,

I am delighted to announce the release of the Northwestern Medical Journal's first issue in 2024, marking the journal's fourth year of publication. Our journal will now be published four times a year due to its growing popularity.

This issue has nine scientific articles, including seven original articles, a case series, and a case report. Yaman et al. reviewed factors affecting medical patent ductus arteriosus closure treatment for hemodynamically significant patent ductus arteriosus in term neonates. Karabörk et al. investigated whether IL-17F in cerebrospinal fluid differentiate normal pressure hydrocephalus from defence. Ege et al. reviewed the effect of conventional physical therapy and median nerve radiofrequency treatment on kinesiophobia in lumbar facet syndrome. Bayraktar et al. evaluated the relationship between uric acid/hdl ratio and total calcium score in coronary ct angiography. Gür Özcan et al. evaluated the measurement of cystic artery diameter by computed tomography in the diagnosis of acute cholecystitis. Küçüköztaş et al. shared their experience with a case series of anaplastic thyroid carcinoma. Güven et al. reported their experience with emergency department admissions and bleeding risk in patients using warfarin-containing drugs. Akbaş Güneş et al. assessed the relationship between uric acid levels and lipid parameters and body mass index. Buz Yaşar et al. reported a case report on the migration of the lippes spiral out of the uterus, discovered accidentally.

We truly value the insightful feedback that our publishers, writers, reviewers, and readers have provided. We look forward to your significant contributions to our next issues.

Best regards,
Prof. Ahmet Ural, M.D.
Editor-in-chief

NORTHWESTERN MEDICAL JOURNAL

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RESEARCH ARTICLE

Is medical therapy succesful in hemodynamically significant patent ductus treatment in term newborns?

Akan Yaman[1], İbrahim Kandemir[2], Zeynep Alp Ünkar[3], Sinem Gülcan Kersin[4], Mehmet Tolga Köle[5], Aslı Çınar Memişoğlu[4]

[1]Department of Pediatrics, Division of Neonatalogy, Faculty of Medicine, Nisantasi University, İstanbul, Türkiye.
[2]Department of Pediatrics, Faculty of Medicine, Biruni University, İstanbul, Türkiye.
[3]Department of Pediatrics, Division of Neonatology, Faculty of Medicine, İstanbul University-Cerrahpasa, İstanbul, Türkiye.
[4]Department of Pediatrics, Division of Neonatalogy, Faculty of Medicine, Marmara University, İstanbul, Türkiye.
[5]Department of Pediatrics, University of Health Sciences, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye.

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ABSTRACT

Aim: To investigate the clinical success of medical patent ductus arteriosus closure treatment for hemodynamically significant patent ductus arteriosus in term babies.

Methods: Our study included patients treated in two neonatal intensive care units with hemodynamically significant patent ductus arteriosus after the 3rd postnatal day and administered medical patent ductus arteriosus closure treatment (ibuprofen and paracetamol) at the discretion of the pediatric cardiologists while awaiting referral for surgical closure treatment.

Our retrospective analysis included anthropometric measurements at birth, the day treatment started postnatally, and other existing clinical conditions that might influence the prognosis of patent ductus arteriosus. Then, treatment success was evaluated by echocardiographic results.

Results: We included all ten patients diagnosed with hemodynamically significant patent ductus arteriosus and administered medical treatment with a mean gestational age at birth of 38.4 ± 1.21 weeks, and median birth weight of 3125 grams (3005-3200). We started medical closure treatment at mean postnatal 11.6 ± 4.9 days with ibuprofen (70%, n=7) or paracetamol (30%, n=3). 40% (n=4) of the infants had complete closure, 20% (n=2) became asymptomatic, and 10% (n=1) underwent surgical ligation. 30% (n=3) of patients died due to different complications during surgical preparation. As we defined treatment success as complete or partial closure and compared paracetamol and ibuprofen success, there was no statistically significant difference between them (p=0.5).

Corresponding author: Mehmet Tolga Köle **E-mail:** mehmet_tolga@hotmail.com
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Conclusion: Medical closure treatment might be effective in the presence of hemodynamically significant patent ductus arteriosus in term infants. There was no statistical superiority of paracetamol or ibuprofen treatments over each other in terms of treatment success.

Keywords: newborn, patent ductus arteriosus, ibuprofen, paracetamol

INTRODUCTION

The ductus arteriosus is a vascular structure in fetuses that connects the junction of the common pulmonary and the left pulmonary arteries to the descending aorta, which creates a vital outlet channel that flows from the right-ventricular outlet to the systemic circulation to prevent high resistance in the pulmonary arterial circulation by connecting the pulmonary and systemic circulation in the fetus (1,2).

An increase in systemic vascular resistance results in the obliteration of the fetal shunts following placental discharge. The closure mechanisms of the ductus arteriosus have two milestones. The first mechanism is the spontaneous closure of the ductus arteriosus induced by the onset of pulmonary respiration at birth, which results in increased oxygenation with the increase in partial oxygen pressure in the blood and loss of vasodilators due to decreased prostaglandin E2 production and its receptors (3). The other mechanism is that the elastic fibers of the ductus arteriosus, unlike the large arteries, are fewer, and the vessel cannot return to its initial state after vasoconstriction (4).

Following birth, spontaneous closure occurs in 8-22% of preterm babies born at 24-28 weeks of gestation, while this rate increases up to 90% at the 30th week of gestation and nearly 100% in term babies (5). Ductus arteriosus closure is complete within the first three days of life in term healthy neonates (2). The term patent ductus arteriosus defines circumstances in which spontaneous closure of the ductus arteriosus is delayed (1). The incidence of patent ductus arteriosus is between 2.9 and 7.8 per ten thousand term-born babies (6,7).

There are several risk factors for patent ductus arteriosus in premature babies, such as low birth weight, respiratory distress syndrome, being not treated with antenatal corticosteroids, chorioamnionitis, postnatal fluid overload/error in fluid management, sepsis, intrauterine growth retardation, genetic factors, perinatal asphyxia, being born at high altitude, and genetic predisposition (5,8). A neutral temperature environment, adequate oxygenation, use of high positive end-expiratory pressure (>5 cmH2O), short inspiratory time (0.35 sec), keeping the hematocrit level between 35-40%, and fluid restriction (while avoiding dehydration) are the targets. Therefore, prostaglandin inhibition via cyclooxygenase inhibitors is the mainstay of therapy for patent ductus arteriosus closure in premature infants (9). Currently, indomethacin, ibuprofen (intravenous or oral), or paracetamol are efficacious for the medical closure treatment of patent ductus arteriosus, with indomethacin and ibuprofen having 70-80% success rate in preterm infants (5).

Elimination of pulmonary-hyper circulation and prevention of obstructive pulmonary vascular disease, endocarditis, and endarteritis are the indications and treatment goals of patent ductus arteriosus closure treatment (10). Apart from medical closure treatment, patent ductus arteriosus occlusion with transcatheter devices can also be applied. Complications of this treatment include device embolization into the pulmonary or systemic circulation unanticipatedly and creating a coarctation in the aorta. Device-related obstruction of the aortic (forming iatrogenic coarctation) or pulmonary flow, transient left ventricular systolic dysfunction, hemolysis, and recanalization may occur, especially in young infants. Complications are more common in infants with a body weight of less than 6 kg (10).

Percutaneous occlusion is preferable to surgical ligation in infants and children weighing ≥6 kg as it is less invasive than surgical treatment and does not result in a surgical scar (6,7). Still, complications of transcatheter patent ductus arteriosus closure treatment are more common in infants weighing less than 6 kg (10). However, surgical ligation is also a safe and effective alternative (8), but the efficacy

of pharmacological treatment in term infants is not known. Therefore, the purpose of this study was to present the responses of term infants with hemodynamically significant patent ductus arteriosus who had been treated with paracetamol and ibuprofen while waiting for surgical closure.

MATERIALS AND METHODS

We conducted this study in two centers (Marmara University, Faculty of Medicine and Gungoren Hospital) between January 2017 and December 2020. We included all term babies diagnosed with hemodynamically significant patent ductus arteriosus according to the American Academy of Pediatrics guidelines (11). Patients had tachycardia, tachypnea, need for respiratory support, abdominal distension, systemic systolic dysfunction, or echocardiographic features (severe left atrial or ventricular dilatation, systolic left ventricular dysfunction, ductus diameter ≥2 to 3 mm, and ductal left-to-right diastolic flow ≥0.5 m/s.) after the third postnatal day. We started medical therapy with the approval of the pediatric cardiologists for hemodynamically significant patent ductus arteriosus in patients awaiting referral for surgical closure treatment. We used ibuprofen 10-5-5 mg/kg/day for three days or paracetamol 4x15 mg/kg/dose for five days with peroral or intravenous ways if we could not give ibuprofen due to their clinical conditions like renal failure, gastrointestinal bleeding, and thrombocytopenia.

Our study included anthropometric measurements of the patients at birth, other existing clinical conditions that may affect the prognosis, the postnatal treatment day and drug type, and evaluated the clinical response with echocardiography. We defined complete closure as total closure of the ductus arteriosus on echocardiography and partial closure as the remission of the hemodynamically significant patent ductus arteriosus to less than 1.5 mm in diameter, resulting in normalization of left heart load and increased pulmonary circulation with improvement of systemic hypoperfusion.

The ethical approval for this study was obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee (09.2022.25). We conducted the study following the ethical principles of the Declaration of Helsinki. As this was a retrospective study, informed consent was not required.

Statistics

We presented continuous data as mean +/- standard deviation or median (interquartile range) according to the distribution pattern. Fisher's exact test was used to compare two groups of categorical variables. A p-value <0.05 was considered statistically significant. We used the Jamovi 2.2.5 package program for statistical analyses.

RESULTS

Ten patients were eligible for the study. The median birth weight, the mean gestational week at birth, length, and head circumference were 3125 grams (3005-3200), 38.4+/-1.21 weeks, 49+/-1.94 cm, and 36+/-3.5 cm, respectively. 90% (n=9) of the patients were born by cesarean section and 10% (n=1) by normal-spontaneous vaginal delivery. In addition, 10% (n=1) of the babies had persistent pulmonary hypertension and 20% (n=2) had a ventricular septal defect (VSD).

We administered ibuprofen to 70% (n=7) of the patients and paracetamol to 30% (n=3). The mean postnatal day of initiation of medical treatment for patent ductus arteriosus closure was 11.6 +/-4.9 days. We observed complete hemodynamically significant patent ductus arteriosus closure in 40% (n=4) and partial closure in 20% (n=2) of the patients. We discharged these patients after treatment and referred them to the pediatric cardiology outpatient clinic. Unfortunately, 40% of the remaining babies did not respond to the treatment, and we referred them for surgical closure. One patient who underwent surgical ligation survived, while the other three died due to various complications (table 1). We administered ibuprofen to 70% (n=7) of the patients and observed total or partial closure in 71% (n=5) of them, while the closure rate was 33.3% (n=1) of the patients who received paracetamol (30%, n=3).

We defined treatment success as complete or partial closure. There was no statistically significant difference

between paracetamol and ibuprofen therapy regarding treatment success (Fisher's exact test, p=0.5).

Table 1 describes the clinical characteristics and treatment responses of all patients.

DISCUSSION

There is no consensus on the efficacy of prostaglandin synthesis inhibitors (indomethacin and ibuprofen) for medical patent ductus arteriosus closure in term newborns; however, the recent pharmacological closure of a patent ductus arteriosus in a term newborn with indomethacin (9) suggests that this issue needs further investigation. In addition, since the risk of complications is higher in patent ductus arteriosus closure with the percutaneous transcatheter method, especially in infants weighing <6 kg, the literature recommends postponing interventional closure if possible and evaluating pharmacological treatment options beforehand (5).

Besides indomethacin and ibuprofen, there is evidence for the efficacy of paracetamol treatment in closing patent ductus arteriosus in preterm neonates (2). A study examined the efficacy of oral paracetamol to close the patent ductus arteriosus effectiveness of in preterm infants (25.7+/-1.5 weeks; 724 +/- 143 grams) in whom ibuprofen cannot be used or was ineffective and evaluated partial closure (at least 50%) and non-closure rates. They reported that they observed complete closure in 50% and a significant reduction in hemodynamic shunt in 20% of patients (12).

There are conflicting results from studies evaluating the efficacy of pharmacological patent ductus arteriosus closure treatments in term infants. A study reported that 5-day oral ibuprofen treatment (doses: 10, 5, 5, 5, 5 mg/kg/day, respectively) had no statistical effect on patent ductus arteriosus closure rate in term newborns compared to placebo. They found that patent ductus arteriosus was closed in 65% of the patients in the oral ibuprofen group and 50% in the placebo group (13). In a similar study, researchers started oral ibuprofen (10, 5, and 5 mg/kg/day for three days, respectively) in 8-14 days-old term infants with patent ductus arteriosus in the intervention group and compared it with the control patients. The patent ductus arteriosus was closed in 62.9% of the patients taking oral ibuprofen and 54.3% in the control group, and there was no statistically significant difference between them (14). However, the researchers did not give detailed information about the hemodynamic insufficiency of these cases in these publications.

Another option is the closure of hemodynamically significant patent ductus arteriosus with the transcatheter device, and the success rate is 94.3% in infants below 6 kg (15). However, there is a risk of 12.6% major adverse events (most frequently acute

Table 1. Clinical features and treatment responses of the patients.

	GW	BW	PN day	Drug	Result (hsPDA)	Additional diagnosis	Survival
1	39	3200	15	Ibuprofen	Closed	Down syndrome	Survived
2	38+6/7	3090	20	Ibuprofen	Asymptomatic	Hydrancephaly	Survived
3	40	2150	19	Ibuprofen	Not closed	Esophageal atresia	Exitus
4	37+2/7	3200	8	Ibuprofen	Closed	-	Survived
5	38	3250	9	Paracetamol	Not closed	PNA	Exitus
6	38+4/7	3050	10	Paracetamol	Not closed	PNA+Down syndrome	Exitus
7	36	2990	11	Ibuprofen	Asymptomatic	-	Survived
8	40	2250	11	Ibuprofen	Need surgery	-	Survived
9	38	3160	8	Paracetamol	Closed	-	Survived
10	38	3640	5	Ibuprofen	Closed	Immunodeficiency	Exitus

*All patients were intubated and were taking at least one inotropic drug. GW: gestational week (week), BW: birth weight (grams), PN day: postnatal day of treatment, hsPDA: hemodynamically significant patent ductus arteriosus, PNA: perinatal asphyxia

arterial damage (3.5%) and device-embolization (2.4%) secondary to this procedure, and the probability of major adverse events is higher in infants younger than thirty days (15). In addition, this study reported that the risk of developing embolization is higher in babies with excessive and low birth weight (15). Therefore, the substantial rate of occurrence of major adverse events related to transcatheter closure and the existence of centers that cannot perform patent ductus arteriosus closure by transcatheter route make it necessary to apply pharmacological patent ductus arteriosus closure treatment before applying for surgical ligation and to switch to transcatheter or surgical patent ductus arteriosus closure treatment by the way in cases refractory to pharmacological therapy.

We detected complete patent ductus arteriosus closure after intravenous paracetamol (n=1) and ibuprofen (n=3) treatment in four patients, also, hemodynamically significant patent ductus arteriosus became asymptomatic in two patients. Unfortunately, three patients awaiting the operation had a multiorgan failure and died due to severe perinatal asphyxia (2 patients) and complications of esophageal atresia (one patient). In addition, one patient died later due to immunodeficiency, but echocardiographic and clinical follow-up revealed that the patent ductus arteriosus was closed.

These results suggest that intravenous paracetamol and ibuprofen treatment may be beneficial in the absence of contraindications while awaiting referral or operation/intervention in centers where emergency transcatheter or surgical intervention is not available.

CONCLUSION

Pharmacological closure of hemodynamically significant patent ductus arteriosus seems possible in term infants. In selected cases, medical treatment may be an option before surgical or transcatheter occlusive treatment. In this case series, we did not find a statistical superiority of paracetamol or ibuprofen treatments to each other in terms of hemodynamically significant patent ductus arteriosus closure. Prospective randomized controlled studies in large case series are needed to provide more conclusive evidence.

Ethical approval

This study has been approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval date 07.01.2022, number 09.2022.25). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: AY, İK, ZAÜ, SGK, MTK, AÇM; Concept: İK, MTK, AÇM; Design: AY, İK, ZAÜ, SGK, MTK, AÇM; Data Collection or Processing: AY, İK; Analysis or Interpretation: İK, MTK, AÇM; Literature Search: AY, İK, ZAÜ, SGK, AÇM; Writing: AY, İK, ZAÜ, SGK, MTK, AÇM. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

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RESEARCH ARTICLE

Does cerebrospinal fluid IL-17F distinguish normal pressure hydrocephalus from dementia?

