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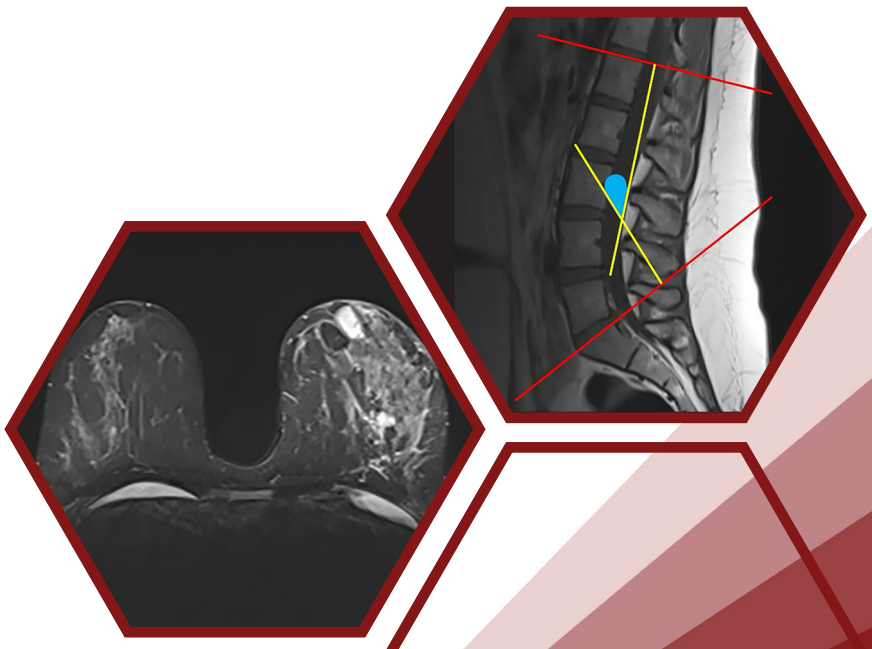

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Research Article

Correlation of Antenatal and Postnatal Maternal Uterine and Renal Artery Doppler Parameters with Proteinuria in Preeclamptic Pregnant Women

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ABSTRACT

Objective: To examine the relation between the mother's renal and uterine artery (UA) Doppler parameters before and during birth in preeclamptic pregnant women and the degree of proteinuria.

Methods: In our study, 30 preeclamptic patients diagnosed in our hospital and 30 healthy pregnant women with matched gestational weeks were evaluated. To determine the amount of protein in the urine, 24-hour urine samples were taken from each patient. Doppler examinations of the UA and renal artery (RA) of the mother were carried out. On the seventh postnatal day, the cases were called in for follow-up, and the uterine and RA Doppler parameters were reevaluated. Spearman correlation analysis was used to assess the association between maternal uterine and RA pulsatility index (PI), resistive index (RI) values, and proteinuria.

Results: The preeclampsia group's antenatal right UA artery PI (1.29 ± 0.5) and RI (0.62 ± 0.13) values were observed to be considerably higher than those of the control group, with PI values (1.01 ± 0.43) and RI values (0.54 ± 0.16). Postnatal right UA PI (1.33 ± 0.56) in preeclampsia group was statistically different compared with postnatal UA PI (1.07 ± 0.32) in control group ($P < 0.05$). Postnatal RA PI and RI values were similar in both groups. In preeclamptic patients, right RA PI (1.03 ± 0.29) was statistically higher compared with postnatal RA PI (0.92 ± 0.18). While a significant correlation was found between right UA Doppler parameters and the amount of proteinuria, no correlation was found between RA Doppler parameters and it.

Conclusion: The degree of proteinuria and maternal UA Doppler parameters are significantly correlated. There was no correlation between RA Doppler parameters and the amount of proteinuria.

Keywords: Preeclampsia, proteinuria, renal artery Doppler, uterine artery Doppler, Doppler US

INTRODUCTION

Four to five percent of pregnancies end in preeclampsia (PE), a serious pregnancy complication. Fetal prematurity and maternal long-term cardiovascular problems are a major cause of maternal and fetal morbidity and mortality.[1] Hemorrhagic stroke, hemolysis, elevated liver enzymes, reduced platelets, renal failure, and pulmonary edema are among the possible complications.[2-4] In the second half of pregnancy, PE is linked to newly diagnosed hypertension and frequently proteinuria. PE can potentially affect many organs. However, proteinuria is a defining feature for the diagnosis of PE, and renal alterations are invariably present. Classically, glomerular endothelial damage is thought to be responsible for the renal deterioration that is present in the setting of PE.[5-7] With the progression of PE, profound systemic vasoconstriction occurs, leading to decreases in glomerular filtration (GFR).

It is thought that insufficient trophoblastic invasion plays a role in the pathophysiology of placental diseases in PE instances, although the exact mechanism is still unclear.[8]

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Impaired placental development causes increased vascular resistance in the uteroplacental circulation. This condition causes an increase in pulsatility (PI) and resistive index (RI) in the uteroplacental circulation on Doppler ultrasonography, as well as an abnormal wave pattern in the uterine artery (UA). Therefore, it has been shown that pregnant women who are at risk for PE and intrauterine growth retardation may be evaluated using Doppler ultrasonography as a screening test.[9-11] Endothelial damage, which is involved in the pathogenesis of PE, and the increase in vascular resistance that develops secondary to endothelial damage are the main causes of both proteinuria and decreased renal and UA blood flow.[8-11] Due to the common etiopathogenesis, there is correlation exists between increased vascular resistance and proteinuria in uterine and renal artery (RA) Doppler parameters. The study aims to determine the relationship between proteinuria and UA and RA Doppler parameters in preeclamptic pregnant women.

MATERIAL AND METHODS

The study consisted of 30 preeclamptic pregnant women who were diagnosed with PE during routine examinations and 30 healthy pregnant women as a control group, all of whom presented to the Department of Obstetrics and Gynecology at Karadeniz Technical University Farabi Hospital between February 2020 and September 2020. On January 28, 2020, the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee approved the prospective study using protocol number 2020/35 on 28.01.2020. Written consent is obtained from every patient admitted to the hospital after they read and sign the informed consent form. After the preeclamptic pregnant women in the study group were formed, 30 normal pregnant women of similar age, gestational age, and body mass index were selected as the control group. Patients presenting to our clinic between the ages of 18 and 35, with no systemic disease, no risk factors for pregnancy, and no history of chronic medication use, were considered the control group. Pregnant women who met the study criteria and agreed to participate voluntarily were included as the control group. UA and RA Doppler examinations were also performed in these patients. For comparison with preeclamptic pregnant women, 24-hour urine protein excretion was recorded for each patient, in addition to routine pregnancy blood tests.

MAIN POINTS

- A significant correlation was observed between the degree of proteinuria and maternal uterine artery Doppler parameters.
- Antenatal right uterine artery pulsatility index (PI) and resistive index (RI) values were significantly higher in the preeclampsia group compared with the control group.
- In patients with preeclampsia, antenatal renal artery PI values were statistically higher than postnatal renal artery PI values.
- No significant correlation was found between renal artery Doppler parameters and the degree of proteinuria.

The requirements for inclusion in this research were being beyond the 20th week of pregnancy, not having any known kidney disease, being a volunteer, and having a singleton pregnancy. Pregnant women diagnosed with multiple pregnancy, chronic hypertension, Hemolysis, Elevated Liver Enzymes and Low Platelets syndrome, eclampsia, gestational hypertension, and kidney disease were not included in the study. All patients who were part of the trial filled out informed consent forms. PE was diagnosed according to the American College of Obstetricians and Gynecologists criteria.[12] Accordingly:

1. A woman who has previously had normal blood pressure should have two readings taken at least four hours apart after 20 weeks of pregnancy. The readings should show a systolic blood pressure of greater than 140 mm Hg and a diastolic blood pressure of greater than 90 mm Hg. A systolic blood pressure of 160 mm Hg or a diastolic blood pressure of 110 mm Hg or higher was considered severe PE.

2. Proteinuria: If quantitative techniques are not available, proteinuria is defined as 300 mg or more in 24-hour urine or a protein/creatinine ratio ≥ 0.3 (each in mg/dL) or + 2 protein with dipstick.

3. Thrombocytopenia: less than 100,000 platelets per microliter.

4. Serum creatinine levels above 1.1 mg/dL or a doubling of serum creatinine levels, independent of other renal disorders, are indicative of renal failure.

5. Impaired liver function: Elevation of liver transaminases to doubling of normal concentration.

6. Edema of the lungs.

7. New onset headache that is unresponsive to medication and not associated with other diagnostic or visual symptoms.

Age, body mass index, gravidity, parity, abortion, birth weeks, medications used, and additional disease information were obtained from the cases included in the study. The amount of proteinuria was analyzed by collecting a 24-hour urine sample. UA and RA Doppler examinations were performed on the antenatal and postnatal 7th day of the cases, and UA and RA and RI, PI values were recorded.

UA Doppler Measurements

A Doppler US study was performed with LOGIQ E10 transabdominal pulsed 3.5-5 MHz transducers. Patients were scanned in the supine position for UA examination. The transducer was positioned medially at a modest inclination and longitudinally in the lower lateral quadrant of the abdomen. The location where the UA crossed the external iliac artery in the iliac fossa was determined, and the probe was placed 1 cm medial to the point of crossing. Then, pulsed Doppler flow forms were printed separately for both uterine arteries, obtained with an insonation angle of less than 30° and a sampling volume of 2 mm. The wall filter was set to 100 Hz. Three consecutive similar waveforms were obtained, and mean PI and RI were calculated for the uterine arteries on the left and right.

RA Doppler Measurements

RA Doppler measurements were performed with the same device and a 3.5 MHz convex transducer. Renal Doppler measurements were performed transabdominally while the pregnant woman was in the supine position. During the paused breathing period, the insonation angle was below 30 degrees, and the wall filter was 100 Hz. First, interlobar vessels in the renal pelvis were identified with color Doppler. Then, Doppler flow waveforms were obtained from the interlobar arteries in both kidneys for the highest Doppler frequency shift. The software on the US device was used to measure the RI and PI values.

Pulsed Doppler waveforms from the interlobar arteries in three distinct areas of the upper, middle, and lower third of the kidney were used to quantify maternal renal RI and PI.

At least three consecutive Doppler waveforms with comparable appearances were used to estimate RI and PI. Lastly, the average RI and PI values for the left and right kidneys were determined and noted. No significant difference was found in RI and PI between the right and left kidneys for each patient ($P > 0.05$).

Statistical Analysis

The Statistical Package Program for Social Sciences 11.5 (SPSS Inc., Chicago, IL) was used for statistical analysis. The independent t-test was used to compare quantitative data the chi-square test to evaluate qualitative data, along with descriptive statistical techniques (mean, standard deviation, and median) in the data review process.

Prenatal and postnatal changes in uterine and RA Doppler parameters were examined using the paired t-test, and the association between Doppler parameters and 24-hour urine proteinuria, was assessed using Spearman correlation analysis.

A 95% confidence interval was used to evaluate the results, and $P < 0.05$ was considered significant.

RESULTS

The demographic data of a total of 60 patients, 30 of whom were diagnosed with PE and 30 healthy pregnant women (who did not develop PE), as Table 1 provides a summary of the control group.

Six of the preeclamptic pregnant women showed severe PE, and the remaining 24 showed mild PE. The two groups did not differ significantly statistically in terms of body mass index, abortion, parity, age, or gravida.

Table 2 summarizes the clinical and laboratory information of preeclamptic pregnant women and healthy pregnant women. The mean proteinuria level in the PE group was 1363 mg/dL, while it was calculated as 173 mg/dL in the control group. The difference was statistically significant ($P < 0.05$).

The PE group had statistically significantly higher systolic and diastolic blood pressure compared to the control group ($P < 0.001$). Hemoglobin, platelet, alanine aminotransferase, aspartate aminotransferase, creatinine, and blood urea nitrogen values of patients in both groups were found to be within normal limits, and no statistically significant difference was observed between the groups in terms of blood values. There was a statistically significant difference between the two groups in terms of gestational age at delivery; the median value was 35 weeks in the PE group and 37 weeks in the control group ($P < 0.01$).

Tables 3 and 4 provide an overview of the antenatal and postnatal uterine and renal Doppler parameters for the PE and control groups.

Among the groups, only the right UA antenatal PI and RI values and postnatal PI value were found to be statistically significantly higher in the PE group in terms of both uterine and RA Doppler PI and RI values compared to the control group ($P < 0.05$).

Comparisons of antenatal and postnatal Doppler parameters of the PE group are summarized in Table 5 and those of the control group are summarized in Table 6. When the postpartum change in UA PI and R1 mean values was examined, no significant change was found in either group. The postpartum decrease in the mean value of right RA Doppler PI was significantly higher in the PE group. This decrease was statistically significant ($P < 0.05$). No statistically significant change was detected in the mean values of RA antenatal and postnatal Doppler PI and RI in all groups ($P > 0.05$). When investigating the association between uterine and RA Doppler values and protein content, right UA PI and RI values and 24-hour urine protein amount were found to be significantly correlated. No relationship was found between RA PI and RI values and 24-hour urine protein amount.

DISCUSSION

In the present study, we found a statistically significant relationship between UA Doppler parameters and the amount of proteinuria in PE cases. Although the right RA antenatal PI value was found to be higher compared to postnatal, no significant relationship was found between RA Doppler parameters and proteinuria. We thought that the small number of cases, or the fact that the Doppler examination was performed as early as the 7th postnatal day, had a negative effect on our results. Three to five percent of pregnant women develop PE, a pregnancy-specific illness marked by proteinuria and hypertension that develops after the twentieth week of pregnancy. In low- and middle-income countries, 10-15% of maternal deaths are directly related to PE and eclampsia.[13]

The early diastolic notch in the UA waveform is usually observed at the 14th week of normal pregnancy, but disappears after the 24th week.[10,11,14] In most studies, it is reported that the RI or

Table 1. Demographic Data of Patients

Demographic characteristics	Preeclampsia group (n=30)	Control group (n=30)	*P*
Age	32.43 ± 7.10	30.50 ± 714	0.29
Gravida	2 (1-5)	2 (1-8)	0.26
Parity	1 (0-4)	1 (0-3)	0.56
Abortion	0 (0-3)	0 (0-4)	0.20
BMI (kg/m^2)	27.69 ± 3.01	26.76 ± 2.51	0.20

Age and BMI (body mass index) are given as mean values, and gravida, parity, and abortion data are given as median values.

Table 2. Clinical and Laboratory Data of Preeclamptic and Normal Pregnant Women

Clinical and laboratory data	Preeclampsia group (n=30)	Control group (n=30)	*P*
Proteinuria (mg/24 h)	1363.23 ± 1636.88	173.53 ± 64.38	**0.00**
Systolic blood pressure (mmHg)	153.70 ± 11.28	104.17 ± 10.99	**0.00**
Diastolic blood pressure (mmHg)	98.17 ± 9.51	63.17 ± 7.71	**0.00**
Hemoglobin (g/dL)	12.08 ± 1.38	12,12 ± 1.28	0.90
Platelet (10^3/mL)	217.23 ± 83.61	209.90 ± 46.96	0.67
ALT (U/L)	13.80 ± 8.91	13.53 ± 10.10	0.91
AST (U/L)	21.30 ± 6.86	20.33 ± 8.29	0.62
Creatine (mg/dL)	0.59 ± 0.16	0.49 ± 0.10	0.13
BUN (mg/dL)	1l.57 ± 5.15	8.30 ± 4.18	0.09
Week of pregnancy at time of birth	35 (25-39)	37 (26-40)	**0.01**

Note: The amount of proteinuria, systolic blood pressure, diastolic blood pressure, hemoglobin, platelets, ALT, AST, creatinine, BUN, gestational week at the time of delivery, and gestational week at which ultrasound evaluation was performed are given as mean values.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen.

systolic/diastolic ratio is more valuable than PI in predicting PE in the mid trimester.[11,14,15] There were no differences in RA Doppler indices between normotensive and hypertensive pregnant women, even though pregnancy-induced hypertension (PPIH) is linked to elevated maternal systemic vascular resistance and luminal narrowing of renal glomerular arterioles.[12,16] Liberati et al.[17] investigated whether there were differences in interlobar RA PI and RI between normal and hypertensive pregnant patients. The measurements were similar in both groups. It was found that mild and moderate PE did not cause changes in the flow velocities and waveforms in the kidney and the interlobar artery.[17]

Similarly, no statistically significant difference between the groups was seen in the renal interlobar artery PI and RI values in our investigation. However, we found that right UA Doppler values in the antenatal period were noticeably higher in the preeclamptic women compared to the healthy control group. Unfortunately, this relationship could not be demonstrated in left UA Doppler parameters. Numerous investigations have documented postpartum UA impedance in patients with persistent hypertension and PE.[12,18,19] Maged et al.[19] evaluated uterine arterial resistance in preeclamptic and healthy women before and after delivery. Both pre- and postpartum measurements of UA PI and RI Doppler indices are significantly higher in women with PE compared with the control group. They claimed that either chronically elevated maternal vascular tone or insufficient trophoblastic invasion in the basal section of the decidua basalis and myometrium is the source of the rise in UA impedance. When comparing the antenatal and postnatal UA PI and RI values in our investigation, we found no discernible differences. We believed that the modest number of instances in the current study was connected to this. Postpartum UA blood flow velocimetry in normal pregnancies and pregnancies complicated by severe PE was studied by Weintraub et al.[20] Although no difference was observed between normotensive patients and preeclamptic pregnant women in terms of postpartum Doppler velocimetry measurements, the preeclamptic group had considerably more unilateral and bilateral early diastolic notches. In our study,

Table 3. Comparison of Antenatal Uterine and Renal Artery Doppler Parameters of Preeclampsia and Control Groups

UA and RA Doppler parameters	Preeclampsia group (n=30)	Control group (n=30)	*P*
Right UA antenatal PI	1.29 ± 0.57	1.01 ± 0.43	**0.03**
Right UA antenatal RI	0.62 ± 0.13	0.54 ± 0.16	**0.03**
Left UA antenatal PI	1.19 ± 0.72	1.04 ± 0.44	0.32
Left UA antenatal RI	0.58 ± 0.19	0.56 ± 0.13	0.57
Right RA antenatal PI	1.03 ± 0.29	1.03 ± 0.24	0.91
Right RA antenatal RI	0.60 ± 0.08	0.60 ± 0.07	0.81
Left RA antenatal PI	1.00 ± 0.27	1.00 ± 0.19	0.93
Left RA antenatal RI	0.60 ± 0.10	0.58 ± 0.08	0.54

UA, uterine artery; RA, renal artery; PI, pulsatility index; RI, resistive index.