Şeyda Karabörk[1], **Hümeyra Çelik**[2], **Şule Aydın Türkoğlu**[3]

[1]Department of Medical Microbiology, Faculty of Medicine, Bolu Abant İzzet Baysal University, Bolu, Türkiye.
[2]Department of Physiology, Faculty of Medicine, Alaaddin Keykubat University, Antalya, Türkiye.
[3]Department of Neurology, Faculty of Medicine, Bolu Abant İzzet Baysal University, Bolu, Türkiye.

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ABSTRACT

Aim: The neurological disorder known as normal pressure hydrocephalus (NPH), which has an unknown cause, may be treatable, and is defined by a clinical triad of symptoms. A phenomenon known as dementia refers to a decline in cognitive performance that goes beyond what may be anticipated from the typical effects of biological aging. The symptomatic similarity between these two diseases causes problems in diagnosis. The objective of our study was to compare the concentrations of IL-17A, IL-17F, IL-34, and CXCL13 in the cerebrospinal fluid (CSF) of patients with NPH and dementia for an informative laboratory diagnosis.

Methods: The study included NPH and dementia cases (n=7, n=5, respectively) taken from the patients's CSF sample by lumbar puncture (LP). The levels of IL-17A, IL-17F, IL-34, and CXCL13 were measured in the CSF of patients' with NPH and dementia by enzyme-linked assay (ELISA) and compared between the two different groups.

Results: There was no difference in age between the NPH and dementia groups (p=0.5). There was no statistically significant difference was found in IL-17A (p=0.7), IL-34 (p=0.9), and CXCL13 (p=0.2) in the inflammatory marker analysis in the CSF. The groups had a statistically significant difference in IL-17F (p=0.04).

Conclusion: IL-17F can be an important laboratory marker used in the differential diagnosis of NPH and dementia.

Keywords: NPH, Dementia, IL-17A, IL-17F, IL-34, CXCL13

Corresponding author: Şeyda Karabörk **E-mail:** seydaozsoy20@hotmail.com
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INTRODUCTION

Neurodegenerative disorders are characterized by a continuous, progressive loss of neuronal structure leading to functional and cognitive deficits. Much research suggests that neurodegeneration is related to neuronal loss, protein aggregation, and immune system dysfunction-neuroinflammation (1). Neurodegenerative disorders include multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), dementia, Parkinson's disease (PD), and normal pressure hydrocephalus (NPH). The etiopathogenesis of neurodegenerative disorders is heterogeneous: endogenous, genetic, and environmental. Therefore, the exact cause of neurodegenerative diseases is unknown (2-4).

NPH is a progressive onset syndrome characterized by gait disturbance, urinary incontinence, and cognitive decline, radiologically defined by ventricular dilatation, and clinical improvement after shunting (5). NPH is a treatable condition. Early diagnosis of NPH may be difficult due to neuroimaging and symptomatic similarity with other neurological disorders like dementia. Prompt and accurate diagnosis plays an essential role in the potential treatment of NPH. To prevent NPH from progressing to the neurodegenerative process, the current symptomatic diagnostic criteria of NPH should be improved by adding new specific biomarkers in CSF (5-8). Like NPH, the etiology of dementia is a multifactorial condition associated with environmental and genetic factors. It can be challenging to determine the etiology of dementia; however, this etiological diagnosis is critical as it facilitates treatment management and informs the patients and their families about the prognosis. There is no specifically defined biomarker for clinically diagnosed dementia, and new studies are needed to increase the reliability of the diagnosis. Recent studies have reported that inflammation plays a vital role in the neurodegeneration of dementia, and it has been shown that some of the markers measured in body fluids are associated with the severity and progression of the disease (9,10).

Cytokines and chemokines are primarily produced by a few different cells, in addition to white blood cells and leukocytes, in response to diverse stimuli in pathological and physiological situations, acting as neuromodulators in the nervous system to control neuroinflammation (11,12). The profile of CSF cytokines allows the exploration of pathogenic mechanisms of different neurological diseases and therapeutic approaches. Members of the IL-17 cytokine family (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F) have diverse biological functions, supporting protective immunity against many pathogens and driving inflammatory pathology during infection and autoimmunity. IL-17A and IL-17F are produced by CD4+, CD8+, and γδ T cells and various innate immune cell populations (13,14). IL-34 has been suggested to have an essential role in maintaining CNS homeostasis through its effects on different cell types, including neurons, microglia, and endothelial cells. Recent researchers have found increasing evidence that IL-34 contributed to the pathogenesis of neurodegenerative disease and autoimmune disorders (15,16).

CXCL13 is known as B-cell attractant chemokine 1 (BCA-1) or B-lymphocyte chemoattractant (BLC) due to its strong chemotaxis to B cells. Studies of CXCL13 in CSF have shown that it is elevated, mainly in association with CNS-specific infectious conditions. In addition, CXCL13 has emerged as a trending chemokine in recent research on neurodegenerative diseases (17,18).

Determining the levels of various biomarkers in CSF may represent underlying neuropathological changes in the brain and may be crucial in identifying potential etiological pathways. In line with this recommendation, the determination of an up-to-date CSF marker in the diagnosis of difficult-to-diagnose neurological diseases such as NPH and dementia is essential for selecting the appropriate therapeutic approach and monitoring the effectiveness of treatment. Therefore, our study aims to compare the concentrations of IL-17A, IL-17F, IL-34, and CXCL13 in the CSF of patients with NPH and dementia to strengthen the laboratory diagnosis in addition to the patient's clinical findings.

METHODS

Ethical consideration and study population

The study was approved by the Clinical Ethics Committee of the Bolu Abant İzzet Baysal University (Number of approval: 2023/12). Seven NPH patients and five dementia cases of similar age and sex distribution were included by the BAİBÜ İzzet Baysal Training and Research Hospital Neurology Clinics, Bolu. The patients were diagnosed following the international NPH guidelines: Guidelines for Management of Idiopathic Normal Pressure Hydrocephalus (19), and dementia using the National Institute for Health and Care Excellence: Guidelines (20). Table 1 summarizes the clinical characteristics of NPH and dementia. Written informed consent was obtained from patients. As part of the diagnostic process for NPH and dementia, the CSF samples were obtained from the NPH and dementia patients via sterile lumbar puncture (LP) from the interspaces of lumbar 1-5. The CSF samples were defrosted just once to aliquot them before analysis. All CSF samples collected up until the time of the investigation were properly preserved at -80°C. The absence of both CSF samples was an exclusion criterion.

Measurement of cytokines with ELISA

For ELISA analysis of CSF samples, we used human IL-17A and IL-17F (Elabscience, USA), IL-34 (Cloud-Clone Corp., USA), and CXCL13 (Euroimmun, Lubeck, Germany) ELISA kits, which have been previously confirmed for CSF samples. Results were expressed as picograms per milliliter (pg/mL) according to the manufacturer's recommendations. The manufacturer's recommendations served as the basis for defining the specificity and sensitivity of the cytokines (specificity: except in IL-17A cytokine measurements, in which cross-reactivity with human IL-17F was negligible, and non-cross-reactivity was observed).

Statistical analysis

Data were analyzed using the statistical package program IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) Descriptive statistics are presented as mean ± standard deviation (x±SD) and median (min-max); "n" corresponds to the number of cases. The normal distribution of the data of numerical variables was evaluated with the Shapiro-Wilk test since the sample size was small. For normally distributed data, an unpaired two-tailed T-test was conducted. For non-normally distributed data, the Mann-Whitney U test was performed. A p-value of <0.05 was considered statistically significant.

RESULTS

We compared CSF cytokine levels between the two groups in NPH (n=7) and dementia (n=5) patients in 12 CSF samples. The mean age of the patients with NPH and the dementia groups was 64 (±11) and 59 (±15) years, respectively, and there was no

Table 1. The clinical characteristics of NPH and Dementia

	NPH	Dementia
Clinical traits/features (According to DSM)	• Cognitive dysfunction • Urination problems/incontinence	Decreasing: • Complex attention • Executive functions • Learning and memory • Language • Perceptual motor functions • Social cognition
Diagnostic criteria	• Usual opening pressure for CSF • MRI modifications: Ventricular system enlargement with or without cortical modifications • After a CSF spinal tap, neurological problems are reversed.	• For etiological background; Vitamin B12 level, complete blood count, thyroid function tests, serum electrolytes, liver and kidney function tests, • For imaging; MRI and CT

*CSF: Cerebrospinal fluid; CT: Computer tomography; DSM: Diagnostic and statistical manual of mental disorders; MRI: Magnetic Resonance Imaging

Table 2. Comparison of mean and p-values of variables between groups

	Dementia (n=5) Mean (±SD) Median (min-max)	NPH (n=7) Mean (±SD) Median (min-max)	p value
Age (year)	59 (±15)	64 (±11)	0.50*
	58 (36-78)	68 (46-79)	
Gender	1 Female	2 Female	0.2°
	4 Male	5 Male	
IL-17A (pg/ml)	38 (±27)	76 (±84)	0.70∞
	48 (8-73)	48 (3-256)	
IL-17F (pg/ml)	5 (±2)	12 (±6)	0.04*
	5 (3-8)	10 (6-23)	
IL-34 (pg/ml)	4 (±1)	6 (±5)	0.90∞
	3 (2-5)	3 (3-16)	
CXCL13 (pg/ml)	10 (±7)	5 (±3)	0.20*
	11 (1-18)	4 (1-11)	

NPH: normal pressure hydrocephalus, ∞: Mann Whitney U test used, *: Independent sample t-test used, °: Chi-square used, p<0.05: there is a significant difference between the NPH and Dementia groups.

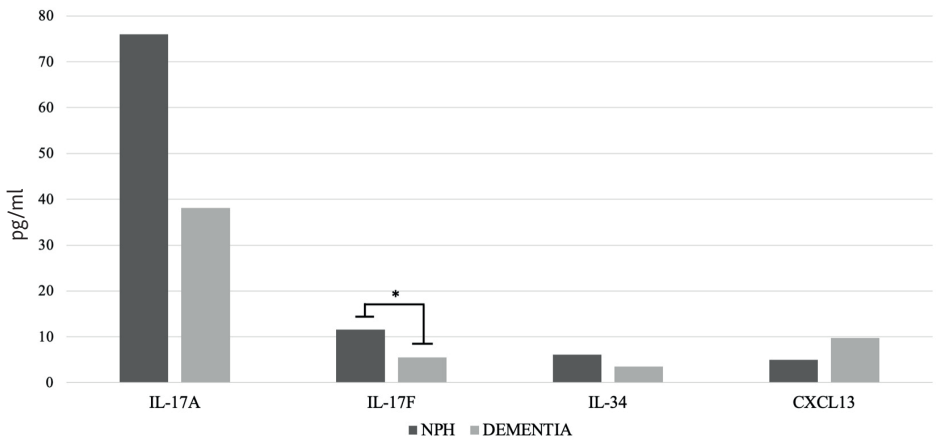

Figure 1. Cytokine and chemokine levels in CSF of NPH and dementia patients.

statistically significant difference between the two groups (p=0.5). In addition, there was no statistically significant difference between the groups regarding gender (p=0.2) (Table 2). In addition, there was no statistically significant difference between IL-17A (p=0.7), IL-34 (p=0.9), and CXCL13 (p=0.2) groups in the analysis of inflammatory markers in CSF. Contrary to the fact that there was no significant difference in IL-17A, IL-34, and CXCL-13 levels between the groups, IL-17 in CSF samples from NPH patients was statistically significantly higher than in the dementia group (p=0.04) (Table 2, Figure 1).

DISCUSSION

In this study, we found that IL-17F in CSF was high in dementia patients and no statistically significant difference was found between the CSF IL-17A, IL-34, and CXCL13 groups. We further revealed their clinical relevance in NPH patients, suggesting that different IL-17 family members may play different pathogenic roles in NPH.

Diagnosing neurological diseases can be challenging due to the overlapping symptoms, progressive nature, limited diagnostic tools, rarity, and patient variability, in spite of the fact that diagnosis of neurological diseases often requires a combination of physical examination, imaging, and laboratory tests. Nevertheless, detecting certain illnesses can be challenging because there are no conclusive diagnostic tests available. Therefore, in order to make an accurate diagnosis, healthcare professionals must do a comprehensive examination and order the necessary tests (21).

The symptoms of dementia and NPH can be identical, making diagnosis challenging because there are no distinct diagnostic tests or coexisting prerequisites for both neurological disorders. Healthcare professionals may employ a variety of diagnostic techniques, including lumbar punctures to test CSF pressure, brain imaging, and cognitive and gait assessments, to differentiate between NPH and dementia. Furthermore, a brief CSF drainage test may be performed in patients with suspected NPH to determine whether the removal of extra fluid improves their symptoms (6,10,19). Despite the need, the CSF biomarker profile in NPH and dementia has not yet been conclusively determined since IL-17, IL-34, and CXCL13-cytokines and chemokines that are now being assessed in the pathophysiology of neuroinflammatory diseases may direct the differentiation process between NPH and dementia.

IL-17F is essential for the immune system's reaction to a range of infections and inflammatory conditions. The brain's glial cells, which support and shield neurons, have also been linked to the regulation of IL-17F (13). According to recent research, there may be a connection between IL-17F and NPH, suggesting that it is produced in reaction to the accumulation of CSF (22). The development of NPH has been associated with abnormal glial cell function and IL-17F is a cytokine that contributes to this process by regulating glial cell activity. Moreover, it has been demonstrated that IL-17F stimulates the synthesis of matrix metalloproteinases (MMPs), which are enzymes that break down extracellular matrix proteins. MMPs play a role in the pathogenesis of NPH by damaging brain tissue and causing ventricular enlargement. While research on the active role of IL-17F in the development of NPH continues, there is increasing evidence indicating that IL-17F may also play a role in the disruption of glial cell functions and immune response in this process (13,22,23). There are two subtypes of IL-17, IL-17A, and IL-17F, with 50% homology. When literature data were evaluated, IL-17A and IL-17F were accepted as more potent inducers of inflammation than IL-17F, although they have similar biological properties (23). It has been demonstrated that IL-17F is a cytokine more involved in acute inflammation and produces more substantial neutrophil aggregation than IL-17A. However, it is known that the most prominent Th17-related cytokine in chronic inflammation is IL-17A, and studies report that IL-17A concentration increases, especially in Alzheimer's (23). Therefore, although IL-17A and IL-17F are homologous, it is appropriate to evaluate these two cytokines differently (14). In our study results, IL-17F showed a significant increase in NPH cases compared to dementia cases, while IL-17A showed a non-statistical numerical increase in NPH cases with similar homology. This is supported by the fact that CSF samples have been studied in the acute phase, confirming that NPH is an acute inflammatory disease.

Evaluating our results, IL-17F as in CSF examination may be a new diagnostic approach-biomarker for NPH and Dementia, which are difficult to differentiate in the acute phase. In addition, IL-17A, IL-17F, and IL-34 show a higher trend in NPH than in dementia in a numerically consistent manner without statistical significance, indicating that this pathway works in favor of NPH in the acute phase. CXCL13, another chemokine we evaluated in the study, is now known to be a prominent protein in Lyme neuroborreliosis (LNB) (17,18). Still, the low levels of CXCL13 in NPH cases may suggest that it can be used to exclude NPH Lyme neuroborreliosis. When we compare CXCL13 in

NPH and dementia cases, the high level of CXCL13 in the dementia group may suggest the coexistence of dementia and Lyme neuroborreliosis. We recommend that other serological diagnostic parameters be evaluated to exclude Lyme in patients with a pre-diagnosis of dementia.

It is a current approach that serum is not suitable for sample selection for the detection of neurological diseases and central tissues such as CSF are more diagnostic. In the 2014 study by Sosvorova et al., in which NPH cases were measured at pro and anti-inflammatory cytokines in CSF and plasma samples, it was concluded that there was not much change in plasma samples. However, cytokine levels increased significantly in CSF samples compared to the control group. According to the data obtained from the study, it was also stated that CSF samples could better show neurodegenerative changes in the brain and that specific cytokines could help clinicians diagnose NPH (7). In the review by Zhang et al., in which they compiled the markers in CSF samples of NPH patients, the markers in CSF samples of Alzheimer's patients were also mentioned because of the overlap/similarity in symptomatic and neuroimaging of NPH (6). The fact that our study was directly investigated in CSF samples proved these similar results and gave our study superiority.

The present data indicate that IL-17F may play a role in the pathogenesis of NPH. The level of IL-17F cytokine in CSF has the potential to be a specific biomarker to be used in the acute phase in the differential diagnosis of the two diseases in patients with NPH and dementia. This is especially important for NPH cases, progressing to dementia if not diagnosed early. In conclusion, this study has some limitations. The number of cases was few and the cases did not have clinical or biochemical parameters. For this reason, further studies should be conducted to examine the pathogenic role of IL-17F in NPH to reflect the underlying neuropathological changes in the brain and to reveal possible etiological mechanisms.

CONCLUSION

Based on our data, it is thought that targeting IL-17F as a biomarker may represent a potential therapeutic strategy in the early diagnosis and treatment of neurodegenerative diseases such as NPH and dementia. However, more research is needed to fully understand the mechanisms underlying the association between IL-17F and NPH and dementia.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (approval date 17/01/2023, number 2023/12). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ŞAT; Concept: ŞK; Design: ŞAT, ŞK; Data Collection or Processing: ŞAT, ŞK; Analysis or Interpretation: HÇ; Literature Search: ŞK, HÇ; Writing: HÇ. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

The effect of conventional physiotherapy and median nerve radiofrequency therapy on kinesiophobia in lumbar facet syndrome

Ferhat Ege[1], **Funda Çiçek Ege**[2]

[1]Department of Algology, Hatay Training and Research Hospital Hatay, Türkiye.
[2]Department of Psychiatry, Hatay Training and Research Hospital Hatay, Türkiye.

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ABSTRACT

Aim: This study was carried out to investigate the effect of conventional physiotherapy (CPT) and median nerve radiofrequency therapy (MNRFT) on kinesiophobia in patients with lumbar facet syndrome (LFS).

Methods: The sample of this study consisted of 60 patients over 18 with facet joint pain persisting for at least 3 months and unresponsive to medical treatment were included in the study. The patients were divided into CPT and MNRFT groups of 30 patients each according to the treatment they received. The patients were evaluated for pain severity, kinesiophobia, sleep quality, functional status, and depression both before the treatment and one month after the treatment using the Visual Analogue Scale (VAS), Tampa Scale for Kinesiophobia (TKS), Pittsburgh Sleep Quality Index (PSQI), Oswestry Disability Index (ODI) and Beck's Depression Inventory (BDI), respectively.

Results: There was a significant difference between the pre- and post-treatment VAS, PSQI, ODI, and BDE scores in both the CPT and MNRFT groups. Additionally, there was a significant difference between the pre- and post-treatment TKS scores in the RFT group, but not in the CPT group. There was no significant difference between the groups in any of the pre-treatment scores. There was also no significant difference between the groups in the post-treatment scores, except for the TKS scores.

Conclusion: The study findings indicated that MNRFT and median nerve blockade reduced kinesiophobia more than CPT.

Keywords: radiofrequency, kinesiophobia, physical therapy, facet joint, pain, depression, oswestry

Corresponding author: Ferhat Ege **E-mail:** dr.ege_ferhat@hotmail.com
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INTRODUCTION

Lumbar facet syndrome (LFS), which is likely to stem from the degenerative and traumatic disorders of the facet joint, presents with local and/or leg pain in the lower back. It has been speculated that in 15% of cases of chronic low back pain, the pain originates from the facet joint (1). LFS is characterized by regional pain radiating to the paravertebral region of the lower back and hip. The pain increases with prolonged sitting and standing, especially with the extension movement. Sensitivity emerges with pressure on the facet joint. There is no nerve dysfunction, hence the degenerative changes in the facets can be visualized with imaging methods (2). In the treatment of LFS, analgesics such as transcutaneous electrical nerve stimulation (TENS), physiotherapy applications such as superficial and deep heating modalities are beneficial in terms of minimizing the load on facets and discs and eliminating pain and muscle spasms. Patients with LFS may be taught proper waist posture that they can use especially during working and may be encouraged to perform regular exercises such as walking, swimming, and cycling as part of daily life activities. In cases where other treatment methods are not successful, facet denervation with radiofrequency thermocoagulation can be resorted (3). Pain can cause behavioral, cognitive, and physical fear responses. It is accepted that pain-related fear is the result of catastrophic thoughts and negative interpretations that pain is equivalent to the harmful sensory effect (4). The prevalence of kinesiophobia in conditions featuring chronic pain varies between 50 and 70% (5,6).

In light of the foregoing, the objective of this study is to investigate the effects of CPT and MNRFT on kinesiophobia in patients with LFS and to determine the early effects of CPT and MNRFT on depression and sleep quality.

MATERIAL AND METHOD

The population of this study consisted of patients over 18 who were diagnosed with LFS at the Hatay Training and Research Hospital Algology Outpatient Clinic. Written informed consent was obtained from each patient included in the study. The study protocol was approved by the Hatay Mustafa Kemal University Clinical Research Ethics Committee before the study was conducted (04/10/2021-26). The study was carried out in accordance with the principles set forth in the Declaration of Helsinki. Anamnesis of the patients who applied to the outpatient clinic was taken, and their physical examinations were performed. In the physical examination, the waist and lower extremity joint range of motion of the patients was evaluated, quadriceps muscle strength was checked, straight leg raise (SLR) test was performed, deep tendon reflexes (DTR) and pathological reflexes such as Babinski sign were evaluated. Sacroiliac and hip joint examinations were performed on all patients. Patients with suspected facet syndrome were included in the study, whereas those with coagulation disorders, pregnancy, mental disorders, malignancy, psychiatric disorders, sacroiliac, and hip joint pathologies, a history of back surgery, a history of the radiofrequency procedure, advanced (grade 3-4) spondylolisthesis defect in the lumbar vertebrae, spinal canal stenosis shown by magnetic resonance imaging (MRI), clinical findings consistent with radiculopathy with a significant spread of pain below the knee, a history of systemic inflammatory disease, advanced cardiac failure, pulmonary disease, and those treated with a physical therapy agent from the waist region in the past year were excluded from the study. Patients' bilateral lumbar radiographs and lumbar MRI scans taken within the past year were evaluated if available. Necessary examinations were requested for patients who did not have imaging examinations. Sixty patients included in the sample were divided into the CPT and MNRFT groups of 30 patients each according to the treatment they received. The patients in the MNRFT group were administered at least two levels of MNRFT according to the localization of pain followed by median nerve blockade. The patients in the CPT group were administered TENS and subjected to superficial heating with hot packs and deep heating with ultrasonography (USG). After the completion of the treatments, patients in both groups were given a home exercise program. The patients were evaluated before the treatment and at the 1st-month follow-up after the treatment. Demographic and clinical characteristics, including age, gender, height, weight, and body mass index (BMI, kg/m^2) of the patients in both groups were recorded. The patients in both groups

were evaluated for pain severity, kinesiophobia, sleep quality, functional status, and depression both before the treatment and one month after the treatment using the Visual Analogue Scale (VAS), Tampa Scale for Kinesiophobia (TKS), Pittsburgh Sleep Quality Index (PSQI), Oswestry Disability Index (ODI) and Beck's Depression Inventory (BDI), respectively. TKS, which was used to assess kinesiophobia, is a 17-item scale that assesses acute and chronic low back pain, fibromyalgia and musculoskeletal injuries and whiplash-related health problems. The Turkish version of the TKS, the reliability studies of which was completed, was used (7). The ODI is a 10-item questionnaire that assesses the functional status of low back pain (8). The BDI is a 21-item questionnaire that assesses the characteristic attitudes and symptoms of depression. The total BDI scores of 10 and above indicate depression (9).

Statistical analysis

The statistical analyses of the collected data were carried out using SPSS 21.0 (Statistical Product and Service Solutions for Windows, Version 21.0, IBM Corp., Armonk, NY, U.S., 2012) software package. The descriptive statistics obtained from the collected data were expressed as mean and standard deviation, minimum-maximum, frequency, and percentage values. The normal distribution characteristics of the continuous variables were analyzed using the Shapiro-Wilk test. Comparisons between the groups based on the normal distribution characteristics of the variables were carried out using Student's t-test and paired samples t-test. A p-value < 0.05 was considered statistically significant.

RESULTS

The distribution of sociodemographic and clinical characteristics of the 60 patients included in the is shown in Table 1 study by the treatment groups. The mean age of the MNRFT group was significantly higher than that of the CPT group ($p<0.05$). There was a significant difference between the pre- and post-treatment VAS, PSQI, ODI, BDE, and TKS scores in the MNRFT group ($p<0.001$) (Table 2). Similarly, there was a significant difference between the pre- and post-treatment VAS, PSQI, ODI, and BDE scores in the CPT group ($p<0.05$) (Table 3). On the other hand, there was no significant difference between the pre- and post-treatment TKS scores in the CPT group ($p = 0.348$) (Table 3). There was no significant difference between the treatment groups in the mean pre-treatment VAS, PSQI, ODI, BDE, and TKS scores ($p>0.05$) (Table 4). Similarly, there was no significant difference between the treatment groups in the mean post-treatment VAS, PSQI, ODI, and BDE scores ($p>0.05$) (Table 5). On the other hand, there was a significant difference between the treatment groups in the mean post-treatment TKS scores ($p=0.025$) (Table 5).

DISCUSSION

The findings of this study revealed a significant difference between the mean pre- and post-treatment TKS scores in the MNRFT group but not in the CPT group, and between the groups in the mean post-treatment TKS scores, but not in the mean pre-treatment TKS scores. In comparison, a meta-analysis of 122 studies, including 11 randomized and 13 observational studies, on the efficacy of injection or RF applications to the facet and its associated structures concluded that RF neurotomy and facet and medial branch blocks had good and moderate to good efficacy, respectively, in reducing lumbar facet pain, respectively, whereas that the intra-articular lumbar facet joint injection had limited efficacy (10). In a systematic review by Datta et al., it was determined that the evidentiary value of median nerve block (MNB) for facet syndrome

Table 1. Distribution of sociodemogprahic and clinical characteristics by the treatment groups.

Variables	MNRFT Group	CPT Group	*p* value
Age (year)	53.67±8.027	48.87±5.64	0.02
Length (cm)	163.6±11.270	166.83±9.30	0.194
BMI (kg/m^2)	29.19±3.97	25.52±3.31	0.043

Abbreviations: MNRFT: Median Nerve Radiofrequency Therapy, CPT: Conventional Physiotherapy

*chi-squared test (likelihood ratio for multi-span setups with few data)

Table 2. The comparison of mean pre- and post-treatment scale scores in the MNRFT group.

Assessment Tools	pre- or post-treatment	Mean ± SD	Min - Max	*p* value
VAS	pre-treatment	7.36 ± 1.62	4 - 10	**0,001**
	post-treatment	3.50 ±1.25	2 - 6	
ODI	pre-treatment	46.63 ±19.68	22 - 96	**0.001**
	post-treatment	27.46 ± 20.44	6 - 84	
TKS	pre-treatment	45.86 ± 7.48	34- 67	**0.001**
	post-treatment	39.83 ± 8.21	24 - 53	
PSQI	pre-treatment	6.033 ± 5.22	2 - 19	**0.001**
	post-treatment	4.96 ± 3.56	2 - 15	
BDI	pre-treatment	20.3± 3.14	4-34	**0.001**
	post-treatment	13.14±5.12	0-25	

Abbreviations: MNRFT: Median Nerve Radiofrequency Therapy, VAS: Visuel Analog Scale, ODI: Oswestry Disability Index, TKS: Tampa Kinesiophobia Scale. PSQI: Pittsburgh Sleep Quality Index, BDI: Beck's Depression Inventory

Table 3. The comparison of mean pre- and post-treatment scale scores in the CPT group

Assessment Tools	pre- or post-treatment	Mean ± SD	Min - Max	*p* value
VAS	pre-treatment	6.66 ± 1.74	4 - 10	**0,001**
	post-treatment	3.26 ±1.96	1 - 7	
ODI	pre-treatment	43.46 ±19.32	10 - 82	**0.001**
	post-treatment	29 ± 15.3	2- 58	
TKS	pre-treatment	44.43 ± 4.18	35- 51	0.348
	post-treatment	43.73 ± 4.20	36 - 53	
PSQI	pre-treatment	5.9 ± 3.79	1 - 15	**0.001**
	post-treatment	3.36 ± 2.29	1- 10	
BDI	pre-treatment	18,6± 4.21	0-41	**0.001**
	post-treatment	12.3±3.22	0-34	

Abbreviations: CPT: Conventional Physiotherapy, VAS: Visuel Analog Scale, ODI: Oswestry Disability Index, TKS: Tampa Kinesiophobia Scale. PSQI: Pittsburgh Sleep Quality Index, BDI: Beck's Depression Inventory

Table 4. The comparison of mean pre-treatment scale scores between the treatment groups.

Assessment Tools	MNRFT Group		CPT Group		*p* value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
VAS	7.36 ± 1.62	4 - 10	6.66 ± 1.74	4 - 10	0.114
ODI	46.63 ±19.68	22 - 96	43.46 ±19.32	10 - 82	0.532
TKS	45.86 ± 7.48	34- 67	44.43 ± 4.18	35- 51	0.384
PSQI	6.033 ± 5.22	2 - 19	5.9 ± 3.79	1 - 15	0.076
BDI	20,3± 3.14	4-34	18,6± 4.21	0-41	0.081

Abbreviations: MNRFT: Median Nerve Radiofrequency Therapy, CPT: Conventional Physiotherapy, VAS: Visuel Analog Scale, ODI: Oswestry Disability Index, TKS: Tampa Kinesiophobia Scale. PSQI: Pittsburgh Sleep Quality Index, BDI: Beck's Depression Inventory

Table 5. The comparison of mean post-treatment scale scores between the treatment groups.

Assessment Tools	MNRFT Group		CPT Group		*p* value
	Mean ± SD	Min - Max	Mean ± SD	Min - Max	
VAS	3.50 ±1.25	2 - 6	3.26 ±1.96	1 - 7	0.586
ODI	27.46 ± 20.44	6 - 84	29 ± 15.3	2- 58	0.743
TKS	39.83 ± 8.21	24-53	43.73 ± 4.20	36 - 53	**0.025**
PSQI	4.96 ± 3.56	2 - 15	3.36 ± 2.29	1- 10	0.059
BDI	13.14±5.12	0-25	12.3±3.22	0-34	0.449

Abbreviations: MNRFT: Median Nerve Radiofrequency Therapy, CPT: Conventional Physiotherapy, VAS: Visuel Analog Scale, ODI: Oswestry Disability Index, TKS: Tampa Kinesiophobia Scale. PSQI: Pittsburgh Sleep Quality Index, BDI: Beck's Depression Inventory

was between 1 and 2, and the evidentiary value of MNB and MNRFT, which were found to be effective in the treatment group, was 2. On the other hand, the efficacy of intra-articular injections was limited (11). Numerous studies have been conducted on the efficacy of physiotherapy in chronic low back pain (12-16). In one of these studies, in which superficial and deep heating agents were utilized along with TENS, Kulaber et al. measured the pain levels with VAS and determined that physiotherapy significantly reduced the pain (12). Şahin et al. randomized the patients with chronic low back pain into two groups. They administered physical therapy modalities, initiated a physical exercise program, and prescribed medical treatments to the first group, while only initiated a physical exercise program and prescribed medical treatments to the second group without administering physical therapy modalities (16). VAS and ODI scales were used to assess pain and functionality in order to determine the efficacies of the treatments applied to both groups. Consequently, they detected a significant reduction in the VAS and ODI scores in both groups, indicating a significant improvement in pain and functionality. However, the reduction in the VAS and ODI scores was more pronounced in the first group, which also received physical therapy modalities, than in the second group (16). In line with the literature, there was a significant reduction in the VAS and ODI scores in both the MNRFT and CPT groups included in this study. Accordingly, the mean pre-treatment ODI score, which was 43.26 in the CPT group with chronic low back pain substantially limiting daily life activities, decreased to 29 after the treatment, reflecting the reduction in pain and the improvement in functionality. Similarly, the efficacy of RFT on VAS and ODI scores has been shown in many studies (17-19). In parallel, there was a significant difference between the mean pre- and post-treatment VAS and ODI scores in the MNRFT group. Accordingly, the mean pre-treatment ODI score, which was 46.63 in the MNRFT group with chronic low back pain substantially limiting daily life activities, decreased to 27.46 after the treatment, reflecting the reduction in pain and the improvement in functionality. Various studies have reported higher PSQI total scores in individuals with chronic pain than in individuals without chronic pain and a moderate positive correlation between PSQI and VAS scores (20-23). Sleep disorders due to chronic pain can cause stress in daily life, difficulties in performing simple tasks, and memory impairment, all of which have a negative impact on quality of life (24). In line with the literature data, the analysis of the mean pre-treatment PSQI scores of the CPT and MNRFT groups (5.9 ± 3.79 and 6.033 ± 5.22, respectively) indicated that the sleep quality was insufficient in both groups. However, the significant difference observed between the mean pre- and post-treatment PSQI scores in both groups indicated that both treatments, i.e., CPT and MNRFT, positively affected sleep quality. There are studies investigating the factors affecting chronic low back pain and how patients' beliefs and behaviors are changed by the pain. The clinical studies conducted in this context have demonstrated that the fear of re-injury and movement due to pain, that is, "kinesiophobia", is very important in patients with chronic low back pain (25). Avoidance behavior makes sense in the acute period, as it can prevent further injury to the person. On the other hand, kinesiophobia, which is a reflection of avoidance behavior in the chronic period, leads to a vicious cycle of deterioration in daily activities,

disability, and mental problems, resulting in further pain (26). As in this study, studies available in the literature have shown that patients with chronic low back pain typically have high kinesiophobia scores (27-29). In a study of 80 patients, CPT resulted in a significant reduction in the TKS scores compared to the mean pre-treatment scores (30). In parallel, a significant reduction in TKS scores was observed in 265 patients with chronic neck, back and low back pain after the administration of a multidisciplinary rehabilitation program. In contrast, there was no significant difference between the mean pre- and post-treatment TKS scores of the patients who were administered CPT. The absence of a significant change in the mean TKS scores, despite the decrease observed in the mean VAS and BDI scores in the CPT group at the first month of follow-up, might be attributed to the lack of an accompanying physical exercise program, the gradual emergence of the benefits of CPT, and the gradual decrease in patients' pain. These findings indicated that the patients' fear of injury has persisted. Accordingly, it can be concluded that CPT alone does not have a sufficient effect on kinesiophobia. Thus, administration of CPT in combination with physical exercise programs may have a more pronounced effect on kinesiophobia. Unlike the CPT group, there was a significant difference between the mean pre- and post-treatment TKS scores in the MNRFT, which might be attributed to the rapid decrease in pain with MNRFT and MNB, thereby resulting in a decrease in negative thoughts originating from pain. With the decrease in the pain, the patient can overcome the fear of movement, and thus the paravertebral muscles can be strengthened more rapidly and pain relief can be achieved more easily. It has been stated that the strength of the lumbar paraspinal muscle decreases in patients with low back pain (31). Therefore, the strengthening of the muscles supporting the vertebral column will likely reduce the pain in these patients. Consequently, patients who spend the resting period without pain will be able to more easily break the vicious circle that inflicts continuous pain, mobilize earlier, and increase their exercise capacity.