Table 4. Preeclampsia and Control Groups' Postnatal Uterine and Renal Artery Doppler Values are Compared

Preeclampsia group (n=30)	Preeclampsia group (n=30)	Control group (n=30)	*P*
Right UA postnatal PI	1.32 ± 0.56	1.07 ± 0.32	**0.04**
Right UA postnatal RI	0.63 ± 0.13	0.59 ± 0.10	0.10
Left UA postnatal PI	1.22 ± 0.48	1.10 ± 0.47	0.36
Left UA postnatal RI	0.63 ± 0.11	0.57 ± 0.13	0.07
Right RA postnatal PI	0.92 ± 0.18	1.02 ± 0.26	0.08
Right RA postnatal RI	0.60 ± 0.06	0.60 ± 0.07	0.83
Left RA postnatal PI	0.92 ± 0.19	0.96 ± 0.19	0.37
Left RA postnatal RI	0.59 ± 0.09	0.58 ± 0.07	0.83

UA, uterine artery; RA, renal artery; PI, pulsatility index; RI, resistive index.

although no observation was made regarding notching in the UA, we encountered higher UA Doppler antenatal and postnatal PI RI values on the right side in the preeclamptic group.

When comparing antenatal and postnatal RA Doppler values, we found that the PI value of the right RA in the preeclamptic women decreased significantly in postnatal measurements. Pregnant hypertension patients often have decreased renal blood flow, as indicated by endogenous creatinine clearance tests. Histopathological alterations in renal microcirculation are linked to impaired renal function. It is debatable whether anomalies in renal arterial blood flow velocity waveforms indicate alterations in renal pathophysiology.[21] Zimmermann and Ranta et al.[11] examined the relationship between PI and RI values in maternal UA and intrarenal arteries as markers of vascular resistance in pregnant women at low and high risk of developing PPIH. In the study, no correlation was found between the RI values of both uterine arteries and the RI value of the right interlobar RA. There was no association between a persistent diastolic notch in the uterine arteries and intrarenal RI values. The intrarenal RI value was not different in patients who developed proteinuria and severe PPIH in later pregnancy compared with normal pregnant women. In another study, Bahser et al.[22] compared the resistance index in the intralobular RA in preeclamptic and healthy pregnant women. Pregnant women with PE were found to have a statistically higher resistance index than normal pregnant women. It was shown that the PI value was related to the amount of proteinuria, and the RI was related to the systolic blood pressure. Intrarenal Doppler indices are an important indicator of PE and provide the opportunity to predict nephropathy. Intrarenal Doppler indices suggested that they may be a prognostic tool for cardiovascular complications in patients with PE.[22]

Table 5. Antenatal and Postnatal Comparison of Uterine and Renal Artery Doppler Parameters in the Preeclampsia Group

Preeclampsia	Antenatal	Postnatal	*P*
Right UA PI	1.29 ± 0.57	1.32 ± 0.56	0.76
Right UA RI	0.62 ± 0.13	0.63 ± 0.13	0.64
Left UA PI	1.19 ± 0.72	1.22 ± 0.48	0.84
Left UA RI	0.58 ± 0.19	0.63 ± 0.11	0.10
Right RA PI	1.03 ± 0.29	0.92 ± 0.18	**0.01**
Right RA RI	0.60 ± 0.08	0.60 ± 0.06	0.42
Left RA PI	1.00 ± 0.27	0.92 ± 0.19	0.11
Left RA RI	0.60 ± 0.10	0.58 ± 0.07	0.63

UA, uterine artery; RA, renal artery; PI, pulsatility index; RI, resistive index.

Table 6. Antenatal and Postnatal Comparison of UA and RA Doppler Parameters in the Control Group

Control group	Antenatal	Postnatal	*P*
Right UA PI	1.01 ± 0.43	1.07 ± 0.32	0.32
Right UA RI			
Left UA PI			
Left UA RI			
Right RA PI			
Right RA RI			
Left RA PI			
Left RA RI			
Right UA PI	0.54 ± 0.16	0.59 ± 0.10	0.09
Right UA RI			
Left UA PI			
Left UA RI			
Right RA PI			
Right RA RI			
Left RA PI			
Left RA RI			
Right UA PI	1.04 ± 0.44	1.10 ±0.47	0.49
Right UA PI	0.56 ± 0.13	0.57 ±0.13	0.53
Right UA PI	1.03 ± 0.24	1.02 ±0.26	0.75
Right UA PI	0.60 ± 0.07	0.60 ± 0.07	0.92
Right UA PI	1.00 ± 0.19	0.96 ± 0.19	0.32
Right UA PI	0.58 ± 0.08	0.58 ± 0.07	0.71

UA, uterine artery; RA, renal artery; PI, pulsatility index; RI, resistive index.

Albuminuria and a lower GFR rate are indicators of renal glomerular injury and renal vasospasm, which are thought to cause impaired renal function secondarily in PE.[23-27] Kublickas et al.[28] looked into how maternal RA Doppler indices were affected by hypertension and illness, as well as by a typical pregnancy. Pregnant women with PE had lower renal blood flow velocity indices than those of women in a healthy pregnancy which suggests that PE is associated with greater reno-vascular resistance.

When we looked at the relationship between UA Doppler values and proteinuria, we discovered a connection between proteinuria and the PI and RI of the right UA. We found no significant correlation between RA Doppler parameters and proteinuria, which was unexpected. We thought that this was related to the small number of PE cases. RA waveforms were obtained by Gudmundsson and Marsâl[28] in non-pregnant, healthy pregnant, and preeclamptic women. In preeclamptic women, RA waveforms were shown to be unrelated to mean arterial pressure and the severity of proteinuria. The placenta's impaired growth results in increased blood flow resistance in the uteroplacental circulation. Impaired development of the placenta means constantly increasing resistance to blood flow in the uteroplacental circulation. Inadequate trophoblastic invasion is thought to be a contributing factor in placental diseases, while the precise process remains unknown.[29] van Asselt et al.[29] assessed whether maternal blood pressure, proteinuria, and placental vascular resistance were correlated, and whether Doppler velocity assessment of placental circulation could predict unfavorable outcomes of pregnancies affected by PE. Abnormalities on both sides of the placenta were associated with adverse pregnancy outcomes. Negative pregnancy outcomes were found to be more prevalent in the

groups with increased vascular resistance on both sides of the placenta than in the groups with increased vascular resistance on just one side. They found significant relationship between proteinuria and UA PI value, but There was no relationship between mean maternal arterial pressure and UA PI.[29,30] Antihypertensive medications that reduce blood pressure without changing placental vascular resistance or the extent of protein leakage into the urine are administered to some patients with more severe PE. This may conceal a potential link between maternal blood pressure and UA vascular resistance.[30]

Study Limitations

The small number of patients in our study is one of its drawbacks; thus, it is possible that the data collected will change when the number of patients taking part in the study rises.

The UA's notch was also investigated in several relevant studies; however, our study did not examine any changes that might be connected to this parameter. Postnatal Doppler parameters include values determined within one week postpartum. Performing postnatal ultrasonography evaluation at a longer interval may yield different results.

In our study, we found UA Doppler parameters to be associated with both PE and proteinuria. In our study, no significant relationship was found between renal Doppler parameters (renal PI, RI) and proteinuria in preeclamptic pregnant women. Studies examining the connection between RA Doppler and PE have produced contradictory findings. As a result, this field requires additional prospective research with a large number of cases.

Ethics

Ethics Committee Approval: It is a prospective study conducted by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee with the approval of the ethics committee with protocol number 2020/35 on 28.01.2020.

Informed Consent: Written consent is obtained from every patient admitted to the hospital after they read and sign the informed consent form.

Footnotes

Author Contributions

Concept – M.E.A., G.D.; Design – M.E.A., G.D.; Data Collection or Processing – M.E.A.; Analysis or Interpretation – M.E.A., G.D.; Literature Review – M.E.A.; Writing, Reviewing and Editing – M.E.A., G.D.

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ABCResearch

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Research Article

Approach to Deep Neck Infections: A Single-Center Experience

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ABSTRACT

Objective: The aim of this retrospective study is to describe the clinical features and management of patients diagnosed with deep neck infection (DNI) and hospitalized in our clinic, and to share our experience, together with a review of the current literature.

Methods: Patients who were diagnosed with DNI and treated in our clinic between January 2020 and June 2025 were retrospectively analyzed. Inclusion criteria: age > 18 years, complete medical records, diagnosis confirmed by clinical, laboratory, and imaging findings. Exclusion criteria: immunosuppressed patients, missing data, and pediatric cases. Diagnosis was based on clinical examination, laboratory tests, and imaging. Intravenous antibiotics were administered to all patients: incision and drainage or repeated aspiration was performed when abscesses were detected. Patients were followed for at least 3 months after discharge.

Results: Sixty-two patients, 36 male and 26 female, were included in the study. Analysis of the etiological factors causing DNI revealed that 25 (40%) cases were odontogenic in origin and 19 (30.6%) derived from tonsillitis. Surgical drainage was required in 50% of patients. The overall complication rate was 9.7%, and no mortality occurred.

Conclusion: Odontogenic infections were the leading cause of DNIs, followed by tonsillitis. Complete recovery was achieved with antibiotics alone in 50% of patients, and surgical intervention was successful in all remaining cases, resulting in 100% overall cure without recurrence. Early diagnosis and prompt combined management are key to excellent outcomes.

Keywords: Antibiotic therapy, complications, deep neck infection, treatment

INTRODUCTION

Deep neck infection (DNI) is an infection of the potential spaces of the neck, accompanied by abscess formation or cellulitis of the cervical fascia.[1] It typically arises from odontogenic sources, tonsils, salivary glands, or lymph nodes. With the widespread use of antibiotics, dental infections have become the leading cause of odontogenic issues. Symptoms may be subtle, resulting in delayed diagnosis. The most common findings are neck swelling, trismus, dysphagia, dyspnea, limited neck movement, and fever.[2] Physical examination may reveal pharyngeal wall asymmetry, tonsil or soft palate displacement, and cranial nerve palsies.[3] DNIs are usually polymicrobial, most commonly involving *Streptococcus* species, *Staphylococcus aureus,* and anaerobes.[4] Potential complications include mediastinitis, airway compromise, pleural empyema, and jugular vein thrombosis.[5] Diagnosis is aided by computed tomography (CT) or magnetic resonance imaging (MRI), and treatment consists of prompt intravenous antibiotics with surgical drainage when indicated.[6] This study aimed to evaluate the etiology, clinical features, treatment approaches, and outcomes of patients with DNI and to compare our results with the current literature.

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MATERIAL AND METHODS

The Erzincan Binali Yıldırım University Clinical Research Ethical Committee approved this study under decision no: 2025-14/01, dated 24.07.2025. The research was conducted in compliance with the principles of the Declaration of Helsinki. This study involved patients who were hospitalized and followed up with diagnoses of DNI at the Erzincan Binali Yıldırım University between January 2020 and June 2025. Patient files were evaluated retrospectively, and those with detailed medical history and examination findings were included in the study. Patients with missing data: isolated salivary gland infections, tuberculosis-related abscesses, superficial neck infections, and head and neck tumors were excluded. Gender, age, presenting complaint, the location of the neck infection, the etiological factors (if any) identified, the accompanying comorbidities, previous antibiotic use, whether abscess drainage was performed, the types of antibiotic used in treatment, the microorganisms grown if cultures were submitted, radiological images, length of hospital stay, and complications were recorded.

Our diagnostic, treatment, and follow-up algorithm was as follows: all patients first underwent detailed history-taking and physical examination, followed by routine laboratory tests, including complete blood count. In our study, all patients underwent at least one imaging modality, specifically ultrasonography (US) and/or contrast-enhanced CT. Additionally, MRI was performed in selected cases with suspicion of deep or atypical involvement. Empirical intravenous antibiotic therapy was initiated immediately after diagnosis. In patients with abscess formation, surgical drainage or needle aspiration was performed, and antibiotic regimens were subsequently adjusted according to culture results. Patients were monitored during hospitalization until clinical stabilization and scheduled for weekly follow-up visits in the early post-discharge period, with longer intervals thereafter, for a total follow-up ranging from 3 weeks to 6 months. The data obtained are discussed in the light of the current literature.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Statistics Version 23.0 (IBM Corporation, Armonk, NY, USA). The data obtained were subjected to statistical analysis. Categorical variables were expressed as numbers and percentage.

MAIN POINTS

- Odontogenic infections were the leading cause of deep neck infections, followed by tonsillitis.
- Complete recovery was achieved in all 62 patients, with 50% treated successfully with antibiotics alone and the rest requiring surgical intervention.
- Early diagnosis and combined medical-surgical management are crucial to prevent life-threatening complications and ensure excellent outcomes.

RESULTS

Sixty-two patients, 36 male and 26 female, with a mean age of 44.6 years (range, 7-82 years), were included in the study. Dental infections were the most frequent cause, accounting for 40% of cases, followed by tonsillitis (30.6%). No etiological factor was identified in 20.9% of patients (Table 1).

The most common presenting symptom was swelling of the head and neck (46.7%), followed by sore throat, and dysphagia. A smaller number of patients presented with restricted neck mobility or tongue swelling. These symptoms were observed both in isolation and in combination. Some patients also exhibited systemic symptoms such as fever, muscle and joint pain, and fatigue (Table 2).

The mean duration from symptom onset to hospital admission was 5.3 days (range, 2-21). Antibiotic therapy had already been initiated in 88.7% of patients. The submandibular and peritonsillar regions were the most commonly affected sites, followed by the parapharyngeal, retropharyngeal, and lateral cervical spaces. Less frequent involvement was observed in the tongue and suboccipital region (Table 3).

Table 1. Etiology of Deep Neck Infections

Etiological factor	Number of patients (n)	Percentage (%)
Odontogenic infection	25	40
Tonsillit	19	30.6
Upper respiratory tract infection	3	4.8
Wound infection	2	3.2
Idiopathic	13	20.9

Table 2. Symptoms of Patients with Deep Neck Infection

Symptom	Number of patients (n)	Percentage (%)
Swelling in the head and neck	29	46.7
Sore throat	20	32.2
Difficulty swallowing and impaired oral intake	19	30.6
Limited neck movement	3	4.8
Swollen tongue	2	3.2

Table 3. Infection Sites in Patients with Deep Neck Infection

Injection sites	Number of patients (n)	Percentage (%)
Submandibular	25	40.3
Peritonsillar	19	30.6
Parapharyngeal	5	8
Retropharyngeal	5	8
Lateral neck regions	5	8
Tongue	2	3.2
Supoccipital	1	1.6

The most frequently employed antibiotics were clindamycin (52%) and penicillin (25%). Tetracyclines, cephalosporins, and vancomycin were less frequently used. US alone was used for diagnosis in 16 (25.8%) cases, CT alone in nine (15%) cases, and both ultrasound and CT in 21 cases. MRI was performed in addition to CT in six (9.6%) cases.