The rapid reduction of pain in patients with high TKS scores indicates that patients can adapt quickly to physical exercise. In addition, there are studies suggesting that stress therapy as well as somatization therapy should be added to the treatment of chronic low back pain (32,33). As a matter of fact, a study of 100 patients reported a relationship between chronic low back pain originating from the facet joint and psychological factors such as general anxiety, somatization, and depression (34). General anxiety may cause a decrease in lumbar paraspinal muscle strength and an increase in pain in the long term, in parallel with an increase in kinesiophobia. The reduction in pain levels in the short term due to MNRFT treatment suggests that MNRFT treatment may also reduce anxiety in patients and their relatives. The reduction in stress for the patient's relatives may in turn contribute to a reduction in additional stress for the patient. All in all, it is likely that the reduction in pain levels in a short time as a result of MNRFT will contribute to the reduction in kinesiophobia.

The primary limitation of the study was its relatively small sample size. Secondly, considering that long-term follow-up data would have provided a broader perspective, the fact that the follow-up period was only one month may be considered another limitation of the study.

In conclusion, the study findings revealed that both CPT and MNRFT reduced the pain, depression levels, and ODI scores, and improved sleep quality in patients with chronic low back pain in the early period. However, there is a need for controlled studies with larger series to determine how long the positive effects of these treatments last. CPT did not have any significant positive effect on kinesiophobia, suggesting that a physical exercise program should be implemented alongside CPT to achieve the desired positive effect on kinesiophobia. In contrast to CPT, MNRFT significantly decreased kinesiophobia scores. The reduction in pain levels achieved in a short time with MNRFT translated into significantly lower kinesiophobia scores. The reduction in pain in a short time in patients with high TKS scores will likely increase patients' compliance with physical exercise.

Ethical approval

This study has been approved by the Mustafa Kemal University Non-invasive Clinical Research Ethics Committee (approval date 04.10.2021, number 26). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: FE; Concept: FE, FÇE; Design: FE, FÇE; Data Collection or Processing: FE, FÇE; Analysis or Interpretation: FE, FÇE; Literature Search:FE, FÇE; Writing: FE, FÇE. All authors reviewed the results and approved the final version of the article.

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RESEARCH ARTICLE

Correlation between uric acid/HDL ratio and total calcium score in coronary CT angiography

Muhammet Fatih Bayraktar

Department of Cardiology, Bolu İzzet Baysal Research and Training Hospital, Bolu, Türkiye.

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ABSTRACT

Aim: Coronary artery disease (CAD) is a common manifestation of cardiovascular disease (CVD). The identification of reliable biomarkers for early CAD detection and risk assessment is crucial for effective prevention and management. This article examines the correlation between the uric acid to HDL cholesterol ratio (UHR) and the total calcium score (TCS) obtained from coronary CT angiography (CCTA) in the assessment of CAD.

Methods: The study included 60 patients (34 males and 26 females) without endocrine diseases or relevant medications to ensure a homogeneous population. Blood samples collected after an eight hour overnight fasting were analyzed for laboratory parameters. CCTA was performed using a standardized protocol. The total calcium score was calculated using established methods.

Results: The analysis showed a significant positive correlation between UHR and TCS (r=0.479, P=0.0001). Patients with coronary artery plaque had significantly higher UHR values compared to those without it (p = 0.001).

Conclusion: These findings suggest that UHR could serve as a promising biomarker for predicting CAD presence and severity, although further research is necessary to validate its clinical utility in CAD diagnosis and management.

Keywords: coronary artery disease, total calcium score, uric acid to HDL cholesterol ratio

Corresponding author: Muhammet Fatih Bayraktar **E-mail:** fatih_bayraktar_1987@hotmail.com
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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and morbidity worldwide (1). Atherosclerotic plaque in coronary arteries is a common feature of coronary artery disease (CAD) (2). Effective prevention and treatment strategies depend on the identification of accurate biomarkers that can help early detection and risk stratification of CAD (3). The total calcium score (TCS) is typically identified by coronary CT angiography (CCTA). The presence and extent of calcified plaque are evaluated using specialized software, and the TCS is calculated based on the quantity and density of calcification (4). TCS can be calculated from CCTA images and it is a reliable predictor of CAD (5). TCS was firstly described by Arthur Agatston and it can be measured by Agatston score. It considers the size and density of the calcifications in the coronary arteries. The score is often divided into four categories: 0 (no calcium), 1-10 (minimum calcification), 11-100 (mild calcification), and 101-400 (moderate calcification) (6).

METHODS

Participants and study design

The study was a retrospective, cross-sectional study that was approved by the University Ethics Council with number 2023/141. The study comprised 60 patients who met the following criteria: having none of the endocrine disorders, taking none of these drugs: anti hypertensives, anti hyperlipidemics and anti gout medications. Patients having these diseases or using these drugs were excluded from the trial to create a homogeneous study population with few confounding factors.

Biochemical examination

Following an eight hour overnight fasting, blood samples were collected from each participant. An autoanalyzer was used to measure serum levels of glucose, uric acid, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), urea, and creatinine. The analyzer measures these biochemical parameters precisely and reliably, allowing for an accurate assessment of UHR. As previously published in the literature (7,8), UHR was calculated as UHR = HDL-C (mg/dL) / uric acid (mg/dL).

Total calcium score measuring

All subjects had CCTA in accordance with a defined imaging technique. Images were taken with a multidetector computed tomography (MDCT) scanner. TCS, reflecting of coronary artery calcification, was calculated using standard procedures. The Agatston scoring system was utilized to assess the amount and severity of coronary artery calcification. The total calcium score was obtained by summing the individual calcium scores of all calcified coronary artery lesions (9-11).

Statistical analysis

SPSS 20.0 statistical software (IBM Inc., Chicago, IL, USA) was used to analyze the data. Descriptive statistics such as means, standard deviations, and frequencies were determined to summarize the demographic and clinical features of the study population. The Spearman correlation coefficient was used to analyze the relationship between the UHR and the TCS. Adjustments were made as needed for potential issues such as age, gender, and other relevant factors. A p value equal or less than 0.05 was accepted as statistically significant.

RESULTS

This study involved 60 patients, 34 males and 26 females, to evaluate the relationship between UHR and TCS in CCTA. The mean age of the study population was 50.1 ± 13.8 years. Uric acid (5.2 ± 1.1 mg/dL), HDL-C (54 ± 12.8 mg/dL), HbA1c (5.6 ± 0.6%), and UHR (10.3 ± 3.9%) were the mean values of key variables (Table 1).

The primary goal of this study was to investigate the link between UHR and TCS. Spearman correlation analysis revealed a statistically significant positive connection ($r = 0.479$, $p = 0.0001$) between these two variables. There was also a significant association between the presence of coronary artery plaque and UHR ($r = 0.368$, $p = 0.003$) (Table 2).

Table 1. Patients' characteristics.	
Age (year)	50.1 ± 13.8
Gender	34 males/26 females
Uric acid (mg/dl)	5.2 ± 1.1
HDL -C (mg/dl)	54 ± 12.8
UHR (%)	10.3 ± 3.9
HbA1C (%)	5.6 ± 0.6
Smoking	Yes, n=25 No, n=35
Hypertension	Present, n=24 Absent, n=36
Diabetes Mellitus	Present, n=6 Absent, n=54

HDL-C: High density lipoprotein cholesterol, UHR: uric acid/HDL-C ratio

Table 2. Correlation of UHR with study parameters.		
	TCS	**Presence of Coronary Artery Plaque**
UHR		
r	0.479	0.368
p	0.0001	0.003

Furthermore, a significant difference in mean UHR was identified when comparing patients with and without coronary artery plaque. Patients with coronary artery plaque had a significantly higher mean UHR compared to those without plaque (13.2 ± 4.7% vs. 9.3 ± 3.2%, respectively) (p = 0.001).

DISCUSSION

In this study, we investigated the correlation between the uric acid to HDL-C ratio (UHR) and the TCS, as gauged by CCTA. The results elucidated a noteworthy relationship between these two parameters, suggesting a probable connection between elevated UHR and an increase in coronary artery calcification.

The observed correlation is consistent with previous research that probed the association between UHR and diverse cardiovascular risk factors and outcomes. For instance, Aktas et al.[12] identified a correlation between unregulated hypertension and elevated UHR, while Yazdi et al.[13] found a positive correlation between UHR and metabolic syndrome. These insights bolster the proposition that UHR may serve as a predictive marker for cardiovascular risk.

Moreover, UHR has been shown to predict metabolic syndrome in patients with type 2 diabetes mellitus (8). This information accentuates UHR's potential importance in pinpointing individuals with elevated susceptibility to metabolic disorders, which in turn have been tied to the onset of CAD.

Beyond the specific focus of our study on the connection between UHR and TCS, there has been wider research into the relationship between uric acid and coronary artery disease. For example, Mansiroglu et al.[14] examined serum uric acid levels and UHR in relation to coronary artery fistulae, highlighting their possible relevance in coronary artery anomalies. Additionally, Kaya et al.[15] revealed that serum uric acid levels could predict the extent and configuration of coronary artery atherosclerosis, as assessed by multidetector computed tomography. Li et al.[16] further revealed that UHR could be a predictive tool for the diagnosis of functionally significant coronary artery stenosis.

These collective findings suggest that UHR could be instrumental in determining the severity and clinical relevance of coronary artery disease, thus underscoring its potential utility in the broader context of cardiovascular health assessment. This study emphasizes UHR's potential utility as a prognostic marker in coronary artery disease. Nonetheless, we must evaluate the intricate relationship between uric acid, inflammation, and cardiovascular disease. Uric acid has been identified as a pro-inflammatory chemical that contributes to systemic inflammation and endothelial dysfunction, both of which are substantial risk factors for coronary artery disease. Elevated UHR levels may thus reflect an inflammatory condition, which contributes to coronary artery calcification (17,18). The study conducted by Kanbay et al.[19] which demonstrated that uric acid-induced inflammation and oxidative stress may contribute to cardiovascular disease, supports the connection between uric acid and inflammation. Furthermore, Krishnan et al.[20] discovered that greater blood uric acid levels were linked to a stronger inflammatory

response as evaluated by C-reactive protein. According to these findings, uric acid is not only a marker but also a possible mediator in the development of coronary artery disease. However, these elements were not addressed in the current study, and future research should focus on better understanding the function of uric acid and inflammation in the development of coronary artery disease.

The total calcium score derived from CCTA is a useful technique for measuring coronary artery calcification and the presence and extent of CAD (5). Our research contributes to the existing body of knowledge by revealing a substantial relationship between UHR and TCS. According to this correlation, an elevated UHR may indicate increased coronary artery calcification and, as a result, a higher risk of CAD.

It is critical to recognize that additional factors may play a role in the association between UHR and coronary artery calcification. For example, inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been linked to the severity of coronary calcium score (21-23). Furthermore, lipid ratios such as total cholesterol/HDL cholesterol and LDL cholesterol/HDL cholesterol have been investigated as predictors of coronary artery calcification (24). More research into these parameters and their potential interactions would provide a more complete picture of the relationship between UHR and coronary artery calcification.

The current study adds to the growing body of evidence suggesting a relationship between UHR and coronary artery disease. The study, however, has significant limitations, including a cross-sectional design and a small sample size. Furthermore, significant confounding factors such as age, gender, smoking status, and medication use were not taken into consideration in the study. As a result, larger sample sizes and adjustments for potential confounding factors are required in prospective studies to corroborate the findings of this investigation.

In conclusion, our study discovered an association between UHR and TCS in CCTA, implying that UHR may be a valuable biomarker for predicting the presence and severity of CAD. However, further research is required to validate our findings and to study the clinical value of the UHR in the diagnosis and treatment of CAD.

Ethical approval

This study has been approved by the Bolu İzzet Baysal University, Faculty of Medicine, Clinical Researches Ethics Commite (approval date 16/06/2023, number 267). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: MFB; Concept: MFB; Design: MFB; Data Collection or Processing: MFB; Analysis or Interpretation: MFB; Literature Search: MFB; Writing: MFB. The author reviewed the results and approved the final version of the article.

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RESEARCH ARTICLE

Measurement of cystic artery diameter by computed tomography in the diagnosis of acute cholecystitis

Seray Gizem Gür Özcan[1], **Nezih Zengin**[2], **Alperen Özdoğan**[2], **Doğukan Durak**[2]

[1]Department of Radiology, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Türkiye.
[2]Department of General Surgery, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Türkiye.

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ABSTRACT

Aim: The aim of this study is to measure the diameter of the cystic artery using computed tomography in patients undergoing emergency surgery for the diagnosis of acute cholecystitis, as well as to understand the role of cystic artery diameter in the diagnosis of acute cholecystitis, and to investigate its association with clinical data, laboratory data, and computed tomography findings.

Methods: A total of 187 patients admitted to the general surgery clinic between 2019 and 2023, comprising 123 individuals as the patient group and 64 individuals as the control group, were reviewed in terms of their radiological images, demographic data, and laboratory parameters. The patients' surgical records, laboratory parameters, and computed tomography scans taken during the diagnosis were investigated.

Results: The diameter of the cystic artery was measured, and a cut-off value of cystic artery diameter >1.9 mm was found to be sensitive and specific for the diagnosis of acute cholecystitis (AUC: 0.852, 94% sensitivity, 75% specificity, p <0.001, 95% confidence interval 0.792-0.899).

Conclusion: A cystic artery diameter >1.9 mm was found to be highly specific for the diagnosis of acute cholecystitis. This study suggests that the measurement of cystic artery diameter can be used as an additional criterion in the evaluation of computed tomography for the diagnosis of acute cholecystitis.

Keywords: acute cholecystitis, computed tomography, cystic artery

Corresponding author: Seray Gizem Gür Özcan **E-mail:** seraygizemgur@yahoo.com.tr
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INTRODUCTION

Abdominal pain is one of the most common reasons for emergency department visits worldwide (1). Acute cholecystitis (AC) accounts for 3-11% of patients presenting to the emergency department with abdominal pain (1). AC refers to inflammation of the gallbladder and can result from cystic duct obstruction (2), bacterial infection, and chemical stimulation (3). The most common cause is gallstones, accounting for 90-95% of all cases (4,5). Clinical, laboratory, and radiologic findings are used in the diagnosis of AC (6). Clinical findings include severe right upper quadrant pain, fever, tenderness, and a positive Murphy's sign (6). White blood cell count (WBC), C-reactive protein (CRP), and neutrophil count are often increased in laboratory parameters. Among the radiological imaging modalities, ultrasonography (USG) is commonly utilized as the initial and least invasive method due to its accessibility, and ability to effectively visualize the gallbladder lumen and stones (7). However, computed tomography (CT) has become the gold standard due to its ability to provide a clearer visualization of surrounding inflammation and a better understanding of accompanying complications (8). CT criteria for diagnosis include gallbladder wall thickness (GWT) (>4mm), pericholecystic fluid collection, increased gallbladder diameter (long axis ≥8cm, transverse axis ≥4cm), and linear density increase in parallel with inflammation in the pericholecystic fat tissue (8).

In this study, an increase in vessel diameter, which is one of the markers of acute inflammation, was investigated as an indicator for the diagnosis of AC on CT imaging. Currently, there is no study that measures the diameter of the cystic artery (DCA) on CT. There is one study available that measures hepatic artery velocity using ultrasonography (USG) (9). In a previous study conducted by Loehfelm et al., they hypothesized that acute inflammation leads to hyperemia in the gallbladder and adjacent liver, resulting in an increase in cystic artery flow velocity (9). The aim of this study is to measure the diameter of a cystic artery using a similar mechanism to determine whether it can be used as a diagnostic criterion in patients with acute cholecystitis and to determine a cut-off value accordingly.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and Turkish Ethical Standards reviewed and approved by the ethics committee of Health Sciences University Bursa High Specialization Training and Research Hospital (Date of approval: 05.07.2023 and No: 2011-KAEK-25 2023/07-24).

Patient population

Between September 2019 and December 2023, a total of 187 patients, including 123 individuals who underwent urgent surgery for AC as a patient group and 64 individuals who underwent elective surgery for cholelithiasis as a control group, were investigated.

The patients were retrospectively reviewed in terms of demographic data (gender, age, height, and weight) and CT scans from the hospital data system.

Inclusion criteria are: Patients aged 18 years or older; patients with a diagnosis of AC based on pathological findings; the presence of CT images, demographic data, and laboratory in the hospital system.

Exclusion criteria are: Patients with no contrast-enhanced Abdominal CT scans in the hospital system prior to surgery; patients with artifact-laden CT scans preventing the evaluation of the DCA; patients under 18 years of age.

Analyses of CT images

Abdominal CT scans were performed using a 128-slice multi-detector-row CT scanner (Toshiba Aquillion, Japan). Contrast-enhanced, thin-slice (1.25 mm slice thickness), and soft-tissue window abdominopelvic CT images were measured. The measured parameters were gallbladder transverse and cranio-caudal diameter, GWT, presence of stones in the gallbladder lumen, and pericholecystic inflammation were investigated. According to the Tokyo criteria, gallbladder transverse diameter (GTD) ≥4cm, cranio-caudal diameter ≥8cm, and wall thickness ≥4mm were considered positive signs of AC (8). The cystic artery, a branch of the right hepatic artery originating from the aorta (Figure 1),

was measured at its origin and recorded numerically in both groups by a single radiologist.

Statistical analysis

The IBM Statistical Package for the Social Sciences software (SPSS ver. 27 for Windows, Chicago, IL, USA) was used for all statistical analyses. The Kolmogorov-Smirnov test was performed to assess the homogeneity of distribution between groups. Mean values, standard deviations, and median values were calculated for normally distributed and non-normally distributed groups. The mean ages of both groups were compared using the t-test, and the homogeneity of distribution was examined using the independent samples test. The Mann-Whitney test was used to evaluate the difference in DCA between the groups. A cut-off value for DCA in the patient group was determined using Receiver Operating Characteristic (ROC) analysis. The correlation and mean values between blood parameters, CT findings, and DCA increase were analyzed using the independent samples t-test and the Mann-Whitney test. A p-value of <0.05 was considered statistically significant.

RESULTS

In this study, a total of 123 individuals (70 females - 56.91% and 53 males - 43.08%) in the patient group and 64 individuals (43 females – 67.18% and 21 males – 32.81%) in the control group were included. The mean age of the patient group was 57.33±16.01 years, whereas it was 51.36±13.95 years for the control group.

The mean DCA was measured 2.35±0.42 mm in the patient group and 1.86±0.34 mm in the control group. ROC analysis was performed to determine the cut-off value for the DCA as >1.9 mm (AUC: 0.852, 94% sensitivity, 75% specificity, p <0.001, 95% confidence interval 0.792-0.899) (Figure 2).

In terms of the cut-off for the DCA, patients were classified as group 1 with DCA >1.9 mm and control group 2 with DCA ≤1.9 mm. In the patient group, 116 patients (94.30%) had a DCA >1.9 mm, while only 16 patients (37.20%) in the control group. The patient group included 7 patients (5.70%) with a CAD ≤1.9 mm, while 48 patients (62.80%) in the control group.

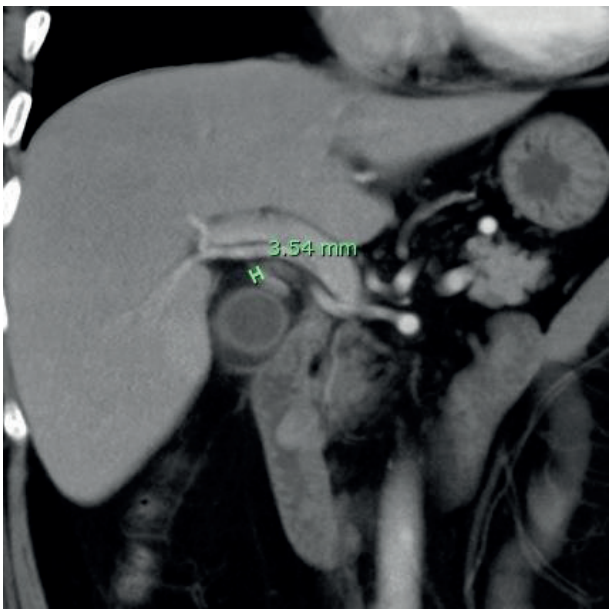

Figure 1. Measurement of cystic artery diameter in a 65-year-old male patient with pain in the right upper quadrant.

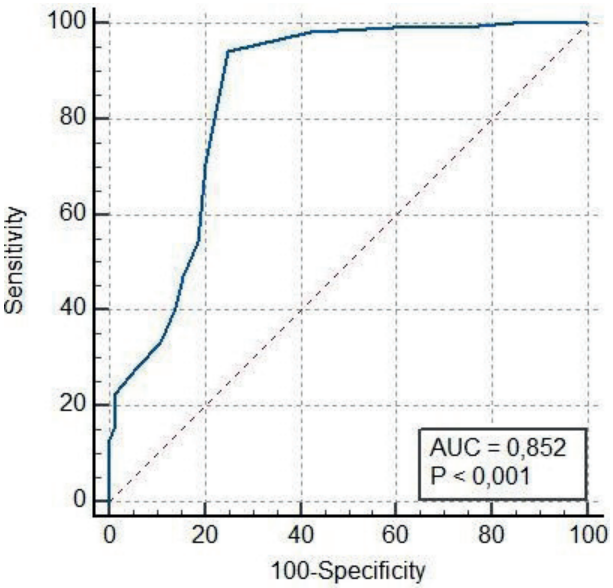

Figure 2. Receiver Operating Characteristic (ROC) analysis depicting the Area Under the Curve (AUC) for cystic artery diameter in the diagnosis of acute cholecystitis.

Detailed measurement parameters for group 1 and group 2 are given in Table 1.

According to Tokyo criteria, 70 patients (56.91%) with GTD ≥4 cm, 110 patients (89.43%) with gallbladder cranio-caudal length ≥8 cm, and 35 patients (28.46%) with GWT ≥4 mm were obtained. Furthermore, 105 individuals (85.36%) in the patient group presented evidence of adjacent inflammation.

Table 1. Mean values and standard deviations of blood parameters and parameters obtained from CT.

	Cutoff- Artery Diameter*	n**	Mean	Standard Deviation	Standard Error Mean
WBC					
Group 1	>1.9	132	12,71	4,86	423.7
Group 2	≤1.9	55	10,96	5,41	730.79
Lymphocyte					
Group 1	>1.9	132	25.46	10.81	8.77
Group 2	≤1.9	55	24.36	12.60	1.70
Neutrophil					
Group 1	>1.9	132	207.49	1.50	131.09
Group 2	≤1.9	55	68.10	15.19	1.91
CRP					
Group 1	>1.9	132	251.06	151.13	13.15
Group 2	≤1.9	55	65.13	105.56	14.23
AST					
Group 1	>1.9	132	120.23	251.13	21.86
Group 2	≤1.9	55	114.27	235.42	31.74
ALT					
Group 1	>1.9	132	121.59	250.16	21.77
Group 2	≤1.9	55	89.47	168.39	22.71
GWT					
Group 1	>1.9	132	3.29	1.24	0.11
Group 2	≤1.9	55	1.83	0.62	0.08
Gallbladder Length					
Group 1	>1.9	132	97.23	16.30	1.42
Group 2	≤1.9	55	78.42	16.94	2.29
GTD					
Group 1	>1.9	132	40.33	40.33	0.80
Group 2	≤1.9	55	29.44	29.44	1.04

WBC: White blood cell, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine amino transaminase, GWT: gallbladder wall thickness, GTD: gallbladder transverse diameter. * mm, ** number of patients.

DISCUSSION

According to the measurements performed, DCA is significantly higher in the patient group compared to the control group. Furthermore, a cut-off value for DCA in AC patients was determined with high sensitivity and specificity. DCA >1.9 mm was highly specific for the diagnosis of AC (94% sensitivity, 75% specificity). Moreover, DCA was higher in patients with complicated AC compared to the non-complicated group. However, statistical analysis could not be performed due to the small sample size of only 4 patients with complicated cholecystitis.

In this study, the measurement of DCA is proposed as an alternative criterion when the findings described in the Tokyo criteria (8) on CT imaging are insufficient for the diagnosis of suspected AC. A positive correlation was found between the significant increase in CT findings and the DCA in patients with AC. This study is the first to measure the DCA in patients with acute cholecystitis, and there is no existing study in the literature that measures the DCA using CT and determines a cut-off value for it. In this study, a similar mechanism was employed as in the study conducted by Loehfelm et al., which measured hepatic artery velocity in patients with acute cholecystitis (9). Loehfelm hypothesized that the increase in cystic artery diameter was related to the increased blood flow due to inflammation, sinusoidal obstruction, and venous congestion (9). In another study by Yamashita et al., contrast-enhanced abdominal CT scans in patients with acute cholecystitis revealed increased attenuation in the adjacent liver parenchyma to the inflamed gallbladder, which was attributed to hyperemia (10). A similar inflammatory mechanism was suggested in a study investigating appendicitis by Sirik et al., where the diameter of the ileocolic artery was measured (11). In their study, the diameter of the ileocolic artery was 3.79±0.7 mm in patients, while it was 2.75±0.31 mm in the control group ($p<0.01$) (11). In our study, there was a significant difference in DCA between the patient and control groups, with 2.35±0.42 mm in the patient group and 1.86±0.34 mm in the control group. The previous study by Sirik et al. attributed the increase in vascular diameter to an increase in blood flow due to inflammation, microvascular changes that permit extravasation of plasma proteins and leukocytes (11).

Acute cholecystitis is an acute inflammatory condition that typically results from obstruction of the gallbladder neck and cystic duct. Three mechanisms may trigger inflammation in the gallbladder, which is a luminal organ: obstruction and circulatory disturbance of the gallbladder, compromised blood supply leading to necrosis of the gallbladder wall, and chemical stimulation and inflammation due to the obstruction of the lumen. This condition is similar to bowel obstruction and associated infectious mechanisms, and its definitive treatment is surgery (12). Although the main cause of acute cholecystitis is cystic duct obstruction, not all cases of cystic duct obstruction may progress to acute cholecystitis. In addition to cystic duct obstruction, it has been suggested that there is ischemic necrosis and inflammation accompanied by obstruction in the branches of the cystic artery (12).

In this study, a significant increase in laboratory parameters such as neutrophils, WBC, and CRP in patients with AC, which positively correlated with an increase in DCA.

Despite the common diagnosis of AC based on clinical investigation and laboratory parameters, USG and CT scans are valuable tools in reducing misdiagnosis rates and protecting healthcare professionals from malpractice issues. USG is considered the gold standard for visualizing the lumen structure of the gallbladder and is usually sufficient for the diagnosis (9). However, CT imaging, including diameter measurements, assessment of accompanying tissue inflammation, and identification of complications, is an indispensable method (6). In a previous study referencing the study conducted by Van Randen et al., CT scans are more sensitive (73%) compared to USG in diagnosing AC (7).

The cut-off values in the Tokyo criteria are determined as 40 mm for the transverse diameter of the gallbladder, 80 mm for the craniocaudal length, and 4 mm for the GWT which were similar for this study. According to the Tokyo criteria, 56.91% of patients had enlarged transverse diameter, 89.43% had increased craniocaudal length, and 35% had increased in wall thickness (8).

Craniocaudal length, which is one of the indicators of hydrops, was significantly high compared to other

criteria. In addition to the relatively lower increase in transverse diameter and wall thickness, DCA is also proposed to be used as a supporting criterion. In a similar previous study, the peak systolic velocity of the hepatic artery was significantly higher in patients with AC (114 cm/s) compared to the control group (66 cm/s), moreover, it is stated that using the peak systolic velocity of the hepatic artery as a diagnostic criterion was rapid and easily measurable, and it was a more objective criterion compared to subjective examination findings such as Sonographic Murphy's sign (9). There are some limitations in this study. Firstly, our study is the pioneer study conducted in this context, and conducting a study with a larger patient population to determine a cut-off value would greatly contribute to our study and the literature. We look forward to further studies with a larger patient population and multicenter studies to introduce the DCA as a new criterion in the literature. Additionally, the number of patients with complicated AC in this study was limited, and although the DCA was higher in complicated cases compared to non-complicated cases, statistical analysis could not be performed due to the limited number of cases. Further studies including a larger quantity of complicated patients could contribute to determining a cut-off value in this regard.

CONCLUSION

In this study, DCA >1.9 mm was found as highly specific for the diagnosis of acute cholecystitis and, it is proposed that, alongside the established Tokyo Guidelines criteria for CT, the elevation in DCA may be regarded as an supplementary criterion for diagnosis.

Ethical approval

This study has been approved by the Ethics Committee of Health Sciences University Bursa High Specialization Training and Research Hospital (approval date 05.07.2023, number 2011-KAEK-25 2023/07-24). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: SGGÖ; Concept: SGGÖ; Design: SGGÖ, DD; Data Collection or Processing: NZ, AÖ; Analysis or Interpretation: SGGÖ, DD; Literature Search: NZ, AÖ; Writing: SGGÖ, DD. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Anaplastic thyroid carcinoma case series

Nadire Küçüköztaş[1], Tuba Taslamacıoğlu Duman[2], Selma Erdoğan Düzcü[3], Samed Rahatlı[4], Ümmügül Üyetürk[5]

[1]Department of Medical Oncology, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Türkiye.
[2]Department of Internal Medicine, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Türkiye.
[3]Department of Pathology, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Türkiye.
[4]Department of Medical Oncology, Faculty of Medicine, Başkent Univesity, Ankara, Türkiye.
[5]Department of Medical Oncology, Faculty of Medicine, Okan University, İstanbul, Türkiye.

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ABSTRACT

Aim: Among the endocrine malignancies, thyroid carcinoma (TC) is the most common. However, anaplastic TC accounts for 1-2% of these cancers. The aim of this study was to evaluate the demographic and pathologic features, treatments, and survival of patients with anaplastic TC.

Methods: Anaplastic TC patients who applied to our medical oncology clinics between 01.01.2012 -01.12.2018 were retrospectively evaluated.

Results: A total of 8 patients were included in the study. There were 4 female and 4 male patients with a median age of 68 (minimum 61-maximum 83) years. The initial complaint of all patients was a fast-growing swelling in the neck. Six patients had total thyroidectomy. Two patients had anaplastic TC with a differential TC. Six patients were at stage 4C. The most common site of metastasis was the lung (75%). Five patients had received a median of 3 (1-6) cycles of chemotherapy. Radiotherapy was applied to 7 patients. All patients except one died during the follow-up period. The median survival time of the patients was 3 (2-15) months.

Conclusion: Anaplastic TC, an aggressive tumor with high metastasic potential, has no effective treatment at present. Effective treatments are needed for this rare and aggressive disease. Developments in the molecular field are promising for the treatment of ATC.

Keywords: anaplastic thyroid carcinoma, overall survival, thyroid

Corresponding author: Nadire Küçüköztaş **E-mail:** dr.nadire@gmail.com
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INTRODUCTION

Thyroid cancers (TCs) are the most common endocrine malignancies, although they constitute 3-4% of all cancers annually (1). The incidence of TCs has increased dramatically in recent decades, due in large part to the identification of subclinical disease. Increase in the occurrence of TCs may be due to the widespread use of diagnostic methods, such as ultrasound, computed tomography, and fine needle aspiration biopsy (FNAB), which incidentally detect subclinical TCs (2).