Eighteen (29%) patients underwent incision and drainage, and 13 (20.9%) patients underwent repeated aspiration. Bacterial growth was detected in 50% of the 31 patients who underwent aspiration or drainage. Complete clinical recovery was achieved with antibiotic therapy alone in 31 patients (50%). Surgical drainage or aspiration was performed in 31 patients, and treatment was successful in all of them. Overall, infection resolved without recurrence in all 62 patients. *Streptococcal* species constituted 68.7% (n=11) of these, followed by *Klebsiella* species (6.2%) and *Bacteroides* species (6.2%). In addition, tularemia testing was performed in 17 patients with clinical suspicion, and five of them (29.4%) tested positive.

Hypertension was present in 14 of these patients, diabetes mellitus in 10, coronary artery disease in nine, and pulmonary disease in seven. Our patients' mean length of hospital stay was 7.1 days (range, 3-14). Complications included mediastinitis in two patients, acute respiratory distress in three, and pleural effusion in one (Figure 1). No mortality due to DNI occurred.

Patients were monitored regularly during hospitalization and were scheduled for weekly follow-up visits in the early post-discharge period, followed by progressively longer intervals thereafter, for a total follow-up period ranging from 3 weeks to 6 months. During follow-up, clinical improvement, resolution of infection, and recurrence were assessed.

DISCUSSION

In our study, odontogenic infections were the most common etiological factor (40%), followed by tonsillar infections (30.6%). These findings are consistent with recent reports indicating that odontogenic infections have replaced tonsillitis as the leading cause of DNI in adults. Tonsillitis, however, remains the most common etiology in pediatric populations.[7] An idiopathic etiology was observed in 20.9% of our patients, which is comparable to previously published series reporting up to 20% of DNI cases with no identified cause, the majority of which were children.[8] In addition, our findings are consistent with previous reports indicating that tularemia, although rare, should be considered in the differential diagnosis of cervical masses.[9]

The subdivisions of DNI generally consist of the submandibular, parotid, peritonsillar, parapharyngeal, and retropharyngeal spaces. It is generally agreed that the submandibular space is the most frequently affected area. This is likely due to the proximity of odontogenic infections, the most common etiological factor, to the submandibular region.[10] In their study of 270 DNI patients, Gujrathi et al.[11] reported that the submandibular region was the most frequently affected area at 30%, followed by the peritonsillar region at 13%. In another study, of 300 patients, Desa et al.[12] described the submandibular region as the most frequently affected area, at 55%, followed by the paraphageal space, at 45%. Those authors also reported the presence of tonsillar infections beneath the parapharyngeal abscesses. In the present study, the submandibular region was the most frequently affected area at 40.3%. The etiological factor in the majority of these patients was odontogenic infections. We also observed that parapharyngeal abscesses generally develop after tonsillopharyngitis infection.

The most common symptoms of DNI include neck swelling, fever, shortness of breath, dysphagia, odynophagia, trismus, limited neck movement, and voice changes. In advanced cases, the abscess may rupture spontaneously, either intraorally or externally, and the patient may present with a discharge complaint. US can facilitate diagnosis due to its high accessibility. However, because evaluation of deep structures such as the retropharyngeal, parapharyngeal, and mediastinal areas can be difficult with this method, detailed evaluation with contrast-enhanced neck CT, or MRI is required, especially in patients with severe infection.[13] This method permits differentiation between cellulitis and abscesses, avoids unnecessary surgical interventions, and allows a clear assessment of the extent of the disease and its proximity to important structures.[14]

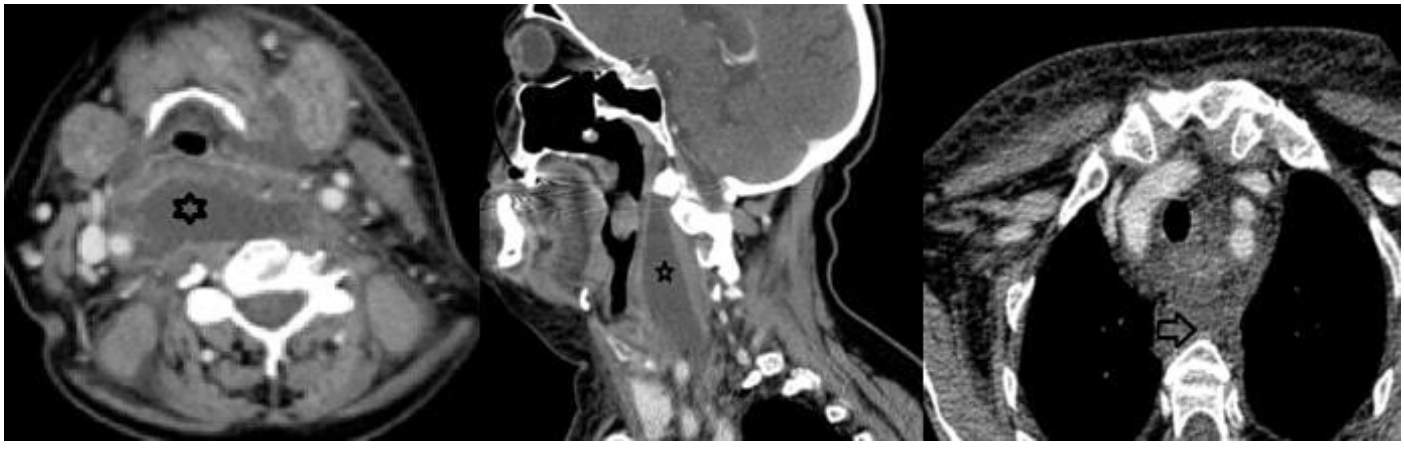

Figure 1. Axial and sagittal CT images of a patient with retropharyngeal abscess and mediastinitis (asterisk, retropharyngeal abscess; arrow, mediastinitis).

CT, computed tomography.

The most frequently isolated microorganisms in patients with DNI are *Streptococcus pyogenes* and *Staphylococcus aureus*, together with agents such as *Fusobacterium necrophorum* and *Actinomyces*, and more than half of cases are polymicrobial.[15] In the present study, we primarily employed contrast-enhanced CT imaging as a diagnostic tool. We also observed that ultrasound was potentially misleading in one patient who developed a retropharyngeal abscess. *Streptococcal* species were the most frequently isolated agents.

Complications of DNI include jugular vein thrombosis; airway obstruction; acute respiratory distress; sepsis and disseminated intravascular coagulation; mediastinitis; pleural effusion; cranial nerve palsies; carotid artery necrosis; thrombophlebitis, and these also represent the causes of morbidity associated with these infections.[16] Mortality rates in patients with these complications can be as high as 40%. Early recognition and prompt intervention are therefore vitally important. Close monitoring of these patients and the ability to anticipate potential complications are also crucial. When such complications develop, it is essential to manage the process in collaboration with other relevant medical specialists.

In terms of treatment, empiric therapy, which may vary regionally, should be initiated until culture and antibiogram results are available. The antibiotics employed should cover Gram-negative, Gram-positive, aerobic, and anaerobic bacteria. Penicillins, third-generation cephalosporins, metronidazole, and clindamycin are generally preferred for initial treatment.[13] Antibiotherapy can be modified if necessary based on culture results. In cases with abscesses, especially those involving multiple sites, drainage protects the patient from potential complications and shortens both hospitalization and treatment. Furthermore, the effectiveness of antibiotic treatment can be evaluated based on the culture results of the material obtained. Incisional drainage was once a routine practice. However, aspiration, especially in isolated cases, has recently been shown to be as effective as incision. Alzaid et al.[17] reported in their meta-analysis that ultrasound-guided aspiration was as effective as incision, and also described aspiration as less costly and causing fewer cosmetic problems. We performed drainage on a total of 31 (50%) patients, including 18 (29%) with open drainage and 13 (20.9) with aspiration. We have also seen that uncommon abscesses can be treated with repeated drainage.

Study Limitations

The limitations of this study include its retrospective nature, which necessitated a medical record-based evaluation, and the relatively small number of patients.

CONCLUSION

Odontogenic infections were the leading cause of DNIs, followed by tonsillitis. Complete recovery was achieved with antibiotics alone in 50% of patients, and surgical intervention was successful in all remaining cases, resulting in 100% overall cure without recurrence. Early diagnosis and prompt combined management are key to excellent outcomes.

Ethics

Ethics Committee Approval: The Non-Interventional Clinical Research Ethics Committee of Erzincan Binali Yıldırım University approved this study under decision no. 2025-14/01, dated 24.07.2025.

Informed Consent: Retrospective study.

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Footnotes

Author Contributions

Concept Design – S.A., A.K., M.C.D., İ.S.; Data Collection or Processing – S.A., A.K., M.C.D., İ.S.; Analysis or Interpretation – S.A., M.C.D.; Literature Review – S.A., A.K.; Writing, Reviewing and Editing – S.A., A.K., M.C.D., İ.S.

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ABCResearch

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Research Article

Primary Bone Lymphoma: A Retrospective Analysis of 15 Patients Treated in a Single Tertiary Center

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ABSTRACT

Objective: Primary bone lymphoma is a rare type of lymphoma that originates in bone tissue without systemic involvement. This study aimed to evaluate the clinical characteristics, treatment approaches, and outcomes of patients diagnosed with primary bone lymphoma at a single tertiary care center.

Methods: Fifteen patients diagnosed between 2013 and 2020 were retrospectively reviewed. Data including patient demographics, tumor localization, histological subtype, disease stage, treatment modalities, and response rates were analyzed using descriptive methods.

Results: The median age was 53 years (range: 30-73), with 7 male and 8 female patients. Most patients presented with localized disease and diffuse large B-cell histology. The pelvic and axial skeletons were the most frequently involved areas. All patients received systemic chemotherapy, and 80 percent also underwent radiotherapy. Complete remission was achieved in 87 percent of cases. After a median follow-up of five years, 87 percent of patients were alive and 80 percent remained in long-term remission. One patient with widespread bone involvement experienced disease progression and died.

Conclusion: Primary bone lymphoma can be successfully treated with systemic chemotherapy and radiotherapy. This study confirms that patients with localized disease in particular may achieve long-term survival with appropriate combined treatment.

Keywords: Primary bone lymphoma, diffuse large B-cell lymphoma, chemoradiotherapy, retrospective analysis

INTRODUCTION

Primary bone lymphoma (PBL) is an uncommon malignancy, accounting for a small fraction of all lymphomas and bone tumors. Recent estimates indicate that PBL comprises approximately 3-7% of primary bone tumors and under 2% of all lymphomas in adults.[1] In other words, fewer than 5% of extranodal non-Hodgkin lymphomas arise in bone. PBL most often presents as diffuse large B-cell lymphoma (DLBCL) confined to the skeletal system, without distant nodal or visceral involvement. It can occur at any age but is typically diagnosed in mid-adulthood; the median age at presentation ranges from the mid-40s to 60 years in most series. There is a slight male predominance (reported male:female ratios around 1.2-1.8:1).[2] Clinical presentation usually includes localized bone pain, swelling, or pathologic fracture, and systemic "B" symptoms (fever, night sweats, weight loss) are present in a subset of patients.

The majority of PBL cases are histologically DLBCL, though rare cases of T-cell lymphoma (such as anaplastic large cell lymphoma) and other subtypes have been reported.[3] The most

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frequently involved sites are the long bones –notably the femur, humerus, and tibia– followed by axial skeleton sites like the spine and pelvis. Imaging often reveals lytic bone lesions, and diagnosis is confirmed by biopsy with histopathological and immunophenotypic analysis.

Optimal management of PBL typically involves a combination of systemic chemotherapy and localized radiotherapy (RT). The introduction of anthracycline-based chemo-immunotherapy [e.g., rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) regimen for B-cell PBL] has significantly improved outcomes. RT to the involved bone provides excellent local control; however, RT alone is associated with high rates of systemic failure. Combined modality therapy has been shown to yield superior overall survival (OS) and lower relapse rates than single-modality treatment. Prior studies have demonstrated 5-year survival rates around 80-90% for PBL patients, especially when treated with chemo, RT.[4] Nonetheless, data are limited due to the rarity of this entity, and most published evidence comes from retrospective series.

In this context, we report a retrospective analysis of 15 patients with PBL treated at a single tertiary center. We describe their clinical characteristics, treatment approaches, and outcomes, and compare these findings with the existing literature. By sharing our single-institution experience, we aim to contribute to the understanding of this rare lymphoma and to highlight factors relevant to its prognosis and management.

MATERIAL AND METHODS

Study Design and Setting

This study is a retrospective case series of patients diagnosed with PBL at our tertiary care academic hospital. We reviewed records from all patients treated at our center with a diagnosis of PBL over a defined period (2013-2020). The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Health Sciences Türkiye Kartal Dr. Lütfi Kırdar Training and Research Hospital (approval no.: 2020/514/177/31, date: 13.05.2020). Our hospital is a tertiary referral center that provides oncology services, and all included patients had both, diagnosis and treatment at this institution.

MAIN POINTS

- Primary bone lymphoma is a rare but highly treatable malignancy when diagnosed early and managed with combined chemo-radiotherapy.
- This study confirms excellent remission and survival outcomes, particularly in patients with localized disease.
- Diffuse large B-cell lymphoma was the most common histological subtype, and the pelvic, and axial skeleton were the most frequently affected anatomical sites.
- A multidisciplinary treatment approach involving chemotherapy, radiotherapy, and surgical stabilization (when needed) can result in long-term disease control and functional recovery.

Inclusion Criteria

Patients were included if they had a pathological diagnosis of lymphoma originating in bone, with disease confined to the skeletal system (with or without regional lymph node involvement) at presentation, consistent with the definition of PBL. Patients with secondary bone involvement from systemic lymphoma were excluded. We identified 15 patients who met these criteria during the study period.

Data Collection

After Institutional Review Board approval of Kartal Dr. Lütfi Kırdar Training and Research Hospital we collected data from medical charts and electronic records. The data abstracted included patient demographics (age at diagnosis, sex), presenting symptoms and duration, diagnostic workup findings, histopathological subtype of lymphoma, anatomic site of the primary bone lesion(s), staging information (Ann Arbor stage, presence of B symptoms), treatment modalities used (chemotherapy regimen, number of cycles, use of RT with dose), treatment response, and follow-up outcomes. Radiological and pathology reports were reviewed to confirm the extent of disease and bone sites involved. Treatment response was assessed using standard response criteria for lymphoma [complete response (CR), partial response (PR), stable disease, progressive disease] based on imaging and clinical evaluation after therapy.

Statistical Analysis

Given the small sample size, analysis was primarily descriptive. Continuous variables (e.g., age, follow-up time) are presented as median and range. Categorical variables (e.g., sex, histological subtype, response rates) are summarized as counts and percentages. No formal hypothesis testing was performed. Survival outcomes such as OS and progression-free survival were estimated descriptively based on available follow-up data, without Kaplan-Meier analysis due to the limited number of events. Data analysis was conducted using basic statistics functions.

RESULTS

Demographics and Clinical Presentation

A total of 15 patients with PBL were analyzed. The median age at diagnosis was 53 years (range: 30-73 years). The cohort included 7 male and 8 female patients, corresponding to a male-to-female ratio of approximately 1:1.14.

All patients had localized bone-related symptoms, most commonly bone pain at the affected site (in 13 patients, approximately 86%), sometimes accompanied by swelling. Four patients (26.8%) sustained a pathological fracture through the lymphoma-infiltrated bone (humerus, distal femur, iliac wing). The median duration of symptoms prior to diagnosis was 6 months. Systemic B symptoms (fever, night sweats, weight loss) were documented in 2 patients (13%). In several cases, the initial differential diagnosis included osteomyelitis or other bone tumors (e.g., multiple myeloma). Definitive diagnosis was established by bone biopsy and histopathology in all cases.

Anatomical Sites and Staging

The anatomical distribution of primary sites is summarized in Table 1. Long bones were frequently affected, however, the pelvic and axial skeleton, including the vertebrae, represented the most common sites overall. Femoral involvement was present in 2 patients (13%), tibial (± fibula) in 1 patient (7%), and humeral in 1 patient (7%). Other sites included the glenoid, distal tibia, proximal humerus, distal clavicle, and sternum (one patient each). Eight patients (53%) had pelvic and axial skeleton involvement, including vertebrae. No cases of skull, mandible, or rib involvement were observed. According to Ann Arbor staging, 12 patients (80%) had early-stage disease (Stage I–II), limited to a single bone or one bone with its regional lymph nodes. Three patients (20%) presented with multifocal bone involvement without other organ spread, which was classified as Stage IV disease, as multiple bone lesions are considered disseminated in lymphoma staging.

Table 1. Distribution of Primary Bone Sites in 15 PBL Patients

Anatomic site	No of patients	Percentage of total (%)
Pelvic and axial skeleton (incl. spine)	8	53%
Femur	2	13%
Glenoid	1	7%
Distal tibia	1	7%
Proximal humerus	1	7%
Distal clavicle	1	7%
Sternum	1	7%
Total	15	100%

Distribution of primary bone lymphoma sites in the study cohort. The pelvic and axial skeleton was the most commonly affected region.
PBL, primary bone lymphoma.

Histopathology

Most cases (14 of 15, 93%) were diagnosed as DLBCL. Immunohistochemistry in these cases was positive for B-cell markers (CD20, etc.). One patient (7%) was diagnosed with anaplastic large cell lymphoma (ALCL, a T-cell subtype). This aligns with expectations that most PBLs are of B-cell origin, 5 with an occasional T-cell lymphoma case. All diagnoses were confirmed by expert hematopathological review. In two DLBCL cases, high-grade morphological features were noted, but they were still classified as DLBCL. No cases of Hodgkin lymphoma or low-grade lymphoma were detected.

Treatment Administered

All patients received systemic chemotherapy as first-line treatment. Most B-cell lymphoma patients received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). The median number of chemotherapy cycles was 6 (most patients received 6-8). The T-cell ALCL case was treated with CHOP (rituximab was not administered, as it was CD30^ + ALCL). In addition to chemotherapy, 12 patients (80%) received local radiotherapy to the primary bone lesion (30-45 Gy). Patients with Stage I or II disease were more likely to receive combined modality treatment (chemotherapy + radiotherapy), whereas Stage IV patients were treated with chemotherapy alone.

Surgical interventions were performed in selected cases for local control and structural stabilization. Tumor resection prostheses were applied in two patients with distal femoral involvement and one patient with proximal humerus involvement. Clavicle resection was performed in the patient with distal clavicle involvement; the Harrington procedure was applied in the patient with an iliac wing-acetabular fracture (Figure 1); and posterior instrumentation was performed in the patient with T11 vertebral involvement (Figure 2). These procedures were

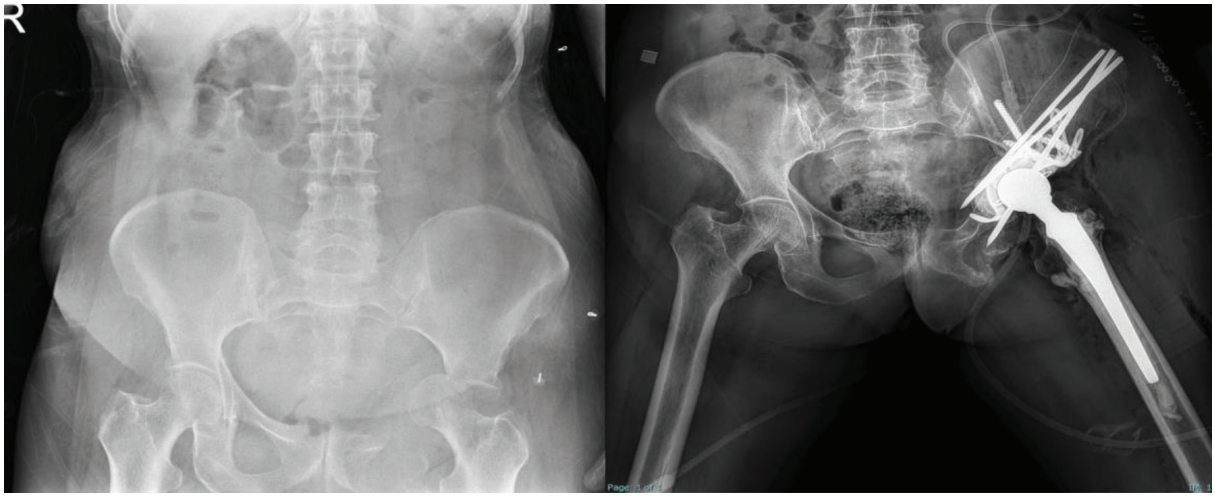

Figure 1. Preoperative and postoperative imaging-Harrington procedure. Preoperative (left) and postoperative (right) pelvic radiographs of a patient with primary bone lymphoma involving the iliac wing and acetabulum. Preoperative imaging shows bone destruction and loss of structural integrity in the left hemipelvis. The patient underwent Harrington reconstruction with total hip arthroplasty, Steinmann pins, plate fixation, and screws, providing structural stabilization and enabling functional restoration after oncologic treatment.

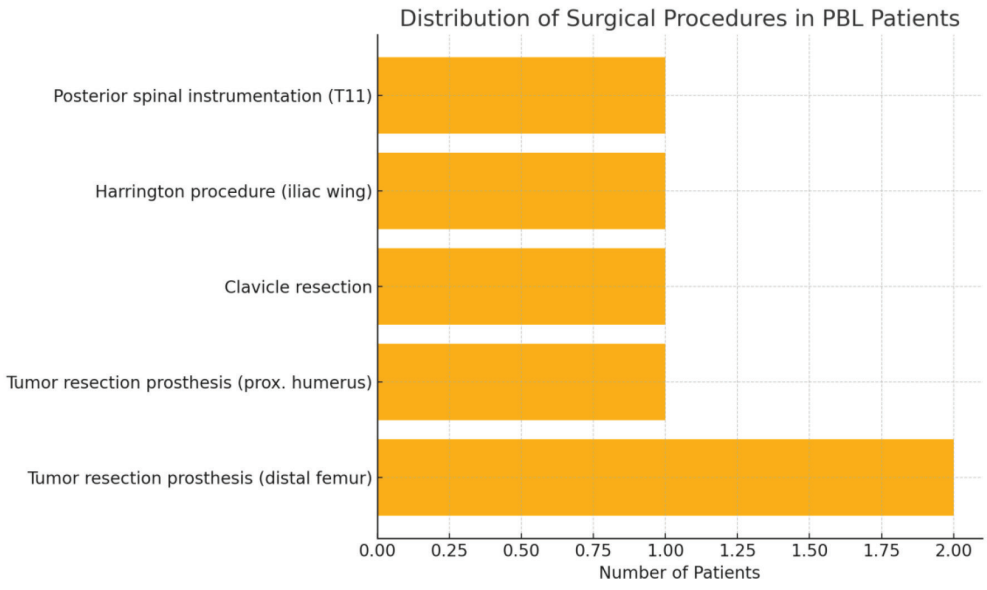

Figure 2. Distribution of surgical procedures in PBL patients. Distribution of surgical procedures in patients with primary bone lymphoma. Tumor resection prostheses were the most frequent, particularly for distal femur and proximal humerus involvement. Other procedures included clavicle resection, Harrington procedure for iliac wing fracture, and posterior spinal instrumentation for vertebral involvement.

PBL, primary bone lymphoma.

performed in conjunction with systemic therapy. Combined chemoradiotherapy, supplemented by surgery when necessary, reflects the current multidisciplinary approach. This approach aims to maximize local control and eradicate systemic disease.[6]

Response and Survival Outcomes

Treatment response was evaluated after completion of first-line therapy (chemo ± RT). A CR, defined as the absence of detectable disease on imaging and resolution of symptoms, was achieved in 13 patients (87%). All patients who received combined modality therapy achieved complete remission (CR), and post-treatment imaging (most commonly positron emission tomography (PET)/computed tomography confirmed complete metabolic remission. Two patients (13%) achieved only a partial remission (PR), defined as either residual lesion activity or size reduction without complete clearance. Both PR cases were observed in patients with multifocal bone disease. These patients were closely monitored, and one subsequently received salvage chemotherapy with radiotherapy to the remaining active lesion. No cases of primary refractory disease (progression during therapy) were observed in this series.

The median follow-up was 37 months (range: 18-66 months), and survival outcomes were encouraging. At the last follow-up, 13 patients (87%) were alive, including 12 (80%) in continuous complete remission. One patient who had initially shown a PR relapsed 18 months after treatment and died of progressive lymphoma despite salvage therapies. Another patient died of a cardiac cause at 30 months, while in remission. The 3-year OS rate was approximately 87% and the disease-free survival rate was similar among patients with localized disease. Due to the small sample size, formal survival curves were not plotted; however, the results are consistent with the high survival rates reported in larger studies.[7] Notably, all early-stage (I/II) patients who received combined chemo-radiotherapy remained in remission, underscoring the efficacy of this approach in localized PBL. Lymphoma-related mortality occurred only in a patient with initially advanced (multifocal) disease.

During follow-up, no major skeletal complications or significant postoperative problems were observed. Functional outcomes were satisfactory in all surviving patients, with adequate mobility. Surgical interventions such as tumor resection, prostheses, clavicle resection, the Harrington procedure, and spinal instrumentation were well tolerated. In the patient with a humeral fracture, bone healing was satisfactory following tumor resection and prosthetic reconstruction. These findings indicate that, in addition to effective lymphoma treatment, appropriately selected surgical interventions can help maintain skeletal integrity and support functional recovery.

DISCUSSION

In this retrospective analysis of 15 patients with PBL treated at a single tertiary center, we observed treatment outcomes consistent with prior literature, reaffirming the favorable prognosis of this rare disease when appropriately managed. The majority of patients (87%) achieved complete response following combination therapy, with estimated 3-year overall survival of approximately 87%.

Nearly all patients in our series had DLBCL histology and presented with localized skeletal disease, which aligns with previous reports that describe DLBCL as the predominant subtype of PBL.[8] The median age of our cohort was 53 years (range: 30-73), slightly younger than the typical 5th to 6th-decadepeak typically seen in the 5th to 6th decades in larger Western series.[7,9] This difference may reflect the inclusion of

a broader age spectrum and the small sample size. Our cohort had a near-equal sex distribution (7 males, 8 females), differing from the mild male predominance reported in some studies.[7] In contemporary series, elevated serum lactate dehydrogenase (LDH) levels and higher International Prognostic Index (IPI) scores have been consistently associated with inferior outcomes, while achieving a complete metabolic response on end-of-treatment PET is one of the strongest predictors of favorable survival. In our cohort, LDH and IPI data were limited, but all patients who achieved PET-CR have remained in remission.[5,10]

Unlike prior series where long bones —particularly the femur— were most commonly involved, our distribution showed more frequent axial skeleton and pelvic bone involvement. The femur was involved in only 2 patients (13%), the tibia (± fibula) in 1 patient (7%), and the humerus in 1 patient (7%). Other isolated sites included the glenoid, distal tibia, proximal humerus, distal clavicle, and sternum. Importantly, 8 patients (53%) had axial or pelvic involvement, including vertebral disease, which is relatively high compared to some Western cohorts, but similar to certain Japanese or multiethnic series, where axial PBL predominates and higher-stage disease is more common.[11] Our cohort's relatively higher rate of axial/pelvic involvement aligns with findings from recent large adult PBL series (Liang et al.[12], Li et al.[13]), which also report that spinal/axial bone involvement is associated with a distinct clinical course and may contribute to increased need for stabilization and symptom-driven interventions.[12,13]

Despite this variation in anatomical distribution, 80% of our patients had Ann Arbor stage I-II disease at presentation, consistent with the general trend that PBL remains localized in most cases at diagnosis.[14] All patients were treated with curative intent, utilizing anthracycline-based chemotherapy (typically R-CHOP) with involved-field radiotherapy in localized cases (Table 2). According to recent multi-institutional data, in limited-stage PB-DLBCL, excellent outcomes can be achieved with systemic therapy alone; routine consolidative radiotherapy may not provide additional benefit after PET-documented complete remission, whereas radiotherapy remains reasonable for partial responders or symptomatic sites. In multifocal disease, RT is typically reserved for palliation or focal control.[15,16] This combined modality treatment is well-established as the standard of care and has shown improved outcomes over single modality approaches.[7]

Beyond fracture stabilization, surgery in PBL may be indicated for mechanical instability threatening functional integrity, intractable pain unresponsive to systemic therapy or radiotherapy, or neural compromise in vertebral disease. In selected pelvic cases, reconstructive approaches such as the Harrington procedure can restore load transfer and mobility.[5] The complete response rate of 87% and the sustained remission observed in our patients support the effectiveness of this approach. Previous studies, including those by Beal et al.[1], have shown 5-year overall survival rates of 80-90% in similarly treated cohorts. Our findings are in line with these data, and notably, all stage I-II patients treated with combination therapy remain disease-free to date.

The only relapse in our series occurred in a patient with multifocal bone involvement, echoing the known poorer prognosis in disseminated PBL.[10] Nonetheless, even this patient initially responded to treatment, underlining the chemosensitivity of PBL.

Study Limitations

This study has limitations due to its retrospective design and small sample size. The absence of standardized reporting on prognostic markers such as LDH and IPI scores restricts further risk stratification. Moreover, variations in follow-up duration limit long-term outcome analysis, especially regarding late complications or secondary malignancies.

Still, our study adds valuable real-world evidence, demonstrating that effective treatment of PBL is achievable even in single-center settings. For clinicians, the key message remains: early biopsy of suspicious bone lesions, appropriate histopathologic confirmation, and multidisciplinary management are essential. Our findings reinforce that with modern chemoimmunotherapy and site-directed radiotherapy, PBL —though rare— is a highly curable lymphoma, particularly when diagnosed in its localized stage.

Clinical Implications

For clinicians, our findings reinforce the importance of treating PBL with curative intent using combination chemo-immunotherapy and site-directed radiotherapy, particularly in patients with localized disease. The high response and survival rates observed in our series —despite a notable proportion of patients having axial or pelvic involvement— highlight the disease's sensitivity to modern therapeutic strategies.

Early and accurate diagnosis remains a critical challenge. Several patients were initially misdiagnosed with benign conditions such as osteomyelitis or other non-neoplastic bone lesions,

Table 2. Treatment Modalities and Outcomes in 15 PBL Patients

Stage	Treatment given	No of patients	Response (CR/PR)
Stage I/II	R-CHOP + RT	12	12 CR / 0 PR
Stage IV	Chemotherapy alone	3	1 CR / 2 PR
Total		15	13 CR / 2 PR

Treatment modalities and therapeutic responses in 15 patients with primary bone lymphoma. All patients with localized disease (Ann Arbor Stage I/II) received combined chemo-immunotherapy (R-CHOP) and involved-field radiotherapy, achieving complete remission (CR). Among three patients with advanced-stage disease (Stage IV), chemotherapy alone yielded one complete remission and two partial responses (PR), demonstrating lower efficacy compared to combined modality treatment. RT, radiotherapy.

consistent with the known diagnostic difficulty of PBL due to its rarity and nonspecific clinical presentation. Increased clinical awareness and prompt biopsy of suspicious bone lesions are essential to avoid delays in treatment initiation.

Optimal management requires a multidisciplinary approach involving hematology/oncology, radiation oncology, and orthopedic surgery, especially when structural compromise or pathological fractures are present. Timely coordination between specialties ensures comprehensive care and enhances the likelihood of long-term remission.

CONCLUSION

In summary, our single-center retrospective analysis of 15 patients with primary bone lymphoma demonstrates excellent treatment outcomes with modern combined modality therapy. Most patients had DLBCL and presented with localized disease; however, our cohort had a relatively high rate of axial and pelvic involvement, highlighting potential variations in disease presentation across different populations.

All patients received systemic therapy, typically R-CHOP, with radiotherapy applied in localized cases. The complete response rate was high, and the only relapse occurred in a patient with multifocal disease, consistent with literature indicating that disseminated PBL may have a higher risk of recurrence.

While limited by small sample size and retrospective design, our findings contribute real-world evidence supporting current treatment standards. Future studies should focus on multi-institutional collaboration to refine prognostic factors (e.g., PET response, molecular subtypes) and further optimize therapeutic strategies.

Given the rarity of PBL, sharing institutional experiences remains essential. Our results affirm that, despite diagnostic challenges, primary bone lymphoma is a highly curable malignancy when diagnosed promptly and managed with a multidisciplinary, evidence-based approach.

Ethics

Ethics Committee Approval: Approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar Training and Research Hospital Hospital Ethics Committee (approval no.: 2020/514/177/31, date:13.05.2020)

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept Design – M.S.A.; Data Collection and/or Processing – M.S.A., Ö.F.S.; Analysis or Interpretation – M.S.A., E.B.; Literature Review – Ö.F.S., S.A.G.; Writing, Reviewing and Editing – E.B., S.A.G.

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Research Article

Psychiatrists' Attitudes and Perspectives Towards Incarcerated Patients: Biases, Ethical Dilemmas, and Clinical Challenges

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ABSTRACT

Objective: This study aims to evaluate the attitudes, biases, ethical dilemmas, and clinical challenges faced by psychiatrists in Türkiye towards incarcerated patients.

Methods: This is a cross-sectional, descriptive, quantitative study. A total of 234 psychiatrists, including psychiatry specialists, academics, and residents from across Türkiye, participated in the study via an online survey. The survey included questions regarding sociodemographic information, experience working with incarcerated patients, attitudes toward incarcerated patients, level of empathy, ethical dilemmas, safety concerns, and therapeutic nihilism, as well as opinions about available services.