TCs are classified into three main histological types. Differentiated TCs divided into papillary and follicular types constitute more than 90% of thyroid malignancies. Dedifferentiated TCs comprise poorly differentiated TCs and anaplastic TCs are rare (5 and 1%, respectively). In contrast, medullary TCs, which represent 5% of TCs, arise from parafollicular C cells (3).

Subclinical TCs have little negative effect on the overall survival of patients, but anaplastic TCs are very rare and also have unfavorable prognoses because of iodine/radioiodine refractoriness and high metastatic potential. The clinical management of anaplastic TC requires a multidisciplinary approach in which surgery, radiotherapy, and/or chemotherapy should be considered (4). Unfortunately, there is no effective treatment for this disease (5). This disease has an average survival time of 3–6 months from the time of diagnosis and is responsible for 50% of cancer deaths in patients with TC (6).

In this study, it was aimed to evaluate the demographic and pathological features of the patients diagnosed with anaplastic TC, the treatment protocols applied to the patients, and their survival.

METHODS

Patients with histologically confirmed anaplastic TC who applied to Bolu Abant Izzet Baysal Univercity and Başkent Univercity, Departments of Medical Oncology between 01.01.2012 -01.12.2018 were retrospectively evaluated. Inclusion criteria were age ≥18 years and evidence of anaplastic TC on histopathological examination of the primary tumor, lymph nodes, or distant metastases. Poorly differentiated TCs were excluded. Data regarding the symptoms, surgical procedures, histopathological findings, and other treatment methods of anaplastic TC cases were recorded. Tumor staging was determined according to the Tumor, Node, Metastasis (TNM) classification proposed by the American Joint Committee on Cancer (7). The data were analyzed using SPSS for Windows, version 15.0.

RESULTS

A total of 8 patients' data were reviewed during the study period. There were 4 female and 4 male patients with a median age of 68 (minimum 61-maximum 83) years. The clinical characteristics of the patients are shown in Table 1.

All patients initially had a firm palpable swelling in the neck, 87.5% of patients had pain, 50% of patients had dyspnea, and 25% of patients had dysphagia due to a tumor or compression or infiltration, respectively. A very small number of patients had accompanying symptoms such as weight loss, fatigue, and night sweats.

There was a history of thyroid nodules in 75% of our patients, 37.5% of whom had FNAB from thyroid nodules. Seventy-five percent of our patients had undergone total thyroidectomy operation.

In the pathology reports, 25% of them had anaplastic TC combined with differentiated TC, while 75% of them had only anaplastic TC. The median diameter of tumors was 7 (range 1.6-8) cm in the pathology reports. Three of the patients were giant cells and spindle cells in the tumor and also one of them was had wide necrosis areas and atypical mitosis (Figure 1). Thyroglobulin was positive in 25% of the patients. Thyroglobulin positivity was observed in anaplastic TC which was developed from papillary TC. Others were thyroglobulin-negative staining (Figure 2). Two patients had tumors limited to the thyroid gland at diagnosis and were classified as stage IVA. Six patients had distant metastases and were in stage IVC at the time of diagnosis. These patients with stage 4C had metastasis in the lung, and one of them (16.6%) had metastases in the sacral bone.

Table 1. The clinical characteristics of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age	61	65	83	66	82	70	62	72
Gender	Male	Female	Female	Female	Male	Female	Male	Male
Co-morbidity	CAD, HT	HT, DM	HT	HF	CAD, DM, HT	HT, DM	HT, DM, ESRD	BPH
Noduler goiter	No	Yes	Yes	Yes	Yes	Yes	No	Yes
FNAB	No	Yes	No	No	Yes	Yes	No	No
Initial compliants	Swelling, Pain, Dyspnea	Swelling, Dyspnea	Swelling, Pain	Swelling, Pain	Swelling, Pain, Dyspnea	Swelling, Pain, Dysphagia	Swelling, Pain, Dyspnea	Swelling, Pain, Dysphagia
Operation	Total thyroidectomy	No	Total thyroidectomy	Total thyroidectomy	No	Total thyroidectomy	Total thyroidectomy	Total thyroidectomy
Pathology	Anaplastic TC	Anaplastic TC	Anaplastic TC	Anaplastic TC+ Differentiated TC	Anaplastic TC	Anaplastic TC+ Differentiated TC	Anaplastic TC	Anaplastic TC
Tumor diameter	1,6 cm	2.2 cm	7 cm	8 cm	8 cm	7.5cm	7 cm	5 cm
Thyroglobulin	Negative	Negative	Negative	Positive	-	Positive	-	-
Morphology	Giant cell	-	-	-	-	Spindle cell	Giant cell	-
Stage	4A	4C	4C	4C	4C	4C	4C	4A
Metastasis	No	Lung	Lung	Lung+ sacral bone	Lung	Lung	Lung	No
Chemotherapy	CisEp	-	-	CaP	-	CisDx	CaP	Dx
Number of cycles	4	-	-	2	-	3	1	6
Palliative radiotherapy	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Palliative Supportive Treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OS (months)	6	2	3	3	2	6	2	15
Last status	Exitus	Exitus	Exitus	Exitus	Exitus	Exitus	Exitus	Alive

CAD: Coronary Artery Disease HT: Hypertension DM: Diabetes Mellitus ESRD: End Stage Renal Disease, BPH: Benign Prostatic Hypertrophy, HF: Heart Failure, FNAB: Fine needle aspiration biopsy, AnaplasticTC: Anaplastic thyroid carcinoma, Differentiated TC: Differentiated thyroid carcinoma, CisEp: Cisplatin Epirubicin, CaP: Carboplatin Paclitaxel, CisDx: Cisplatin Doxorubicin, Dx: doxorubicin, OS: Overall survival

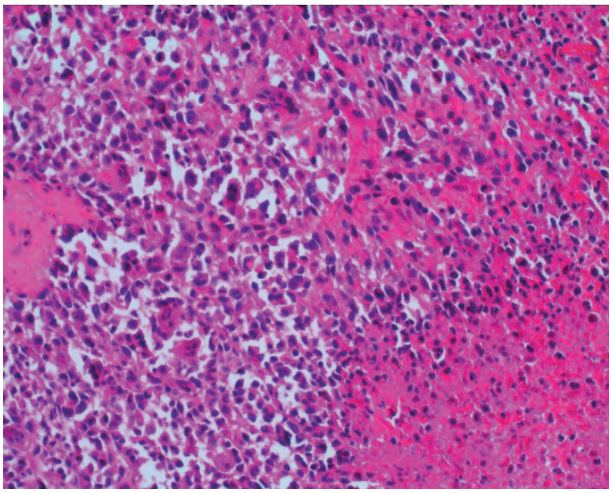

Figure 1. Pathological sign of multinuclear giant cells and necrosis of ATC.

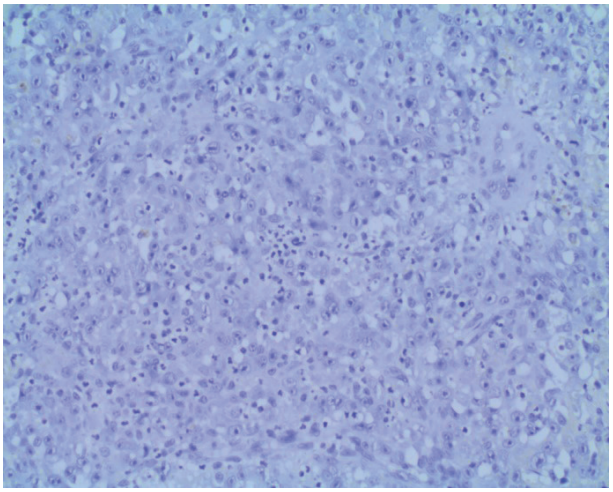

Figure 2. Thyroglobulin negative staining of ATC.

Two patients with stage IVA had taken cisplatin epirubicin (CisEp) and doxorubicin (Dx), 2 patients with stage IVC, 2 patients had taken Carboplatin Paclitaxel (CaP), 1 patient had taken CisDx, and 3 patients had not received chemotherapy. 87.5% of the patients had received palliative radiotherapy. All patients received palliative supportive care. 7 patients (87.5%) died during the study period. Contrary to expectations, one patient was alive. The median survival time of the patients was 3 (2-15) months.

DISCUSSION

The incidence of anaplastic TC typically peaks in the 6-7th decade of life, with a higher occurrence in women compared to men. This gender disparity may be attributed to the inherent biological characteristics of the cancer (5,8,9). In our study, all cases were over 60 years old, but the proportion of men and women was equal.

Although the complaints of the patients vary depending on the state of the in anaplastic TC, mass on the neck, neck pain, dispnea, dysphagia, and hoarseness due to rapidly growing mass in the thyroid are the most common complaints (8-10). The primary complaints of our patients were a rapidly growing neck mass and pain due to this swelling, and the other symptoms were also seen.

Although differentiated TC is diagnosed by FNAB from thyroid nodules, the diagnosis of anaplastic TC is based on typical clinical symptoms and is confirmed pathologically via surgical biopsy. The pathological appearance of anaplastic TC varies. Examining various sections by obtaining multiple slices from the tumor and employing immuno-histochemical (IHC) staining methods is recommended. Pathologically, the most common morphology of anaplastic TC is biphasic spindle and giant cells. Anaplastic TC has wide necrotic areas, surrounding invasion, angiotropism, high mitotic activity, and atypical mitosis (11,12). Sometimes it may be difficult to distinguish anaplastic TC from medullary TC, thyroid lymphoma, and other tumors that metastasize to the thyroid gland (13). IHC staining should be performed to make this distinction. We performed IHC staining to differentiate anaplastic TC from papillary TC, medullary TC, lymphoma, and malignant melanoma for our cases. Negative staining for thyroglobulin is expected in anaplastic TC, while differentiated TC is stained positive for thyroglobulin. However, thyroglobulin may stain positive in anaplastic TC which is developing from differentiated TC (14).

Coexisting thyroid diseases such as multinodular goiter and differentiated TC may be the risk factor for anaplastic TC (8,15,16). Iodine deficiency has also been involved in the etiology of anaplastic TC (17). Anaplastic TC develops from more differentiated TC

as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor gene. The mechanisms leading to the anaplastic transformation of differentiated TC are uncertain (18,19). There are studies that emphasize that anaplastic TC is seen more common in areas where endemic goiter is common. In a study conducted by Demeter et al, it was found that 76% of anaplastic TCs were found to have a history of thyroid disease, such as primary benign goiter or differentiated TC, and among these patients, 46% had a history of papillary TC (46%) (20). Eighty percent of anaplastic TC patients have a goiter history. As we mentioned above; in our patients as a rate of 75% of them had thyroid nodules and 25% of them anaplastic TC development was present on the ground of papillary TC. All anaplastic TCs are considered as stage IV. Stage IVA only in the thyroid, extrathoracic, and cervical lymphadenopathy in stage 4B and distant metastasis in stage IVC (7,21,22).

Anaplastic thyroid cancers (TCs) are frequently diagnosed at an advanced stage, posing challenges in identification during stages IVA and IVB due to their aggressive nature. Characterized by rapid growth, local invasiveness, and metastatic potential, anaplastic TC exhibits aggressive behavior with a substantial 90% local spread upon initial presentation. This local spread typically involves adjacent structures such as muscle and fat tissue around the thyroid, as well as the lymph nodes, larynx, trachea, esophagus, tonsils, large vessels, and mediastinum. Distant metastases are found in 15 to 50 percent of patients at the time of the diagnosis, and with a rate of 90%, the most common distant metastasis is the lung. In anaplastic TC, 5 to 15% of patients have bone metastasis (11). Similar to the literature, 75% of our patients had the most common metastasis in the lung and one of them had a metastasis in the sacral bone with lung metastasis.

Anaplastic TC is one of the most aggressive diseases (23). Death is due to complications of local and distant disease and/or therapy. Age, sex, tumor size, resectability, and tumor spread are important factors affecting the prognosis (23,24).

Despite multimodality therapies such as surgery, external beam radiation and systemic chemotherapy, in anaplastic TC, response rates to these therapies are <15% and long-term outcomes remain dismal, with no curative options for patients who have exhausted conventional therapies (25). Active surgical treatment is beneficial for patients with anaplastic TC, but the benefits of extensive surgery are limited. Locoregional resection may be necessary for the palliation of the airway or esophagial obstruction (26,27). 75% of our patients had palliative total thyroidectomy.

External beam radiotherapy (EBRT) or intensity modulated radiation therapy (IMRT) can be used as radiotherapy may increase survival in some patients (28,29). IMRT can also be used to reduce toxicity. External irradiation should be considered for skeletal metastases or brain lesions (3,10). In our study, radiotherapy was applied to the neck area of 7 patients by IMRT technique. One patient who had sacral bone metastasis was applied additional EBRT for bone metastasis and one patient could not receive radiotherapy. Unfortunately, systemic chemotherapy is unable to prolong the survival of patients with anaplastic TC; however, in certain cases, conventional treatments might improve symptoms and quality of life (4). Chemotherapy can be started in anaplastic TC after surgery and radiotherapy or if these treatments are not possible. Taxanes (paclitaxel or docetaxel) and/or anthracyclines (doxorubicin) and/or platins (cisplatin or carboplatin) are recommended (4).

Systematic treatments are consistently under exploration for anaplastic TC. In a study, a response rate of 29 percent was observed in patients with BRAF-mutant anaplastic TC who received treatment with the BRAF inhibitor vemurafenib (29). Another study focused on patients with rare malignancies, including anaplastic TC, characterized by BRAF V600E mutations. In this study, the BRAF inhibitor dabrafenib (150 mg twice daily) was administered in combination with the MEK inhibitor trametinib (2 mg once daily). These data indicate that tumor mutation screening should be performed in patients with anaplastic TC as it has the potential to transform the outcome for these patients (25). Larotrectinib may be another option in neurotrophic receptor tyrosine kinase (NTRK) gene fusion-positive anaplastic TC patients regardless of their age or the tumor type (30). Unfortunately, we were unable to implement these treatments. However, we think that these treatments based on genetic mutations could be considered for future patients.

Anaplastic TCs are rare, highly aggressive, undifferentiated tumors, and the median survival of these patients is 5 to 12 months and the 1-year overall survival rate is 20% to 40%. (27). In our study, the median survival of the patients was 3 months, except for one patient who had a survival of 15 months. The biopsy material from this patient with extended overall survival was attempted to be re-evaluated, but the pathology material couldn't be accessed as the pathology blocks were stored at a different hospital.

CONCLUSION

Treatment response rates and overall survival in ATC are poor, and there are very limited treatment options for patients who have exhausted standard multimodality treatments such as surgery, IMRT, and systemic chemotherapy. The effect of cytotoxic chemotherapy on survival and quality of life in ATC patients is limited. Effective treatments are needed for this rare and aggressive disease. Developments in the molecular field are promising for the treatment of ATC.

Ethical approval

This study has been approved by the Bolu İzzet Baysal University, Faculty of Medicine, Clinical Researches Ethics Commite (approval date 04/07/2023, number 2023/235). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: ÜÜ, NK; Concept: ÜÜ, NK, TTD; Design: ÜÜ, NK; Data Collection or Processing: NK, SED, SR; Analysis or Interpretation: TTD; Literature Search: ÜÜ, NK; Writing: ÜÜ, TTD. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Emergency department admissions and hemorrhage risk in patients on warfarin-containing drugs: a retrospective study

Oya Güven[1], **Merve Demireller**[2]

[1]Department of Emergency Medicine, Kırklareli University, Kırklareli Training and Research Hospital, Kırklareli, Türkiye.
[2]Department of Emergency Medicine, Kırklareli Training and Research Hospital, Kırklareli, Türkiye.

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ABSTRACT

Aim: Warfarin-containing medications are commonly prescribed anticoagulants for preventing and treating arterial and venous thromboembolism. As such, it may present a risk of hemorrhage. In this study, we aimed to investigate the occurrence of hemorrhage associated with warfarin, along with the contributing factors, by analyzing data obtained from emergency requests.

Methods: Patients who presented to the emergency department within one year and requested an INR analysis have been included. Among these patients, the demographic characteristics and risk factors of patients using warfarin and having signs of hemorrhage and those with increased INR levels and hemorrhage symptoms without using warfarin were studied retrospectively.

Results: Two hundred and seventy-three patients were included in the study. Two hundred and eleven patients (76.9%) were taking warfarin, 94.8% of whom had initiated the drug for cardiac reasons. INR value below 2.5 were found in 39.3% of these patients. Only 8.1% were identified with hemorrhage.

Conclusion: Warfarin poses a significant challengefor clinicians and patients due to its associated risk of hemorrhage. In this study, the risk of major hemorrhage was generally low.