Results: The majority of participants had worked with incarcerated patients in the past or currently. This group identified several factors that make providing psychiatric services challenging in the prison environment: personality disorders, addiction, safety concerns, inadequate resources, and ethical dilemmas. Those who struggled to empathize with incarcerated patients were younger and less experienced, and this group had lower hope for recovery, lower confidence in treatment, and higher fear for their safety. The majority of participants perceived prison psychiatric services as inadequate and emphasized the importance of post-release psychiatric support. The importance of family and social support systems was also highly recognized.

Conclusion: The findings reveal that psychiatrists face significant professional and ethical challenges in the prison environment and may develop biases. To effectively treat incarcerated patients, prison mental health services must be strengthened, staff training increased, safe working conditions ensured, and supervision and empathy-focused training supported for young clinicians. These steps will improve the quality of care for incarcerated patients, and contribute to the provision of higher-quality healthcare services by reducing burnout and stress among psychiatrists.

Keywords: Incarcerated patients, prison psychiatry, psychiatrist attitudes, ethical dilemmas, therapeutic nihilism, difficulty in empathy

INTRODUCTION

The prevalence of mental disorders in prisons is significantly higher than in the general population. However, providing mental health services in correctional settings poses significant challenges and limitations.[1]

During hospital-based evaluations of incarcerated patients, several ethical dilemmas arise, including the inability to ensure privacy, conducting assessments while the patient remains handcuffed, and the presence of security personnel in the examination room. These factors further complicate the psychiatric evaluation process.[2] The conditions within correctional facilities also significantly hinder the psychiatric evaluation process for both incarcerated patients and psychiatrists. The overriding emphasis on maintaining security can undermine the development of a therapeutic alliance

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between the patient and the clinician.[3] Psychiatrists may struggle with the dual responsibility of safeguarding the mental health of incarcerated patients while simultaneously adhering to institutional rules. This dynamic also makes it more difficult for incarcerated patients to trust their psychiatrist, thereby limiting effective communication.[4]

Some of the most challenging aspects of the physician-patient relationship in correctional settings involve concerns about the reliability of incarcerated patients and concerns about attempts at manipulation.[5] Such situations may lead, over time, to the development of bias, excessive caution, or increased emotional distancing. Psychiatrists' perceptions and attitudes toward incarcerated patients can negatively impact diagnostic and treatment planning processes. Prescription drug misuse, in particular, remains a significant concern in correctional facilities. Overall, the suspicion of manipulation, ethical dilemmas, and lack of trust may contribute to heightened stress and an increased risk of burnout among psychiatrists working in correctional settings.[6] During this process, psychiatrists may develop certain biases toward incarcerated patients, such as the belief that those convicted of severe crimes exaggerate their symptoms or are malingering. Over time, such beliefs may give rise to a countertransference reaction known as "therapeutic nihilism", characterized by the perception that treatment is futile.[7] Therapeutic nihilism denotes a skeptical or pessimistic stance toward the effectiveness of medical interventions, often leading clinicians to limit or avoid treatment. This perspective influences clinical decision-making, at times contributing to undertreatment or neglect of patient needs.[8]

Psychiatrists must remain attuned to a range of challenges when working with incarcerated patients, including the regulation of empathy, managing personal biases, resolving ethical dilemmas, addressing safety concerns, and detecting malingering or manipulative behavior. Although prior studies have explored ethical dilemmas and factors affecting the therapeutic relationship in correctional settings, there is a notable lack of research that systematically examines psychiatrists' attitudes, biases, and approaches toward incarcerated patients, particularly regarding determinants such as prior experience with this population. Moreover, the impact of correctional psychiatry experience on empathy, attitudes, and bias during clinical evaluations remains underexplored in the literature.

This study aims to assess psychiatrists' attitudes and perceptions toward incarcerated patients, as well as the ethical dilemmas they encounter. By doing so, it seeks to offer meaningful recommendations for improving psychiatric assessment processes, reducing bias, enhancing access to mental health care, and drawing attention to the unique challenges faced by both incarcerated patients and the psychiatrists who work with them. Additionally, the study highlights the value of clinical exposure, supervision, and awareness of correctional psychiatry during psychiatric training. It also aims to contribute to the development of more effective mental health services and policies within correctional settings, ultimately helping to improve care delivery for incarcerated patients and support psychiatrists in providing treatment under more appropriate conditions.

MAIN POINTS

- Psychiatrists who were younger and had fewer years of experience were significantly more likely to report difficulty empathizing with incarcerated patients.
- More than 60% of psychiatrists believed that incarcerated patients are prone to lying or manipulation, reflecting high levels of distrust and therapeutic nihilism.
- The majority of psychiatrists considered prison-based mental health services inadequate and highlighted the importance of continued psychiatric care after release.
- Nearly all psychiatrists supported the need for specialized training, regular supervision, and improved safety protocols in correctional mental health settings.

MATERIAL AND METHODS

Study Design and Data Collection

This study is a cross-sectional and descriptive quantitative research that examines the attitudes, biases, and ethical dilemmas of psychiatrists in Türkiye toward incarcerated patients. Data were collected through an online survey.

The sample consisted of psychiatrists, including specialists, academic faculty members, and residents working across Türkiye. A total of 234 psychiatrists, recruited through a convenience sampling method between April and July 2025, participated in the study. The online questionnaire was distributed via professional email groups, social media platforms, and personal professional networks. Participants were provided with detailed information about the study and gave informed consent. The survey was completed anonymously and on a self-administered basis.

The inclusion criteria were actively working in the field of psychiatry in Türkiye, completing the survey fully and validly, and voluntarily participating in the study. Exclusion criteria included incomplete or invalid responses and being employed in a non-psychiatric medical specialty.

The data collection tool was a questionnaire developed by the research team based on relevant literature. The survey consisted of 45 items, covering the following themes: sociodemographic characteristics (6 items), attitudes and perceptions toward incarcerated patients (11 items), general views on the prison environment and treatment process (16 items), areas in need of improvement in prison-based psychiatric services (6 items), and perceived usefulness of support mechanisms for psychiatrists working in correctional settings (6 items).

The study was approved by the Ethics Committee of Giresun Training and Research Hospital (decision no.: 16.04.2025/19, date: 16.04.2025) and conducted in accordance with the principles of the Declaration of Helsinki and current ethical guidelines.

Statistical Analyses

Data were analyzed using IBM SPSS Statistics version 27. Descriptive statistics included means, standard deviations, medians, and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Normality assumptions were assessed using histograms. For non-normally distributed continuous variables, the Kruskal-Wallis test was used for comparisons across multiple groups, and the Mann-Whitney U test for two-group comparisons. To control for type I error in multiple non-parametric comparisons, Bonferroni correction was applied where appropriate. Associations between categorical variables were evaluated using the chi-square test. One-way analysis of variance was applied to assess the variance between certain continuous variables. A significance level of $P < 0.05$ was accepted for all analyses.

RESULTS

A total of 234 psychiatrists participated in the study. Of these, 167 were female (71.4%) and 67 were male (28.6%). Regarding professional groups, 157 (67.1%) were specialists, 32 (13.7%) were residents, and 45 (19.2%) were academic physicians. The mean age of participants was 37.1 ± 7.6 years. Most participants were employed in institutions located in urban centers (83.8%). The most common workplaces were training and research hospitals (33.3%) and state hospitals (31.2%), followed by university hospitals (16.2%).

A total of 81.2% of participants reported that they had worked with incarcerated patients either currently or in the past. Among those with such experience, psychiatrists reported evaluating an average of 31 incarcerated patients per month, spending approximately 13 minutes per patient. The perceived difficulty of working with this group was rated as 6.3 out of 10 on average. Most evaluations were conducted in outpatient hospital consultation rooms (78.4%), followed by prison-based examination rooms (40.5%). Incarcerated patients were most commonly assessed in the presence of law enforcement personnel, with the most frequent method being evaluation while handcuffed (45.3%), followed by unrestrained evaluations under security supervision (33.7%). The most common reasons for referral were requests for psychiatric medication (68.0%) and psychiatric symptom evaluation (67.9%). Willingness to continue working with incarcerated patients was relatively low (21.1% Yes, 45.3% No). Key challenges identified in working with incarcerated patients included a high prevalence of comorbid personality disorders (89.5%) and risk of substance misuse (84.2%). Other frequently reported issues were substance use disorders (67.4%) and the impact of prison conditions on treatment (50.5%). When more time was needed for evaluation, over half of the participants (56.8%) reported extending the interview, while 18.9% preferred to conclude with symptom-oriented treatment. Pharmacological treatment was the most commonly used therapeutic approach (56.3%), while no participant reported using psychotherapy alone in this population.

A significant proportion of participants reported disagreement with certain statements reflecting prejudicial attitudes toward incarcerated patients. Most participants reported that incarcerated patients had relatively low expectations of recovery. The majority (approximately 56%) reported no difficulty empathizing with incarcerated patients, while only 18% agreed with the statement indicating such difficulty. According to participants, the most frequently reported reason for difficulty in empathizing with incarcerated patients was the belief that the individual might be manipulative. More than half of the participants reported experiencing safety-related fear during face-to-face interviews with incarcerated patients. The most commonly cited reason for this fear, based on multiple response options, was perceived security vulnerabilities within the prison setting. On average, the perceived effectiveness of pharmacological treatment in this population was around 50%, whereas the effectiveness of psychotherapy was perceived to be approximately 30%. The distribution of participants' attitudes and perceptions towards incarcerated patients is shown in Table 1.

The vast majority of participants agreed that the prison environment has a negative impact on the mental health of incarcerated patients. Similarly, most participants believed that existing psychiatric services in prisons are insufficient and that access to these services is limited. Most participants acknowledged facing ethical challenges when working with incarcerated patients and noted the difficulty of balancing public safety with patients' rights. Psychiatrists' general views on the prison environment and treatment process are shown in Table 2.

The vast majority of participants indicated that improvements are needed across nearly all aspects of mental health services in correctional settings (Table 3). There was broad agreement that most of the proposed support mechanisms would be beneficial (Table 4).

Among all participants, several notable differences emerged when groups were compared according to their responses to the statement "I have difficulty empathizing with incarcerated patients." Participants who reported difficulty empathizing (either "agree" or "strongly agree") were younger. Similarly, the median number of years working in psychiatry was lower among those who reported difficulty empathizing. Participants who had difficulty empathizing were also more likely to believe that incarcerated patients have a lower potential for recovery. Additionally, nearly all participants in the empathy-difficulty group agreed with the statement "I generally feel distrustful of incarcerated patients due to the likelihood of lying or manipulative behavior." The proportion of participants who reported experiencing fear during interviews with incarcerated patients was also significantly higher in the empathy-difficulty group. Furthermore, participants who reported difficulty empathizing rated the effectiveness of pharmacological treatment in incarcerated patients significantly lower than other groups. The comparison of participants based on difficulty in empathizing with incarcerated patients (full sample) is shown in Table 5.

Among psychiatrists who had previously worked with incarcerated patients, several differences were observed between those who reported difficulty empathizing and those who did not. Willingness to work with this population

Table 1. Participants' Attitudes and Perceptions Toward Incarcerated Patients

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
The type of crime committed by the incarcerated patient consciously or unconsciously affects my clinical approach or treatment plan.	76 (32.5%)	54 (23.1%)	40 (17.1%)	54 (23.1%)	10 (4.3%)
News coverage or public opinion influences my general perceptions and expectations regarding incarcerated patients.	101 (43.2%)	56 (23.9%)	37 (15.8%)	34 (14.5%)	6 (2.6%)
I believe that incarcerated patients have a lower potential for recovery compared to others.	27 (11.5%)	64 (27.3%)	33 (14.1%)	94 (40.2%)	16 (6.8%)
I have difficulty empathizing with incarcerated patients.	49 (20.9%)	83 (35.5%)	60 (25.6%)	39 (16.7%)	3 (1.3%)
I generally feel distrustful of incarcerated patients due to the likelihood of lying or manipulative behavior.	51 (21.8%)	61 (26.1%)	15 (6.4%)	121 (51.7%)	27 (11.5%)
				n	**%**
What do you think are the reasons for difficulty in empathizing with incarcerated patients? (you may select more than one)					
The fact that the patient is incarcerated				49	23.2
Safety concerns				69	32.7
Feelings of anger toward the patient				70	33.2
Suspicion that the patient is manipulative				179	84.8
Other				18	9
Do you experience fear for your safety when interviewing incarcerated patients?					
Yes				123	52.6
No				111	47.4
What are the reasons for your safety-related fears during interviews with incarcerated patients? (you may select more than one)					
The fact that the person is a convicted offender				93	38.7
Risk of lying or manipulative behavior				104	44.4
Security vulnerabilities in the correctional setting				169	72.2
Other				17	6.8
				Mean	**SD**
In your opinion, what percentage of incarcerated patients' psychiatric conditions and treatment needs are influenced by legal processes and prison conditions?				39.7	21.0
In your opinion, what is the effectiveness rate (%) of pharmacological treatment in incarcerated patients?				48.8	18.1
In your opinion, what is the effectiveness rate (%) of psychotherapy in incarcerated patients?				29.8	19.0

n, sample size; SD, standard deviation.

varied significantly between groups. Similarly, participants who experienced empathy difficulties were more likely to rank incarcerated patients among the most challenging or least preferred patient groups. A substantial portion of those with empathy difficulties believed that incarcerated patients have a lower potential for recovery. Nearly all in the empathy-difficulty group expressed distrust regarding the likelihood of lying or manipulation by incarcerated patients, whereas this view was much less common in the comparison group. Fear during face-to-face interviews with incarcerated patients was also significantly more frequent in the empathy-difficulty group. A comparison of psychiatrists with and without empathy difficulties among those with experience working with incarcerated patients is shown in Table 6.

Psychiatrists with prior experience working with incarcerated patients and those without such experience generally exhibited similar attitudes and beliefs. There were no significant differences between the two groups in agreement with the statements "Incarcerated patients have a lower potential for recovery" (P = 0.955), "I have difficulty empathizing with incarcerated patients" (P = 0.637), or "I generally feel distrustful of incarcerated patients" (P = 0.378). However, a significant difference emerged regarding safety-related concerns. Among psychiatrists without prior experience, 79.5% reported that they would feel fearful during face-to-face interviews with incarcerated patients, compared to 46.3% of those with experience, a statistically significant difference (X^2 = 14.517, P < 0.001). Perceptions of the effectiveness of pharmacological and psychotherapeutic treatments in incarcerated patients were similar between the two groups (P > 0.05).

DISCUSSION

The reported mean difficulty level of working with incarcerated patients (6.3/10) is consistent with findings in the literature

Table 2. General Views on the Prison Environment and Treatment Process

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
The prison environment negatively affects the mental health of incarcerated patients.	2 (0.9%)	31 (13.2%)	29 (12.4%)	145 (62%)	27 (11.5%)
The effects of the prison environment on mental health depend on individual circumstances.	15 (6.4%)	35 (15%)	49 (20.9%)	124 (53%)	11 (4.7%)
Psychiatric services in prisons are sufficient.	116 (49.6%)	52 (22.2%)	48 (20.5%)	17 (7.3%)	1 (0.4%)
Access to psychiatric services in prisons is easy.	83 (35.5%)	61 (26.1%)	57 (24.4%)	26 (11.1%)	7 (3%)
Psychiatric services in prisons need to be improved.	5 (2.1%)	12 (5.1%)	35 (15%)	124 (53%)	58 (24.8%)
Psychiatric support is important for the reintegration of incarcerated patients after release.	1 (0.4%)	10 (4.3%)	20 (8.5%)	130 (55.6%)	73 (31.2%)
Families and other support systems play an important role in the treatment of incarcerated patients.	2 (0.9%)	2 (0.9%)	10 (4.3%)	127 (54.3%)	93 (39.7%)
Ethical difficulties are encountered when working with incarcerated patients.	7 (3%)	14 (6%)	44 (18.8%)	131 (56%)	38 (16.2%)
It is difficult to balance public safety with the individual rights of incarcerated patients.	11 (4.7%)	27 (11.5%)	41 (17.5%)	124 (53%)	31 (13.2%)
Stigma and prejudice play a significant role in the treatment of incarcerated patients.	7 (3%)	21 (9%)	34 (14.5%)	141 (60.3%)	31 (13.2%)
I believe prison conditions negatively affect the treatment process.	9 (3.8%)	27 (11.5%)	31 (13.2%)	133 (56.8%)	34 (14.5%)
There are inequalities in access to treatment and quality of care for incarcerated patients.	12 (5.1%)	19 (8.1%)	50 (21.4%)	122 (52.1%)	31 (13.2%)
Legal processes and the prison environment affect psychiatric diagnoses.	9 (3.8%)	20 (8.5%)	33 (14.1%)	146 (62.4%)	26 (11.1%)
A history of trauma and abuse plays an important role in the treatment of incarcerated patients.	4 (1.7%)	12 (5.1%)	24 (10.3%)	149 (63.7%)	45 (19.2%)
Substance use disorders and addiction are major challenges in the treatment of incarcerated patients.	1 (0.4%)	1 (0.4%)	8 (3.4%)	97 (41.5%)	127 (54.3%)
Suicide risk and self-harming behaviors are significant problems in the treatment of incarcerated patients.	0 (0%)	7 (3%)	11 (4.7%)	105 (44.9%)	111 (47.4%)

that associate correctional psychiatry with high levels of stress, professional burnout, and safety concerns.[9] The frequent use of mechanical restraints such as handcuffs may undermine trust between patient and clinician, trigger aggressive behavior, and negatively affect the quality of the therapeutic relationship.[10]

Nearly half of the participants indicated reluctance to work with incarcerated patients, underscoring the high-stress and burnout-prone nature of correctional psychiatry. This finding aligns with the existing literature.[11] The prevalence of burnout among general psychiatrists has been reported at approximately 26%, and this figure is even higher in forensic or correctional settings.[12] Similarly, frequent reports of stress and trauma among correctional staff are thought to contribute to limited interest and high levels of reluctance toward working in this field.[13]

An examination of participants' treatment strategies revealed that the majority relied primarily on psychopharmacological interventions, and none reported using psychotherapy alone. This finding may reflect the limited availability of psychotherapy in correctional settings, as well as the practical preference for shorter-term solutions, like pharmacotherapy, due to the characteristics of the patient population.[14] The high prevalence of personality disorders, substance use, and low treatment motivation among incarcerated individuals also presents barriers to psychotherapy, such as these, and may contribute to the prioritization of pharmacological approaches.[15]

A considerable proportion of participants disagreed with statements reflecting prejudicial attitudes toward incarcerated patients and stated that the type of crime committed by the patient did not influence their treatment planning. This suggests that efforts are being made to uphold ethical standards in correctional psychiatry and to maintain a clinical approach that is independent of the offense. The literature similarly emphasizes that adherence to ethical principles should remain consistent regardless of the nature of the crime, and that allowing the offense to shape the psychiatric treatment plan is inconsistent with professional integrity.[16] Likewise, the majority of participants rejected the idea that media narratives or societal prejudices influence their clinical attitudes, which may reflect an effort among psychiatrists to preserve the independence of their evaluations.

Table 3. Areas in Need of Improvement in Prison-Based Psychiatric Services

	Yes	No	No opinion
The number of psychiatrists and other mental health professionals in prisons should be increased.	193 (82.5%)	22 (9.4%)	19 (8.1%)
Correctional staff should be trained in mental health.	228 (97.4%)	3 (1.3%)	3 (1.3%)
More diverse treatment options should be offered.	209 (89.3%)	13 (5.6%)	12 (5.1%)
Follow-up appointments should be scheduled for after release.	208 (88.9%)	8 (3.4%)	18 (7.7%)
Incarcerated patients should be provided with information about community resources and support groups.	224 (95.7%)	5 (2.1%)	5 (2.1%)
Communication with family members should be supported.	219 (93.6%)	4 (1.7%)	11 (4.7%)

Table 4. Perceived Usefulness of Support Mechanisms for Psychiatrists Working in Correctional Settings

	Useful	Partially useful	Not useful
Regular supervision and peer support.	191 (81.6%)	37 (15.8%)	6 (2.6%)
Adequate training and resources.	189 (80.8%)	43 (18.4%)	2 (0.9%)
Safe working environment and security protocols.	219 (93.6%)	15 (6.4%)	0 (0%)
Formation of specialized psychiatric teams for treating incarcerated patients.	189 (80.8%)	40 (17.1%)	5 (2.1%)
Establishing a distinct training area or subspecialty in correctional psychiatry.	144 (61.5%)	54 (23.1%)	36 (15.4%)
Increasing opportunities for working with and researching incarcerated patients.	177 (75.6%)	50 (21.4%)	7 (3%)

Table 5. Comparison of Participants Based on Difficulty in Empathizing with Incarcerated Patients (Full Sample)

Mean ± SD / Median (Q1-Q3) / n (%)	Strongly disagree / disagree	Neutral	Agree / strongly agree	Statistic	*P*
Age (years)	36 (33-41.8)	34 (32-39)	33.5 (31-37.3)	KW = 9.539	**0.008**
Years of experience in psychiatry	10 (7-14.8)	8 (6-12)	7.5 (5-12.3)	KW = 8.763	**0.013**
I believe incarcerated patients have a lower potential for recovery than others.				X^2 = 51.095	**< 0.001**
Disagree	73 (55.3%)	14 (23.3%)	4 (9.5%)		
Neutral	18 (13.6%)	13 (21.7%)	2 (4.8%)		
Agree	41 (31.1%)	33 (55%)	36 (85.7%)		
I generally feel distrustful of incarcerated patients due to the likelihood of lying or manipulative behavior.				X^2 = 43.818	**< 0.001**
Disagree	59 (44.7%)	11 (18.3%)	1 (2.4%)		
Neutral	10 (7.6%)	4 (6.7%)	1 (2.4%)		
Agree	63 (47.7%)	45 (75%)	40 (95.2%)		
Do you experience fear for your safety during interviews with incarcerated patients?				X^2 = 14.764	**< 0.001**
No	76 (57.6%)	24 (40%)	11 (26.2%)		
Yes	56 (42.4%)	36 (60%)	31 (73.8%)		
What is your estimate of the effectiveness (%) of pharmacological treatment in incarcerated patients?	49.9 ± 18.0	51.0 ± 18.0	42.62 ± 17.8	F = 3.159	**0.044**

n, sample size; *P*, significance level; Q1, first quartile; Q3, third quartile; KW, Kruskal-Wallis test; F, statistic; ANOVA, analysis of variance; SD, standard deviation; X^2, chi-square test.

Table 6. Comparison of Psychiatrists with and Without Empathy Difficulties Among Those with Experience Working with Incarcerated Patients

Median (Q1-Q3) / n (%)	Strongly disagree / disagree	Neutral	Agree / strongly agree	Statistic	*P*
Would you prefer to work with incarcerated patients?				X^2 = 18.180	**0.001**
Yes	31 (28.2%)	10 (21.7%)	1 (3.1%)		
No	40 (36.4%)	17 (37%)	23 (71.9%)		
Undecided	39 (35.5%)	19 (41.3%)	8 (25%)		
If you ranked the most difficult or least preferred patient groups to work with, where would incarcerated patients fall?	6 (5-8)	6 (5-7)	8 (6-8)	KW = 9.142	**0.010**
I believe incarcerated patients have a lower potential for recovery than others.				X^2 = 41.600	**< 0.001**
Disagree	59 (53.6%)	11 (23.4%)	3 (9.1%)		
Neutral	16 (14.5%)	10 (21.3%)	1 (3%)		
Agree	35 (31.8%)	26 (55.3%)	29 (87.9%)		
I generally feel distrustful of incarcerated patients due to the likelihood of lying or manipulative behavior.				X^2 = 38.415	**< 0.001**
Disagree	49 (44.5%)	8 (17%)	1 (3%)		
Neutral	8 (7.3%)	2 (4.3%)	0 (0%)		
Agree	53 (48.2%)	37 (78.7%)	32 (97%)		
Do you experience fear during interviews with incarcerated patients?				X^2 = 12.708	**0.002**
No	70 (63.6%)	22 (46.8%)	10 (30.3%)		
Yes	40 (36.4%)	25 (53.2%)	33 (69.7%)		

n, sample size; *P*, significance level; Q1, first quartile; Q3, third quartile; KW, Kruskal-Wallis test; SD, standard deviation; X^2, chi-square test.

The study found a relatively high proportion of psychiatrists who believed that incarcerated patients have a lower potential for recovery. In the literature, this attitude has been described as a common phenomenon among professionals working in forensic and correctional psychiatry, and is conceptualized as "therapeutic nihilism".[17] Contributing factors may include high psychiatric burden, difficulties with treatment continuity and follow-up, poor adherence, comorbid psychiatric disorders and personality pathology, substance use, behavioral disturbances, risk of violence, limited resources, and the moral weight of the offense. Previous studies have noted that psychiatrists working in prisons may develop a belief that meaningful change is unlikely in incarcerated patients, which can lead to reduced empathy and diminished motivation to treat patients.[18] Such attitudes have been recognized as a major barrier to providing adequate mental health care for stigmatized populations like incarcerated patients.[19] Taken together, our findings suggest that therapeutic nihilism remains a noteworthy tendency in correctional psychiatry. To address this, it is essential to promote access to research and clinical experiences with incarcerated populations, share evidence demonstrating positive treatment outcomes, enhance staff training, and reinforce ethical awareness.

While more than half of the participants reported no difficulty in empathizing with incarcerated patients, 18% indicated agreement with the statement "I find it difficult to empathize with incarcerated patients." This finding suggests that a substantial proportion of psychiatrists working in correctional settings are not prone to stigmatizing attitudes and can maintain their empathic capacity as part of their professional role. Indeed, a recent meta-analysis found that despite the prevalence of stigma in correctional settings, the empathic capacity of prison mental health professionals can be preserved to a certain degree within the framework of professional identity.[20] However, the fact that a subset of participants reported difficulties in empathizing aligns with concepts such as negative countertransference and therapeutic nihilism.[21] This may be related to perceptions of incarcerated individuals as inherently "dangerous" or "untreatable" due to their criminal history, which in turn may impede the formation of an empathic therapeutic stance.

The statement "Incarcerated patients are more likely to lie or manipulate" was endorsed by 63.2% of participants. This high rate may reflect a general mistrust among psychiatrists working in correctional environments toward their patients. This finding is consistent with previous research demonstrating that a significant proportion of healthcare professionals in forensic settings tend to interpret incarcerated patients'

behaviors through the lens of secondary gain, manipulation, and dishonesty.[21]

A large majority of participants believed that the prison environment negatively affects the mental health of incarcerated patients. This finding is consistent with the existing literature emphasizing that the physical conditions of prisons, social isolation, and control-oriented approaches contribute to both the onset and exacerbation of psychiatric morbidity.[22] These findings align with studies demonstrating that prison mental health services have historically remained insufficient due to systemic shortcomings, lack of resources, and staffing shortages.[23] Contributing factors include the lack of training among personnel, high caseloads, and the prioritization of security concerns over therapeutic goals.[19]

More than two-thirds of participants indicated that prison psychiatric services need improvement, and the vast majority emphasized the importance of post-release psychiatric support for successful reintegration. This supports the need for continuous mental health care to ensure rehabilitation and social reintegration of incarcerated individuals. Furthermore, the majority of participants emphasized the importance of family and social support systems in treatment and highlighted the ethical challenge of balancing public safety with the rights of the individual. This reflects a central dilemma frequently discussed in forensic psychiatry literature, namely, the tension between risk management and patient-centered care.[24] Mental health professionals working in forensic settings are tasked with safeguarding both individual well-being and the broader public interest.

The near-unanimous responses from participants regarding the need to improve mental health services in prisons highlight that prison psychiatry continues to face substantial structural and organizational shortcomings. Systematic reviews have shown that prison personnel often lack adequate knowledge and sensitivity regarding inmates' mental health problems, which negatively impacts both patients' access to care and the overall atmosphere within correctional facilities.[23]

The strong support (95.7%) for providing incarcerated individuals with information about community resources and support groups aligns with contemporary rehabilitation models aimed at social reintegration. One of the most significant risks faced by formerly incarcerated individuals upon release is the lack of social support, which can lead to recidivism and psychiatric decompensation.[25] Likewise, the high level of agreement (93.6%) on the importance of supporting communication with family members is consistent with robust evidence indicating that social support systems are critical protective factors for the mental health of incarcerated individuals. This finding suggests that psychiatrists prioritize patient well-being beyond ethical dilemmas, biases, or stigmatizing attitudes.

Participants' emphasis on the need for more diverse treatment options and post-release follow-up planning reflects the limitations of current services and the lack of continuity in care. Mental health services in prisons often remain restricted to crisis management, brief psychiatric evaluations, and pharmacotherapy. Psychotherapy, group therapy, addiction treatment, or rehabilitative approaches are frequently unavailable or extremely limited.[23] Given the heterogeneous burden of psychiatric illness in prison populations, treatment approaches should extend beyond medication to include diverse and individualized interventions such as cognitive behavioral therapy, substance use programs, and trauma-informed psychotherapy.[14,23] Therefore, mental health services for incarcerated patients must be expanded not only to ensure treatment but also to promote rehabilitation and reintegration.

One of the prominent findings of our study is that the majority of proposed support mechanisms in prison psychiatry were rated as highly beneficial by participants. This aligns with the literature highlighting frequent exposure of prison-based psychiatrists to violence risk, threats, emotional exhaustion, and burnout.[26] Systematic reviews have shown that regular supervision not only enhances clinical competence but also strengthens the ability to manage ethical dilemmas and improves self-efficacy.[27] The support expressed by 80.8% of participants for adequate training, resources, and the establishment of a dedicated psychiatric team for incarcerated patients reflects growing recognition that prison psychiatry requires specialized knowledge and skills. Evidence suggests that mental health services in correctional settings are more effective when delivered through multidisciplinary teams, which improve treatment continuity, crisis management, and patient satisfaction.[22] Furthermore, 75.6% of participants supported increased opportunities for working with and conducting research on incarcerated populations, indicating that prison psychiatry remains a neglected field that requires empirical development. However, the proposal to establish prison psychiatry as a formal subspecialty was the most divisive among respondents. Some experts advocate for formalizing prison/forensic psychiatry as a distinct specialty to enhance service quality, improve clinicians' ability to manage ethical dilemmas, and increase professional satisfaction.[28] Others argue that further fragmenting an already limited mental health workforce may weaken overall service capacity and, instead, recommend integrating forensic competencies into general psychiatric training.[29]

Our findings also provide key insights into how empathy capacity interacts with individual characteristics and perceptions in psychiatric practice with incarcerated patients. Notably, participants who reported greater difficulty in empathizing tended to be younger and less experienced, an association previously observed in other studies.[30]

The belief that incarcerated patients have a "low potential for recovery" and concerns about "manipulation" were also found to be more prevalent among clinicians reporting difficulty empathizing with this population. The literature indicates that overestimating psychopathic traits in individuals with criminal backgrounds can negatively impact treatment motivation and the therapeutic alliance, as noted in reference.[31] On the contrary, as the therapeutic alliance strengthens, positive behavioral change becomes more likely. This suggests that as motivation for recovery increases, perceived manipulativeness may decrease.[32] The significant association between heightened security concerns and empathy difficulty is noteworthy. Prior studies have emphasized that elevated perceived threat levels in prison environments can diminish both empathy and the

capacity to deliver patient-centered care.[33] Among clinicians working in high-security units, the generalization of patient behaviors and the dominance of "offender identity" are frequently observed phenomena.[34]

It is also notable that clinicians experiencing empathy difficulties reported significantly lower confidence in the effectiveness of pharmacotherapy for incarcerated patients. Studies suggest that clinicians working in correctional settings often demonstrate low treatment optimism, particularly regarding biological interventions.[35] Negative perceptions of biological treatments among clinicians with low empathy may undermine both the therapeutic relationship and patients' treatment expectations and engagement.

Among those with prior experience working with incarcerated individuals, clinicians reporting empathy difficulties were significantly less willing to work with this population, more likely to consider them an undesirable and challenging group to treat, and held more pessimistic views about their recovery potential. These clinicians also exhibited higher levels of distrust regarding inmates' honesty and manipulation potential, as well as increased security-related concerns during clinical encounters. Moreover, both experienced and inexperienced psychiatrists scored relatively high on key attitudinal items such as "low recovery potential" and "general distrust," suggesting that direct experience alone may not fully mitigate stigmatizing views. Previous studies have highlighted that even psychiatrists without prison experience can develop similar prejudiced attitudes, indicating that such perspectives are shaped more by broader educational and societal influences than by individual clinical exposure.[36]

Study Limitations

This study has several strengths. First, it includes a relatively large and diverse sample of psychiatrists from across Türkiye, which enhances the representativeness of the findings. Second, to our knowledge, this is the first nationwide study systematically examining psychiatrists' attitudes, biases, ethical dilemmas, and empathy-related difficulties when working with incarcerated patients in Türkiye. Third, the study provides a novel contribution by linking empathy difficulties with factors such as age, clinical experience, and therapeutic nihilism, offering important insights for psychiatric training and practice. Finally, the findings highlight actionable areas for policy development and clinical improvement, particularly the need for post-release support, staff training, and strengthened correctional mental health services. However, it has several limitations. First, as the data were collected via a self-report online survey, responses may have been subject to social desirability bias. Second, the questionnaire was developed by the researchers and did not include standardized scales for assessing complex psychosocial constructs such as attitudes and empathy. Third, the cross-sectional design of the study prevents the establishment of causal relationships. The sample was based on voluntary participation, which may have introduced selection bias and limited representativeness. Specifically, psychiatrists who do not work in correctional settings or who are less involved in forensic psychiatry may be underrepresented. Lastly, since the study was conducted solely in Türkiye, the cross-cultural generalizability of the findings is limited. Future research is recommended to address these limitations by employing mixed methods, longitudinal designs, and cross-national samples.