Keywords: emergency department, hemorrhage, INR, warfarin

Corresponding author: Oya Güven **E-mail:** ersinoya@yahoo.com
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INTRODUCTION

Warfarin, which contributes significantly to the anticoagulant efficacy, is usually prescribed to cardiac and neurological patients. It is the medication of choice for patients with atrial fibrillation (AF), pulmonary embolism (PE), and stroke. Its effectiveness is measured by the International Normalized Ratio (INR). Its interaction with food is high. For example, yogurt bacteria effectively increase the production of vitamin K from the intestine. Therefore, it is inappropriate for warfarin users to eat too much yogurt (Table 1) (1). Warfarin inhibits the activation of vitamin K-dependent coagulation factors (Factors II, VII, IX, and X) and regulatory proteins (proteins C, S, and Z) (2). It typically demonstrates effectiveness within two to seven days. Because of its slow onset of action, it is not preferred in acute situations. Treatment begins with heparin (3). Genetic variation and the cytochrome p450 system metabolizing warfarin cause inter-individual variability and affect dose-response estimation (4,5). Consequently, the INR level is checked regularly.

Low molecular weight heparin (LMWH) should be initiated with warfain and stop after INR level reached 2. The INR rate for patients treated with warfarin varies depending on the underlying condition but is typically targeted at 2.0 to 3.5. An INR below 2.0 is associated with an increased risk of thromboembolism. An INR greater than 4.0 indicates an elevated risk for hemorrhage (6).

The most feared side effect of warfarin is hemorrhage. It can occur with minor trauma (even when brushing teeth) or spontaneously. It can be seen as a subcutaneous, intramuscular, ocular, gastrointestinal (GIS), or intracranial hemorrhage or hematuria, epistaxis, or menometrorrhagia. In addition, side effects such as dizziness, headache, nausea, vomiting (indicative of intracranial hemorrhage), and allergic reactions may develop. Consequently, patients on warfarin should be warned about potential problems and advised to adopt lifestyle precautions.

Systematic follow-up and patient education are essential for successful treatment. Although fatal hemorrhage is generally not observed, emergency departments are the first point of care for acute hemorrhage. In this study, the variety of hemorrhage observed in people on warfarin was examined by analyzing data from emergency department (ED) admissions.

MATERIALS AND METHODS

Study design

From January 1 to December 31, 2020, the records of 507 patients who applied to the ED for any reason and had their INR levels tested were analyzed. A total of 273 patients on warfarin and patients with INR>2.5 who were not on warfarin were included in the study. Patients diagnosed with acute hemorrhaging who were registered in the system but did not have an INR analysis request were excluded from the study. Demographic

Table 1. Drugs and foods that affect warfarin level.

Drugs that increase the effect of warfarin	Paracetamol, antibiotics (penicillin, cephalosporins, chloramphenicol, trimethoprim-sulfamethoxazole, ciprofloxacin, erythromycin, sulfonamides), amiodarone, cimetidine, cortisone, etoposide, fluconazole, lovastatin, quinidine, thyroid hormone, tricyclic antidepressants, vitamin E
Drugs that reduce the effect of warfarin	Anti-thyroid drugs, ascorbic acid, azathioprine, barbiturates, carbamazepine, oral contraceptives, spironolactone, teicoplanin, mercaptopurine, antihistamines
Foods containing high doses of vitamin K	Cabbage, spinach, chard, parsley, purslane, lettuce, chickpeas, liver, green tea, broccoli, Brussels sprouts, turnip, fish oil
Foods containing moderate doses of vitamin K	Asparagus, cauliflower, cheese, peas, coffee, avocado
Foods containing low doses of vitamin K	Red meat, chicken, eggs, milk, bread, butter, carrots, celery, corn, green beans, onions, rice, tomatoes, potatoes, peppers, peanuts, pumpkin, apples, oranges, strawberries

characteristics of the patients were recorded. If the patient was on warfarin, had signs of hemorrhage and/or complained of having a hemorrhage on admission, the reason for starting warfarin was also noted. In the case of hemorrhage, the factors affecting the condition were examined.

In this study, major hemorrhages were defined as intracranial or retroperitoneal bleeding requiring hospitalization, two or more units of blood transfusions, or those occurring in critical areas. Those classified as minor hemorrhage were skin hematoma larger than 25 cm^2, spontaneous epistaxis or gingival hemorrhage lasting longer than five minutes, any hemorrhage that did not require hospitalization, or any hemorrhage that required less than 2 units of blood transfusion (7).

Statistical analysis

Descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency and ratio, were calculated using SPSS 28.0. The Kolmogorov-Smirnov test was used to measure the distribution of variables. The Mann-Whitney U test was used to analyze independent quantitative data, and the Chi-square and Fischer tests were used to analyze independent qualitative data. $p<0.05$ was accepted as statistically significant level.

RESULTS

Of the total patients examined, 163 were women (59.7%) and 110 were men (40.3%). The mean age was 68.6±15.4 years. Of these, 211 were on warfarin, with an average age of 66.9±15.1 years.

The INR of 190 people (69.6%) was >2.5. and hemorrhages occurred in 24 patients (8.8%). Ten patients (41.7%) were found to have major hemorrhage, and five (29.4%) of these patients were on warfarin (Table 2). The most common symptom observed in patients, whose INR level were checked was cardiac (chest pain [20.5%]) (Figure 1).

In 200 patients (94.8%) on warfarin, the prescriptions were predominantly for cardiac reasons (94.8%), with neurological prescriptions following (2.8%), and pulmonary prescriptions constituting 2.4% (Table 3). In the warfarin group, the utilization of various medications (especially cardiac drugs such as calcium channel blockers and angiotensin-converting enzyme inhibitors) was significantly higher ($p<0.05$). In addition, cardiac symptoms (25.6%) were the most common reason for ED utilization in this group.

High level of INR was also detected in the non-warfarin group. The highest INR level among these patients was reported for patients on rivaroxaban (53.2%) and apixaban (11.2%), respectively. The other patients had a history of liver disease (4.8%), addiction

Table 2. Demographic characteristics of all patients.

		Min-Max	Median (Q1-Q3)	Mean±SD / n (%)
Age		18.0-96.0	71.0 (58-81)	68.6±15.4
Gender	Female			163 (59.7%)
	Male			110 (40.3%)
INR value	<2.5			83 (30.4%)
	>2.5			190 (69.6%)
Hemorrhage	No			249 (91.2%)
	Yes			24 (8.8%)
Minor hemorrhage				14 (58.3%)
Major hemorrhage				10 (41.7%)

SD: Standard Deviation, INR: International Normalized Ratio

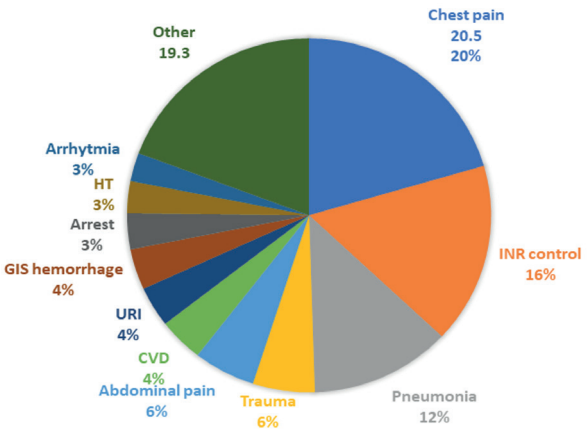

Figure 1. Reasons for admission and diagnosis in all patients.

CVD: cerebrovascular disease, stroke; URI: upper respiratory infection; HT: hypertension; INR: International Normalized Ratio; GIS: gastrointestinal; Other: headache, Covid pneumonia, urinary tract infection, gastritis etc.

(1.6%), and dabigatran use (1.6%). In other patients, it was impossible to determine the cause of the high INR (27.6%). No anticoagulant or antiaggregant drugs were found in the records of the patients not receiving warfarin. There was no significant difference in hemorrhage rates between the warfarin and non-warfarin groups (p >0.05). However, the incidence of prior hemorrhage was significantly higher in the warfarin group compared to the non-warfarin group (p <0.05). The incidence of minor hemorrhage was higher in patients with acute hemorrhage (70.6%) (Table 4).

Table 3. Outcomes for patients using warfarin.

		Median (Q1-Q3)	Mean±SD / n (%)
Age		68 (54-81)	66.9±15.1
Warfarin Usage	No		62 (23.1%)
	Yes		211 (76.9%)
Usage Period (Year)		3.0 (1-8)	4.4±3.2
Cause of onset of medication.	Arrhythmia		173 (82.0%)
	CVD		6 (2.8%)
	Valve Repl.		27 (12.8%)
	PE		5 (2.4%)

SD: Standard Deviation; CVD: Cerebrovascular disease, stroke; Valve Repl: Heart valve replacement; PE: Pulmonary embolism

The rate of hemorrhage was high (62.5%) in males. Patients with an INR higher than 2.5 who did not have hemorrhages were predominant (69.1%). The percentage of patients on warfarin who did not experience hemorrhages (77.9%) was higher than the rate of those who did. The most common presentation of hemorrhage was GI hemorrhage (41.7%), followed by epistaxis (25%) (Table 5).

Table 4. INR levels and occurrences of hemorrhage in warfarin users and others.

		Warfarin (-)		Warfarin (+)		p
		n	%	n	%	
INR value	<2.5	0	0%	83	39.3%	**0.000 x^2**
	>2.5	62	100%	128	60.7%	
Hemorrhage	No	55	88.7%	194	91.9%	0.429 x^2
	Yes	7	11.3%	17	8.1%	
Minor hemorrhage		2	28.6%	12	70.6%	0.058 x^2
Major hemorrhage		5	71.4%	5	29.4%	
Hemorrhage history	No	62	100%	188	89.1%	**0.007 x^2**
	Yes	0	0%	23	10.9%	

X^2: Chi-square test (Fischer test); INR: International Normalized Ratio

Table 5. Distribution of hemorrhagic patients.

		Hemorrhage (-)		Hemorrhage (+)		p
		Mean±SD / n (%)	Median (Q1-Q3)	Mean±SD / n (%)	Median (Q1-Q3)	
Age		68.7±15.7	71.0 (58-82)	67.2±13.0	67.5 (57-77)	0.440 m
Gender	Female	154 (61.8%)		9 (37.5%)		**0.020** X^2
	Male	95 (38.2%)		15 (62.5%)		
INR value	< 2.5	77 (30.9%)		6 (25.0%)		0.547 X^2
	> 2.5	172 (69.1%)		18 (75.0%)		
Warfarin usage	No	55 (22.1%)		7 (29.2%)		0.429 X^2
	Yes	194 (77.9%)		17 (70.8%)		
Previous hemorrhage	(-)	233 (93.6%)		17 (70.8%)		**0.000** X^2
	(+)	16 (6.4%)		7 (29.2%)		
Cause of application or diagnosis						
GIS		25 (10.0%)		10 (41.7%)		**0.000** X^2
Cardiac		70 (28.1%)		0 (0.0%)		**0.003** X^2
Respiratory		60 (24.1%)		1 (4.2%)		**0.025** X^2
INR control		45 (18.1%)		0 (0.0%)		**0.023** X^2
Neurological		28 (11.2%)		1 (4.2%)		0.282 X^2
Trauma		13 (5.2%)		2 (8.3%)		0.629 X^2
Urology		5 (2.0%)		4 (16.7%)		**0.004** X^2
Epistaxis		0 (0.0%)		6 (25.0%)		**0.000** X^2
Infection		3 (1.2%)		0 (0.0%)		1.000 X^2

SD: Standard Deviation, m Mann-Whitney U test / X^2 Chi-square test (Fischer test)

Complaints reported by patients experiencing hemorrhage

GIS: Gastrointestinal hemorrhage; Respiratory: Hemoptysis; Neurological: Intracranial hemorrhage; Trauma: Arrest (vascular injury and intra-abdominal hemorrhage), Rectus hematoma; Urology: Hematuria

DISCUSSION

This study showed that patients on warfarin generally did not have severe hemorrhage. Warfarin is frequently used in cardiology (8). Because the risk of heart disease increases with age, it is anticipated that people who use warfarin are more likely to be in the older population. This may account for the higher mean age of the study sample. Lindh et al.[9] found that men had a higher rate of hemorrhage. Similar results were observed in the present study. Genetic factors, lifestyle, and consistent drug use may have influenced this result.

Many studies have shown that the annual incidence of major hemorrhage in patients using warfarin ranges from 0.4% to 7.2% (10,11). Rates of minor hemorrhage can be up to 15.4% per year (11,12). This study determined that a history of warfarin use and a high level of INR did not make a significant difference in hemorrhage rates. According to the literature, many patients who develop bleeding experience minor bleeding (epistaxis). This study found that antihypertensive drugs were the most frequently used medications among patients taking warfarin. Therefore, epistaxis may have developed as a result

of high blood pressure. In addition, in the literature, the rate of major hemorrhage was low (29.4%) in the warfarin user group, and the most common type was GI hemorrhage (13). If the INR is below 1.5, surgery can be performed with minimal risk of hemorrhage. If the INR rate is between 4.5 and 10.0 and there is no hemorrhage, the warfarin dose should be skipped. If hemorrhage is detected, intravenous (IV) vitamin K, fresh frozen plasma (PFC), and prothrombin complex (PCC) concentrate should be administered (14).

Furthermore, it was observed that patients in this study self-reported the use of anticoagulant drugs. However, as the specific drug names were unknown, the INR levels were measured. Upon thorough examination of the prescription records, it was discovered that not all patients were prescribed warfarin. Moreover, the INR is routinely included in emergency tests, serving as a crucial indicator for emergency surgeries. In this study, the INR levels of patients who use anticoagulants other than warfarin, especially rivaroxaban, vary significantly. Therefore, it is appropriate for the emergency physician to request the INR level for all patients presenting with a situation that requires urgent medical intervention such as unconscious patients who have taking anticoagulant medication. This study also included data on the COVID-19 pandemic. In older patients with symptoms of COVID-19 or a history of nearly cured from COVID-19, INR levels may have increased without warfarin use since anticoagulants (LMWH) were added to their treatment.

The therapeutic and hemorrhagic risk thresholds for warfarin are closely aligned, posing a challenge for clinicians managing patients on this medication. However, the majority of patients in the warfarin group in this study exhibited no signs or history of hemorrhage. Consequently, the risk of hemorrhage associated with warfarin may be less pronounced than initially perceived. Hylek et al.[15] reported a 4.4% risk of major hemorrhage in patients with INR > 6, noting that there was a low level of risk because patients were followed up frequently. Çat et al.[16] found that the risk of minor and major hemorrhage increases as the level of INR increases. Similar findings were observed in this study. According to this result, although the number of patients on warfarin admitted to the ED is high, effective hemorrhage control could be achieved more efficiently when managed under the supervision of the physician who initially prescribed the drug.

Visser et al.[17] stated that metabolism would be impaired in patients with heart failure taking warfarin. They stated that due to the effect of the disease, hepatic veins will be affected, and drug metabolism will be impaired. Therefore, the INR level and bleeding risk will increase. The dose of warfarin may need to be monitored frequently in this group of patients. Most patients in this study were on warfarin for cardiac reasons, and the mean duration of use was more than three years. Therefore, the elevated level of INR may have increased as a result, but the risk of major hemorrhage have not increased.

Meeker et al.[18] found ineffective levels of INR in 49% of ED patients with a history of warfarin use. We also had similar results in our study. Still, since it was not possible to determine whether the patients discontinued the drug or whether other factors may have affected the INR level in these retrospective studies, generalizations cannot be made from the specified results.

Studies have shown that the effect of warfarin is higher and the risk of hemorrhage increases in the elderly (19,20). The main reason for this could be attributed to the existence of comorbidities and the concurrent use of multiple drugs. The risk of hemorrhage due to warfarin use is not very high in the literature. Different anticoagulants can be considered for elderly patients with poor drug compliance, those unable to control INR, and individuals dependent on others for medication management. Because of these factors, it may be more advisable to use warfarin in younger patients.

Contrary to common perception, warfarin may not be as high-risk as widely believed. The risks associated with its use can be minimized by advising patients on lifestyle changes, risk factor control, and regular INR monitoring.

Ethical approval

This study has been approved by the Kırklareli University Health Sciences Institute Ethics Committee (approval date 25/05/2021, number PR0330R0/10). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: OG, MD; Concept: OG; Design: MD; Data Collection or Processing: OG, MD; Analysis or Interpretation: OG; Literature Search: OG; Writing: OG, MD. All authors reviewed the results and approved the final version of the article.

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NORTHWESTERN MEDICAL JOURNAL

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RESEARCH ARTICLE

The relationship of uric acid levels with lipid parameters and body mass index in healthy individuals*

Nurcan Akbaş Güneş

Department of Family Medicine, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Türkiye.

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ABSTRACT

Aim: The relationship between hypertension, dyslipidemia, atrial fibrillation, obesity, and diabetes, which are cardiovascular risk factors, and a high serum uric acid level has been reported in the literature. However, the effectiveness of the adjustments to be made in uric asid levels on these diseases has not been clearly demonstrated yet. This study focuses on the relationship between serum uric acid levels and body mass index and lipid profile of healthy individuals.