CONCLUSION

The findings of this study demonstrate that psychiatrists encounter significant challenges, resource limitations, and ethical dilemmas when working with incarcerated patients. Participants reported that prison conditions negatively affect mental health and that current psychiatric services are inadequate. The results underscore the urgent need to improve and diversify mental health services in correctional facilities, particularly by enhancing education, supervision, and safety protocols. To reduce prejudicial attitudes and the tendency toward "therapeutic nihilism," it is recommended that prison-based experiences be integrated into psychiatric training and that support mechanisms be provided to clinicians. Ultimately, the insights gained from this study may contribute to improving the quality and continuity of mental health care for incarcerated individuals while also enhancing professional satisfaction and ethical competence among psychiatrists working in this challenging field.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Giresun Training and Research Hospital (decision no.:16.04.2025/19, date: 16.04.2025)

Informed Consent: Informed consent was obtained from all participants who participated in this study.

Footnotes

Author Contrbutions

Concept Design – U.K., F.G.H.Ç.; Data Collection or Processing – U.K., F.G.H.Ç., M.H.Ş.; Analysis or Interpretation – U.K.; Literature Review – U.K., F.G.H.Ç., M.H.Ş.; Writing, Reviewing and Editing – U.K., F.G.H.Ç., M.H.Ş.

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ABCResearch

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Research Article

The Influence of Gender and Age on Lumbar Lordosis: A Magnetic Resonance Imaging Study

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ABSTRACT

Objective: The researchers aimed to verify the mean values and range of Cobb's angle to measure the lumbar lordosis on magnetic resonance (MR) images and to reveal any possible differences between genders or among age groups regarding the lumbar lordosis.

Methods: After exclusions, 527 patients, with a mean age of 48.73 ± 14.65 years, were measured for lumbar lordosis using the Cobb's angle of L1-S1 levels of the spine on MR images. A Kolmogorov-Smirnov test was performed to verify the data distribution properties. The comparison of the female and the male group was considered by the Mann-Whitney U test and the correlation with age was revealed using Spearman's Rho test.

Results: Cobb's angle measurements revealed a mean value of 51.45 ± 10.71 degrees. Regarding the angle measurement results, the female group had higher lordosis than the male group ($P < 0.001$). A low grade, positive, and significant correlation between age and the Cobb's angle was observed for the total study population and the male group. A moderate, positive, and significant correlation between age and lordotic angle measurement results was reached for the female group.

Conclusion: Females had higher lumbar lordosis than males and age is positively correlated with lumbar lordosis according to the results of this investigation. Many other scientific investigations are required to verify the outcome of this research to ensure the mean value and the normal ranges of Cobb's angle.

Keywords: Age, gender, lumbar lordosis, magnetic resonance

INTRODUCTION

Lumbar lordosis in an optimal anatomical range compensates for the sacral tilt, restores an upward orientation, and consequently enables one to avoid an excess forward inclination.[1] In the lateral lumbar X-rays or on the mid-sagittal planes of cross-sectional imaging modalities, it is observed as a convexity aligned anteriorly. Biomechanically, this curvature provides a certain resilience to the spine, and helps avoid compressive axial forces. If the spinal anatomic alignment was straight, compressive axial forces would be directly transferred via the bodies of the vertebrae and the discs between the vertebrae. Curvature of the lumbar spine, the axial compressive force is partially counteracted and absorbed by the anterior longitudinal ligaments.[2] The alterations of the physiological curvature of the lumbar spine may lead to low back pain and disabilities.

There have been various attempts to measure the lumbar lordosis in the literature using different modalities and several measurement techniques. Among the other methods, Cobb's angle, also known as the lordotic angle, is widely used as the gold standard of measuring lumbar lordosis.[3] Besides the radiographic measurements, other modalities are also used to evaluate the quantitative lordosis. Magnetic resonance (MR) imaging is a well-known modality in today's clinical practice. Low back pain, radiculopathies, disc herniations, degenerative diseases, scoliosis, and physiological alignment of the lumbar

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spine can easily be detected by MR imaging without radiation exposure. Not only radiologists, but also other clinicians and surgeons use this modality for the assessment of lumbar spinal diseases or pre-operative planning.

This study is planned to verify the mean values and range of Cobb's angle measurements of the lumbar lordosis on MR images, using a relatively large population. The gender differences and the influence of age are studied to reveal any significant differences in the lordotic angle.

MATERIAL AND METHODS

Patients

This study was approved by the institutional ethics committee of Erzincan Binali Yıldırım University Non-Interventional Clinical Research Ethics Committee (approval number: 2025-14/02, date: 24.07.2025). The requirement for informed consent from each patient participating in this study has been waived by the same ethics committee, regarding the methodology of the research. The investigation was conducted as a retrospective, cross-sectional study and all patients who had undergone lumbar MR imaging between 23rd of June 2025 and 22nd of July 2025 were scanned. There were 668 patients listed on the Picture Archiving and Communication System (PACS) of our institutional hospital. The study aimed to measure the lordotic angle of the skeletally mature individuals; therefore, the patients under 18 years old (n=5) were excluded. Any vertebral fracture in the field of view on lumbar MR imaging (n=19), 3 patients with sacralization of the L5 vertebra, 16 patients with high grade osteoarthritis (Kellgren-Lawrance type III or IV), patients with scoliosis (n=41), patients with spondylolisthesis (n=23), 3 patients with spondylodiscitis, 30 patients with postoperative fixation materials or history of operation, 1 patient with vertebral medullar signal alterations consistent with hemopoietic system involvement, totally 141 patients were excluded. Therefore, the lumbar MR images of 527 patients, without any biomechanical alterations, were included in the statistical calculations (Figure 1). All patients were measured by a radiology specialist with 7 years of experience, and the measurement results were noted with two decimals after the decimal. A PACS (Akgün PACS Viewer v7.5, Akgün Software, Ankara, Türkiye) was used in the re-assessment of the MR images and to perform measurements in standard Digital Imaging and Communication in Medicine Formats.

MR Imaging

The lumbar MR images were handled by standard protocol adjusted to the intervertebral disc pathologies. All lumbar MR images were acquired by a 1.5 T MR machine (Magnetom Aera, Siemens, Erlangen, Germany) using 32-channel lumbar coils. All patients were examined in the supine position during the scanning process. Sagittal plane T1-weighted images (TR: 646 ms, TE: 9 ms, average: 2, field of view: 280 mm, slice thickness: 4 mm, voxel size: 0.9 × 0.9 × 4 mm), sagittal plane T2-weighted images (TR: 4120 ms, TE: 104 ms, average: 2, field of view: 280 mm, slice thickness: 4 mm, voxel size: 0.9 × 0.9 × 4 mm), and axial plane T2-weighted images (TR: 5070 ms, TE: 88 ms, average: 1, field of view: 190 mm, slice thickness: 4 mm, voxel size: 0.7 × 0.7 × 4 mm) were acquired for each patient.

Measurement of Cobb's Angle

The midsagittal planes among the image series of the T1-weighted MR imaging sequence were used to measure Cobb's angle. T1 weighted images were used for measurements, which better delineate the anatomical borders and depict the endplates of the vertebral bodies. The line tangential to the upper endplate of the lumbar 1 (L1) and sacral 1 (S1) vertebral bodies was drawn.

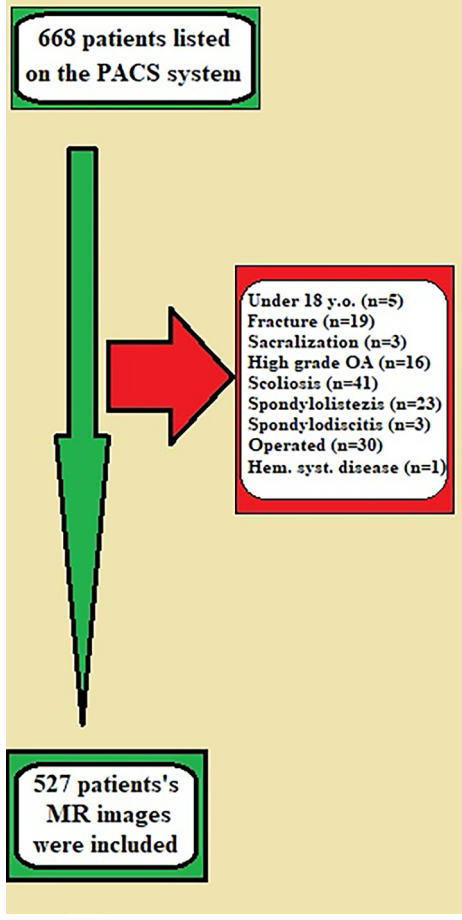

Figure 1. The workflow of the study

PACS, Picture Archiving and Communications System; y.o., years old; OA, osteoarthtiris; Hem. syst. disease; Heomopoetic system disease; MR, magnetic resonance

MAIN POINTS

- Cobb's angle measurement is widely used to measure lumbar lordosis.
- According to this study results, females had higher lumbar lordosis than males.
- Age shows a correlation with lumbar lordosis for the female and male groups, or the total study population in this current study.

The angle between the two lines, drawn perpendicular to each other, was determined as the Cobb's angle (Figure 2).

Statistical Analysis

The statistical calculations were carried out using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was carried out to determine the property of the data distribution. The boxplot graphics were used to present the data distribution of angle measurement results for the total study population, females, and males. The independent samples t-test was used to compare the results of female and male groups. The correlation between age and Cobb's angle measurement results was analyzed using the Pearson correlation test. For all the statistical results, *P* values of < 0.05 were considered to represent statistical significance.

RESULTS

The lumbar MR images of 312 female and 215 male patients, for a total of 527, were re-assessed regarding Cobb's angle measurements. The mean age of the study population was 48.73 ± 14.65. There was no statistically significant difference between females and males regarding age (Table 1).

The data distribution was analyzed by the Kolmogorov-Smirnov test in the total study population, females, and the male group.

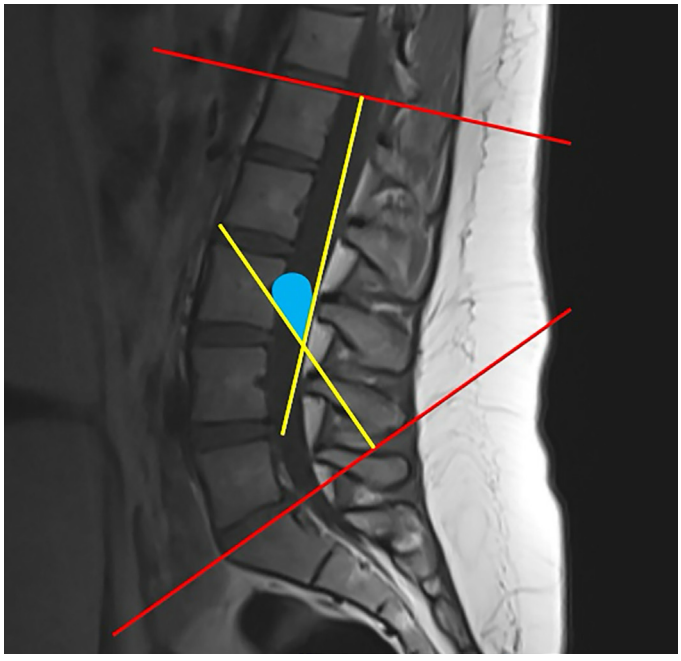

Figure 2. On the midsagittal plane of the T1-weighed lumbar magnetic resonance imaging series, the red lines tangential to the superior endplate of the L1 vertebra corpus and S1 vertebra corpus were drawn. Then the perpendicular lines to these red lines were drawn on the image (yellow-colored lines). Cobb's angle (presented with blue color) is formed in the intersection of the two perpendicular lines to these tangential lines.

Normal data distribution could not be reached according to the statistical results, however the skewness and kurtosis values of quantitative data were in a narrow enough range, and the researchers were able to use parametric tests (Independent Samples t-test) to compare the difference between female and male groups. The data distribution results were represented in boxplot analyses (Figure 3). Females had statistically higher Cobb's angle measurements than males ($P < 0.001$) (Table 2).

The correlation between age and angle measurements was calculated by Pearson correlation analysis. For the total study population, the female group, and the male group, the analyses indicated a low-grade, positive, and significant correlation between age and the Cobb's angle (Table 3).

DISCUSSION

This research was conducted on a relatively large population, determining the mean values and ranges of the Cobb's angle values regarding female and male groups. The current study results revealed that females had higher lordosis compared with males. Moreover, age shows a correlation with lumbar lordosis for the female and male groups, or the total study population.

A review mentioned that nine of the thirteen researchers reported a lower lumbar lordosis angle in patients with low back pain compared to healthy subjects, with a statistically

Table 1. The Study Population's Demographic Data

Gender (n)		Number		Percentage	
Females		312		59.2%	
Males		215		40.8%	
Total		527		-	
Age	**Mean**	**Std. Deviation**	**Min**	**Max**	***P***
Females	49.52	14.03	18	88	0.144
Males	47.59	15.48	18	80	
Total	48.73	14.65	18	88	-

Std. Deviation, standard deviation.

Table 2. Comparison of Cobb's Angle Between Females and Males

	Mean	**Std. Deviation**	***P* value**
Females	54.10	10.72	**<0.001**
Males	47.61	9.50	
Total	51.45	10.71	**-**

Std. Deviation, standard deviation.

Table 3. The Correlation (Pearson Correlation) Analysis Between Age and Cobb's Angle Measurement Results for Total Study Population, Females and Males

		Total	**Females**	**Males**
Age	**Correlation Coefficient**	0.303	0.246	0.379
	***P* value**	<0.001	<0.001	**<0.001**
	n	527	312	215

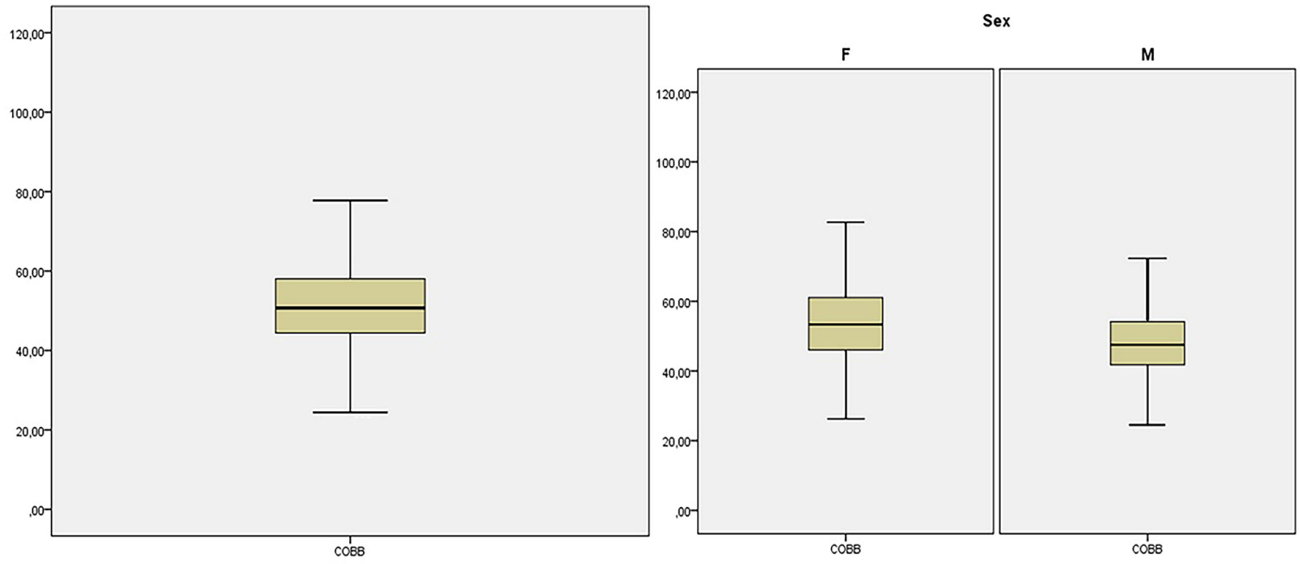

Figure 3. The data distribution for the total study population (on the left) and the specific data distributions for each gender (on the right). Female group had significantly greater lumbar lordosis than the male group.

significant difference. It is also mentioned that although statistically significant differences were not achieved, the remaining four studies also reported lower lumbar lordosis angle for patients with low back pain. In the same review, five factors were highlighted as the clinically significant determinants of the lumbar lordotic curve. The factors considered were the age, gender, of the participants, the severity of the lower back pain, and chronicity, and the spinal disease.[4]

To perform the most common version of the Cobb's angle measurement, a line is drawn through the upper endplate of the L1 vertebral body, and another line is drawn tangentially to the upper endplate of the sacral base (S1) or the inferior articular endplate of the L5 vertebral body. After demarcating these lines parallel to the endplates, two more lines are drawn perpendicularly to the initial lines. The angle formed at the intersection of these perpendiculars indicated the Cobb's angle.[3,5] The L1-S1 version of Cobb's angle measurement technique is generally recommended over other versions, due to the significant contribution of the L5-S1 disk to lumbar lordosis.[3,6]

Zhu et al.[7] have found a mean value of 48.2 ± 9.6 degrees of lumbar lordosis in 260 asymptomatic Chinese volunteers. Chanplakorn et al.[8] studied 100 healthy volunteers and one of the parameters measured was the angle formed by T12 inferior endplate and S1 superior endplate to reflect the lumbar lordosis. The mean value for the lumbar lordosis angle was 54.7 ± 9.9.[8] From the analysis of 60 asymptomatic adults, Janssen et al.[9] reported a mean value of 58.5 ± 9.6 degrees for lumbar lordosis. The mean value of lumbar lordosis measured using the superior articular plateaus of L1 and S1 was 51.45 ± 10.71 in the current research.