Methods: Records of healthy volunteers obtained form the Family Medicine outpatient clinic were reviewed. Body mass index, serum uric acid, low-density lipoprotein, high-density lipoprotein, total cholesterol and triglyceride levels were analyzed retrospectively.

Results: Data from a total of 126 participants (90 female [71.4%], 36 male [28.6%]) were examined. Serum uric acid levels were correlated with body mass index (p=0.000, r=0.571) and serum triglyceride levels (p=0.001, r=0.397). No correlation was found between serum uric acid and lipoproteins and total cholesterol.

Conclusion: This study found that increased serum uric acid levels are associated with increased body mass index and increased serum triglyceride levels. Additionally, serum uric acid levels were higher in men. We recommend the routine assessment of uric acid levels during periodic health examinations.

Keywords: Body mass index, triglyceride, uric acid

Corresponding author: Nurcan Akbaş Güneş **E-mail:** drnurak@hotmail.com
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INTRODUCTION

Uric acid (UA) is the end product of the catabolism of adenosine and guanosine nucleotides (1). In recent years, the acceptance of UA levels as an independent risk factor for cardiovascular diseases has been discussed. Studies have found that elevated UA levels are associated with comorbidities such as hypertension, atrial fibrillation, dyslipidemia, coronary artery disease, obesity, and diabetes (2). It has also been shown that UA is associated with mortality in all patients with coronary artery disease (3). There are studies in the literature stating the opposite of these studies (4).

Hyperuricemia is defined as higher than 6.8 mg/dL, and as it rises, urate crystals begin to accumulate (5). European guidelines recommend UA level as ≤ 6 mg/dL (6). Although elevated UA levels are most commonly associated with gout disease, it has also been associated with hypertension, vascular diseases, renal disease, and cardiovascular events. UA crystals accumulate in the urinary tract and human tissues and cause diseases. In addition, UA has an antioxidant and pro-inflammatory mechanism of action (7).

Asymptomatic hyperuricemia is a high (>6.8 mg/dL) UA level without signs of crystal deposition disease (8). Although asymptomatic hyperuricemia is not considered a disease, it is considered a predisposing factor (9). The need for treatment and whether it can reduce the risk of comorbidity have not been clarified yet (10,11).

In this study, we aimed to evaluate the relationship between UA levels and body mass index (BMI), triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol levels in healthy individuals.

MATERIAL AND METHODS

Study design

The necessary permission was obtained from the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (2020/284) for our study. We designed this study as a cross-sectional study.

One hundred and twenty-six healthy participants who applied to the family medicine outpatient clinic of Izzet Baysal Training and Research Hospital between October 2019 and March 2020 were included in the study. Patients with comorbidities requiring continuous medication were excluded from the study.

Height and weight serum uric acid levels measured after 12 hours of fasting, LDL, HDL, total cholesterol, triglyceride levels, and other hematological parameters were evaluated retrospectively. Body mass index (kg/m^2) was calculated by dividing weight (kg) by the square of height (m^2).

Statistical analysis

SPSS version 25.0 was used for the statistical analysis of the data. Arithmetic mean ± standard deviation was calculated for numerical data. Categorical data were expressed as a percentage (%). The Mann-Whitney U test and t-test were used for statistical evaluation. P-values less than 0.05 were considered as statistically significant.

RESULTS

A total of 126 healthy individuals were included in our study. Mean age of the participants was 46.98±12.86. 28.6% (n=36) of the participants were male and 71.4% (n=90) were female. The UA levels were found to be higher in men than in women, and a statistically significant relationship was found (p=0.013) (Table 1).

The mean BMI values of the participants was 28.05±6.68 kg/m^2 (min: 16.00- max: 47.47). The mean UA levels was 5.21±1.19 mg/dL (min: 2.60- max: 8.60). The distribution of other hematological parameters are shown in Table 2.

We found a significant, positive correlation between BMI and UA (p=0.000, r=0.571). A significant correlation was found between UA levels and triglyceride levels (p=0.001). The relationship between UA levels and other parameters is shown in Table 3.

Table 1. UA levels and gender assessments

	Gender	n	Mean± Standard Deviation	p
UA (mg/dL)	Male	36 (%28.6)	5.76±0.97	0.013
	Female	90 (%71.4)	5.00±1.21	

*UA: Uric acid

Table 2. Minimum, maximum values and mean±standard deviations of age, BMI, and other hematological parameters of the participants

	Minimum	Maximum	Mean± Standard deviations
Age	18	73	46.98±12.86
BMI (kg/m^2)	16.00	47.47	28.05±6.68
Glucose (mg/dL)	76	164	99.00±15.81
Urea (mg/dL)	7	26	12.54±3.587
Creatinin (mg/dL)	0.40	1.70	0.71±0.19
AST (U/L)	11	35	18.65±4.58
ALT (U/L)	6	47	16.16±7.835
LDL (mg/dL)	40	219	132.73±41.48
HDL (mg/dL)	27	70	47.95±10.60
Triglyceride (mg/dL)	46	307	146.56±64.24
Total Cholesterol (mg/dL)	88	315	207.98±46.02
Vit B12 (ng/L)	93	519	222.37±92.624
Ferritin (mg/dL)	3	235	38.46±41.45
UA (mg/dL)	2.60	8.60	5.21±1.19
Hemoglobin (g/dL)	9.7	17.4	14.05±1.47
Neutrophil (K/uL)	1.76	6.99	4.03±1.28
Lymphocyte (K/uL)	0.87	4.97	2.44±0.72
NLR	0.70	3.94	1.73±0.62
MPV (fL)	8.10	13.60	10.47±1.01

*BMI: Body Mass Index, UA: Uric acid, NLR: Neutrophil/ Lymphocyte Ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MPV: Mean Platelet Volume

DISCUSSION

It has not been clarified whether increased levels of UA is a risk factor for cardiovascular diseases (2). Studies have found that hyperuricemia increases when BMI increases, and that UA elevation and weight gain show parallelism (12). A study conducted in patients with chronic kidney disease showed that BMI, glucose levels and UA levels are related (13). Hikita et al. emphasized that both total and visceral fat mass and UA levels are closely related (14). Our results are similar to the literature. Hyperuricemia is detected before obesity and diabetes in most cases, therefore it was emphasized that patients with high UA levels should be followed very closely and treatment should be started early.

A study found that there was a significant and positive correlation between UA levels and BMI in men (15). In another study, UA levels were found to be higher in men than in women, and it was stated that hyperuricemia

Table 3. Evaluation of UA levels and BMI and other parameters

		Uric acid
BMI	r	0.571
	p	**0.000**
NLR	r	0.003
	p	0.980
MPV	r	-0.056
	p	0.662
LDL	r	0.117
	p	0.362
HDL	r	-0.085
	p	0.508
Triglyceride	r	0.397
	p	**0.001**
Total Cholesterol	r	0.210
	p	0.099

* UA: Uric acid, BMI: Body Mass Index, NLR: Neutrophil/ Lymphocyte Ratio, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MPV: Mean Platelet Volume

can be considered among the indicators of metabolic syndrome (16).

In a study evaluating all age groups, it was shown that men have higher UA levels than women and that UA levels decrease with increasing age (17). In our study, UA levels were found to be higher in men than in women. A comparison based on increasing age was not included in our study. Studies have suggested that the reason for this gender difference may be estrogen, which induces UA excretion in women (18). The majority of the participants were in the reproductive period in our study and this may have caused it.

In a study evaluating the UA levels in Obstructive sleep apnea syndrome (OSAS) patients, it was found that as the severity of the disease increased, UA levels increased (19). It has been stated that UA levels should be evaluated as an independent risk factor in patients with non-alcoholic liver disease (20). Another curiosity is the relationship between different co-morbidities and the nature of their relationship.

One study showed that as HDL cholesterol levels decrease, UA values increase, and as total cholesterol and triglyceride levels increase, UA values increase (14). There are also several studies showing the relationship between high triglyceride levels and UA levels (13,21). The results of these studies are similar to those of our study. In another study, no relationship was found between UA and lipid levels. Many studies support the association between UA levels and cardiovascular risk. Nevertheless, the optimal approach to manage UA levels and their impact on comorbidities remains uncertain (10). Further studies involving larger populations are needed to provide clarity in this regard.

The main limitation of our study is the small sample size. Another limitation is that our study is planned cross-sectionally and performed in a single center, and the results cannot be generalized. Prospective studies with larger populations are needed.

CONCLUSION

In this study, we found that serum UA levels were positively correlated with BMI and triglyceride levels. We found that UA levels in men were higher than in women. We think that UA elevation should be evaluated during the periodic health examinations.

Ethical approval

This study has been approved by the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (approval date 24.11.2020, number 2020/284). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: NAG; Concept: NAG; Design: NAG; Data Collection or Processing: NAG; Analysis or Interpretation: NAG; Literature Search: NAG; Writing: NAG. The author reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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NORTHWESTERN MEDICAL JOURNAL

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CASE REPORT

Incidentally discovered extrauterine migration of a Lippes loop: should we let it stay?

Ayşenur Buz Yaşar[1], **Emine Dağıstan**[1], **Oktay Halit Aktepe**[2]

[1]Department of Radiology, Research and Training Hosptial, Abant Izzet Baysal University, Bolu, Türkiye.
[2]Department of Medical Oncology, Research and Training Hosptial, Abant Izzet Baysal University, Bolu, Türkiye.

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ABSTRACT

Intrauterine devices (IUDs), a form of long-acting reversible fertility control, are often preferred for preventing pregnancy. The Lippes loops, made of plastic, are inserted into the uterus via the cervix, fitting into the uterine cavity. The non-medicated (inert) structure of the loop allows for long-term IUD use. Uterine perforation and translocation of the IUD are the most threatening complications. In this case report, we present an asymptomatic 79-year-old woman with a forgotten IUD that migrated into the abdominal cavity and was discovered during her follow-up for lung cancer.

Keywords: Lippes loop, Intrauterine devices, Intrauterine device migration

INTRODUCTION

An intrauterine device (IUD) is a small plastic and copper material inserted into the uterine cavity and protects against pregnancy (1). The Lippes loop is a primitive form of IUD, which was introduced in the early 1960s by Jack Lippes as a contraceptive method (2). The double-S shaped polyethylene loop can be easily placed into the uterine cavity (3). The Lippes loop lost popularity and was replaced by other copper-containing contraceptive devices in the 1980s (2,3). Lippes loops do not contain bioactive components and their main mode of action is to block fertilization and implantation by creating a sterile inflammatory response. Prolonged use of the Lippes loop is common; however, it may cause complications including bleeding, infection, perforation of the uterus, and translocation of the Lippes loop into the abdominal cavity, as observed in our case (3-6).

CASE REPORT

We present a case of an intrauterine contraceptive device that migrated to the abdominal cavity without causing any complaint. The patient was a 79-year-old Turkish woman with a history of wedge resection for lung adenocarcinoma, who also received radiation therapy and erlotinib. During her follow-up,

Corresponding author: Ayşenur Buz Yaşar **E-mail:** aysenurbuz@gmail.com
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abdominothoracic computerized tomography (CT) scan revealed a retained and translocated double S-shaped loop in the abdominal cavity incidentally (Figure 1). The patient's medical history included seven pregnancies and one miscarriage, with menopause occurring 38 years ago. The IUD was inserted 53 years ago, following her last birth in 1970. A retrospective review of past medical records and images revealed that the IUD was in a similar position in the lumbar spine X-ray obtained four years ago and an erect posteroanterior (PA) abdomen X-ray acquired a year ago. She was symptom-free during the entire period. The patient consulted with both a general surgeon and a gynecologist four years ago. She refused surgical intervention, and opted to attend regular physical examinations.

DISCUSSION

The primary effect of different types of IUDs is to prevent fertilization by inducing an inflammatory response that disrupts the uterine environment (7,8). Lippes loops are non-medicated IUDs that are cost-effective, easy to install, and do not need to be replaced regularly (2,3,6). IUD is recommended to be removed after menopause, however, Lippes loops can be left for an extended time if it is not causing any complaint (2,3,6). Our patient had forgotten about the Lippes loop and reported that she had been symptom-free for many years. The most common complications of IUDs are pelvic infections, increased menstrual bleeding, pain, expulsion, and perforation of the uterus. Uterine

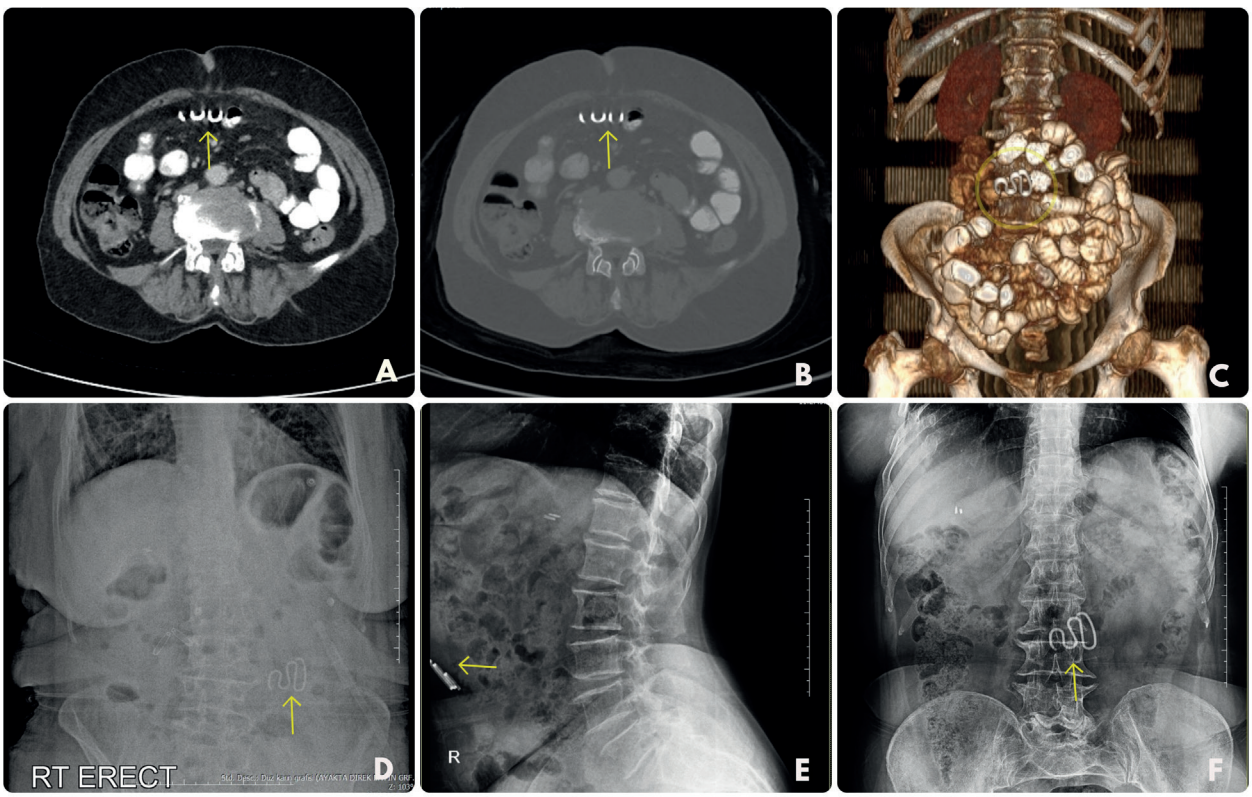

Figure 1. Images A and B are axial CT images abdomen window and bone window respectively and image C reveals a volume-rendering CT image. Image D is a PA Erect abdomen X-ray obtained one year prior to CT scan, images E and F are lateral and PA lumbar spine X-rays four years prior to CT scan. The lippes loop is indicated by an arrow or a circle in each image.

perforation is the most dangerous complication of all, often occurring at the time of insertion, particularly during the puerperium (4,9). The incidence of IUD migration is 1-4 cases per 1000, depending on the degree of myometrial penetration classified as partial or complete (3,4). The duration of retained uterine devices ranged from 22 to 50 years according to a study conducted by Bharathi et al (3). In our case, the Lippes loop was inserted 53 years ago, and according to previous images of the patient, IUD was outside of the uterus for at least four years without complaints. The low perforation rates might be associated with the misdiagnosis of complications (6). Fifty-three years of use of the Lippes loop, and a history of at least four years of extrauterine migration had no negative effect on the patient's health. The concerns about the safety of the Lippes loop may warrant reconsideration in light of this particular case, and it could be avisable to evaluate the necessity of surgical interventions.

Ethical approval

Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: OHA; Concept: ABY; Design: ABY, ED; Data Collection or Processing: ABY; Analysis or Interpretation: ABY, ED; Literature Search: ABY, OHA; Writing: ABY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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