Gender differences in lumbar lordosis were another aspect of this study. No significant difference was observed between females and males regarding lumbar lordosis in some past studies.[10,11] Takao et al.'s[12] study was conducted on patients with spondylolisthesis, and the authors noted no sex difference in their research. However, some other studies found greater values for females than males regarding lumbar lordosis angles.[13,14] Some authors[4] considered that this situation may be explained by the greater buttock size of females. Our current study has also indicated higher lordosis angles in females than males in the study population.

The possible alterations in lumbar lordosis due to age-related degenerative changes of the musculoskeletal system were also discussed in the literature. Even though the lumbar spine is expected to flatten with degenerated changes as mentioned by some authors[14], there are many studies that could not indicate a relationship between age and lordosis in their investigations.[10,14] Kalichman et al.[15] revealed no association between age and wedging of vertebral bodies and intervertebral discs. Therefore, there is not enough evidence to support the common opinion that lordosis flattens with age. The correlation analysis of this study indicated a low-grade, positive, and significant correlation between age and the Cobb's angle for our total study population, directly opposite to this expectation.

Our research was based on the measurement of lumbar lordosis using Cobb's angle on MR images.

Study Limitations

There were important conditions to discuss along with the results of this study which can be considered the limitations of the research. First, many research results were discussed and compared with the current study results; however, many of them used radiological modalities other than MR imaging. Moreover, some of the measurement results obtained in this

study, where the results were acquired in patients with supine positions during MR scanning, were compared with those conducted in standing positions. There are studies indicating a significant difference in lumbar to pelvic parameters and the major curvature between the erect position and the supine position in patients with adult spinal deformity.[16] In another study, the researchers used positional MR imaging on healthy individuals and reported that the Cobb's angle decreased in the standing position.[17] With the evidence in the literature, it should be stated that, the effect of axial forces on lumbar lordosis angle was underestimated in this study. Although the angle measurements were performed meticulously for this research, the possibility of human error should also be considered for the study results. Repeated measurements or measurements with more than one interpreter can reduce potential measurement bias and enhance the generalizability of the findings.

CONCLUSION

To conclude, lumbar MR imaging is now a widely used technique, not only to reveal the altered signals of the soft tissue, bone marrow, causes of low back pain, radiculopathies, and intervertebral disc pathologies, but also and can easily be used to detect lumbar lordosis. Measuring Cobb's angle on MR images, is an easy way of determining the degree of lordosis on midsagittal planes. However, radiologists, clinicians and surgeons should be aware of the normal ranges of the lumbar lordosis and more research is required to verify its mean value and range for Cobb's angle measured on MR images of different age and gender groups.

Ethics

Ethics Committee Approval: This study was approved by the institutional ethics committee of Erzincan Binali Yıldırım University Non-Interventional Clinical Research Ethics Committee (approval number: 2025-14/02, date: 24.07.2025).

Informed Consent: The ethics committee has waived the need for informed consent due to the methodology of the study.

Footnotes

Author Contributions

Concept Design - B.K.; Data Collection or Processing - H.A.; Analysis or Interpretation - B.K., H.A.; Literature Review - B.K., H.A.; Writing, Reviewing and Editing - B.K.

Declaration of Interests: The authors declare that they have no competing interests.

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ABCResearch

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Research Article

Multiparametric MRI Assessment of Atypical Transitional Zone Nodules in PI-RADS v2.1

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ABSTRACT

Objective: In Prostate Imaging Reporting and Data System v2.1, atypical nodules that are mostly encapsulated or homogeneously circumscribed obtain a score of 2. If the diffusion score is marked at ≥ 4, the nodule is upgraded to category 3. This study aims to determine the prevalence of clinically significant prostate cancer (csPCa), in diffusion-weighted imaging (DWI)-upgraded atypical nodules and compare it with T2-weighted score 3 transitional zone (TZ) nodules.

Methods: Patients who underwent multiparametric magnetic resonance imaging before targeted transrectal ultrasound-magnetic resonance imaging fusion biopsy between January 2021 and February 2022 were retrospectively evaluated. Patients with the TZ lesions category ≤ 3 were included in this study. Lesions were classified as category 2, 2 + 1, and 3. The prevalence of prostate cancer (PCa) in each group was presented as number and percentage using descriptive statistics. The Kruskal-Wallis test and the chi-squared test were used to compare the groups.

Results: Forty-four patients with 64 lesions were included in the study. Sixteen of 64 were classified as category 2, 36 of 64 as category 2 + 1, and 12 of 64 as category 3. Among 36 DWI-upgraded atypical nodules (category 2 + 1), two (5.5%) had csPCA. Of the twelve nodules with T2-weighted score 3, three (25%) had csPCA. There was no significant difference between the groups, regarding the rate of csPCA. Pca was not diagnosed in 16 category 2 TZ nodules.

Conclusion: We found a lower rate of csPCA in DWI-upgraded TZ nodules (5.5%) compared to nodules with T2-weighted score 3 (25%), although this difference was not statistically significant. Our study demonstrates the value of DWI in identifying PCa in atypical nodules.

Keywords: Atypical nodule, multiparametric prostate MRI, PI-RADS v2.1, transitional zone, TRUS-MRI fusion biopsy

INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) of the prostate has been used for the detection and localization of clinically significant prostate cancer (csPCa). The Prostate Imaging Reporting and Data System (PI-RADS) was established in 2012 by the European Society of Urogenital Radiology for the evaluation and reporting of mpMRI data.[1] In 2015, PI-RADS was updated to version 2 (v2) and adopted much more widely.[2] PI-RADS v2 was updated in 2019 and termed PI-RADS v2.1 to address system limitations and inconsistencies that had been identified since its release in 2015.[3] Transitional zone (TZ) lesions are categorized based on T2-weighted image characteristics. According to PI-RADS v2, all TZ lesions are assigned a score of 3, except for normal TZ (score 1), typical benign prostatic hyperplasia (BPH) nodules (score 2), and clearly suspicious lesions (scores 4 or 5). However, this category includes atypical cases, ranging from stromal type BPH nodule to TZ prostate cancer (PCa).[2]

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Therefore, the clinical diagnosis of TZ cancers remains challenging since BPH is present in almost all elderly patients, and mpMRI findings overlap with csPCa.[4,5] The updated PI-RADS v2.1 includes significant changes for TZ assessment, particularly concerning lesions with low T2 weighted imaging (T2WI) scores. A typical nodule with a complete hypointense capsule was downgraded to a score of 1. Atypical nodules that are mostly encapsulated or homogeneously circumscribed obtain a score of 2, and if there is marked diffusion restriction, they are upgraded to category 3 (diffusion score of 4 or higher). This modification has the potential to influence the decision to perform a biopsy on TZ lesions upgraded to category 3, thus guiding diagnostic strategies to reduce false positives and minimize unnecessary biopsies.[6]

Compared to category 2 TZ lesions, category 2 + 1 TZ lesions demonstrated a markedly higher likelihood of detecting International Society of Urological Pathology ≥ 2 cancer, suggesting that the use of the DWI upgrade rule increases the probability of identifying clinically significant disease.[6]

Although these revisions highlight the importance of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping in PCa detection, few studies have investigated the prevalence of csPCa in upgraded atypical TZ nodules that restrict diffusion in PI-RADS v2.1.[3] The purpose of this study was to investigate the rates of csPCa detection in atypical TZ nodules that were upgraded to category 3 according to PI-RADS 2. One due to diffusion restriction.

MATERIAL AND METHODS

This retrospective observational study was approved by the Institutional Ethics Committee of Selçuk University (approval no.: 2023-39, date: 17.01.2023). The ethics committee approved the waiver of informed consent due to the retrospective nature of the study. In addition, permission was obtained from the institution for the use of medical records and databases in this retrospective study.

Patients

A total of 246 patients who had mpMRI before targeted transrectal ultrasound-magnetic resonance imaging (US-MRI) fusion biopsy between January 2021 and February 2022 were retrieved retrospectively from the picture archiving and communication system. The study included category 2 and 3 transition zone lesions on MRI with targeted transrectal US-MRI fusion biopsies. Patients with peripheral zone lesions, TZ lesions category 1, 4, and 5, low-quality mpMRI scans, or a history of previous surgery and treatment were excluded from the study (Figure 1).

The following data were collected from the patients' electronic medical records: indication, age, prostate-specific antigen (PSA), free PSA, prostate volume, PSA density, and biopsy results. Biopsy results were considered the reference standard.

Prostate MRI Technique and Interpretation

Multiparametric prostate MRI was performed using a 3T system (MAGNETOM Skyra; Siemens Healthineers AG, Erlangen, Germany) with a pelvic-phased array coil in line with PI-RADS v2.1. The MRI techniques comprised axial, coronal, and sagittal T2WI, DWI, and dynamic contrast-enhanced (DCE) imaging. On DCE, 0.1 mmol/kg gadobutrol (Gadovist; Bayer-Schering, Berlin, Germany) was administered intravenously at a rate of 3 mL/sec using an automated injector, followed by a 30 mL saline flush. Table 1 summarizes the MRI technique in detail. At our institution, a standardized reporting format compatible with PI-RADS v2. One is employed, and the report specifies the localization, size, and PI-RADS score (overall assessment and score for each pulse sequence) of each lesion.

One board-certified radiologist (A.K., with 3 years of experience in prostate mpMRI interpretation) established the patient population retrospectively based on study inclusion criteria and recorded their clinical information. In the initial sessions, two other board-certified radiologists (H.Ö. and M.K., with 4 and 6 years of mpMRI experience, respectively)—who were aware of the prior mpMRI report but blinded to biopsy results—independently scored TZ lesions on mpMRI according to the PI-RADS v2.1 at a dedicated workstation (Syngo.via, Siemens Healthineers, Forchheim, Germany). In the second session, the same two radiologists (H.Ö. and M.K.) reached an agreement on the final PI-RADS score, mean ADC value, and longest diameter of each TZ lesion.

Biopsy Technique

Since 2020, our institution has been performing mpMRI scanning in line with PI-RADS v2.1, and since 2021, we have been performing targeted transrectal US/MRI fusion biopsies. Transrectal US-MRI fusion biopsy was performed for the targeted lesions with the Vnav, Logic S8, GE Healthcare system. Transrectal US-MRI fusion biopsies of the prostate were performed by a radiologist, with three years of experience (more than 200 biopsy procedures), using an 18 -gauge side-cutting needle.

Prior to transrectal US-MRI fusion biopsy, suspected TZ lesions were targeted on multiparametric MRI. Each lesion was targeted and tagged separately in patients who had multiple TZ lesions, enabling direct imaging-histological correlation. At least two cores were obtained for the targeted lesions, and a transrectal US-guided 12-core systematic biopsy was performed immediately after the targeted cores were obtained. All biopsy cores were evaluated histopathologically.

MAIN POINTS

- Diffusion-weighted imaging (DWI) plays a crucial role in upgrading atypical transition zone nodules, improving the classification of Prostate Imaging Reporting and Data System (PI-RADS) category 3 lesions and potentially enhancing clinically significant prostate cancer (csPCa) detection.
- In our study, no prostate cancer was detected in category 2 patients without DWI restriction.
- Although PI-RADS v2.1 has improved the performance of category ≥ 3 lesions in diagnosing csPCa, our study found no significant difference in the detection rates of any prostate cancer and csPCa in DWI-upgraded lesions.

Statistical Analysis

The Shapiro-Wilk test was used to determine whether the distribution of continuous numerical variables was normal. Descriptive statistics were reported as mean ± SD or median (range) for continuous data (age, prostate volume, lesion size, free PSA, PSA, PSA density, mean ADC value) and count and percentage (%) for categorical data (biopsy result). The Kruskal-Wallis test and chi-square analysis were used to compare continuous and categorical data among category 2, 2 + 1, and 3 TZ lesions. All data were evaluated using version 21.0 of the Statistical Package for the Social Sciences (IBM Corporation, Armonk, NY, USA). In this study, a p value of 0.05 was selected to represent statistical significance in all statistical tests.

RESULTS

The study enrolled a total of 44 patients with 64 category 2, 2+1 and 3 TZ lesions in accordance with PI-RADS v2.1. The mean age was 64.41 ± 7.65 years (range, 41-82 years). The mean prostate volume was found to be 85.06 + 44.37 mL. The mean PSA level was 11.63 ± 8.92 ng/mL and the mean lesion size was 10.84 ± 4.45 mm. Based on PI-RADS v.2.1, 16 out of 64 nodules in the TZ were classified as category 2, 36 as category 2 + 1, and 12 as category 3. Table 2 provides a detailed explanation of

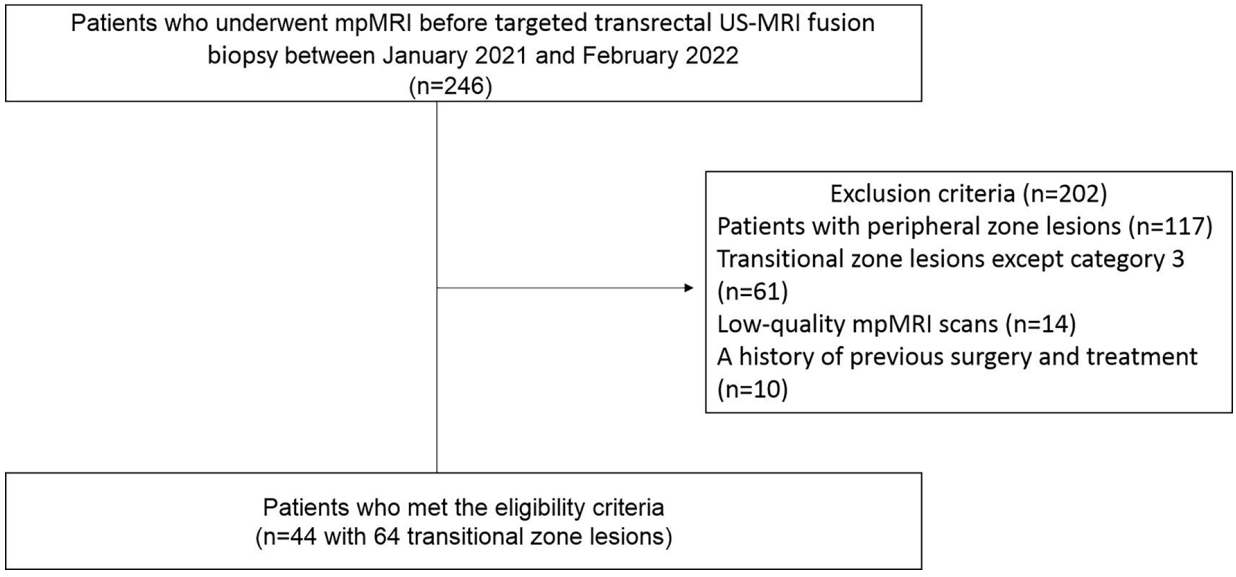

Figure 1. Study population flow chart.

US-MRI, ultrasound-magnetic resonance imaging; mpMRI, multiparametric magnetic resonance imaging.

Table 1. Multiparametric MRI Acquisition Parameters

Type of imaging	Parameters							
	TR (msec)	TE (msec)	FOV (mm)	b value (s/mm²)	Flip angle (°)	Slice thickness (mm)	Turbo factor	NSA
T2W (axial)	5060	106	200 x 200	-	129	3	23	3
T2W (coronal)	5000	110	200 x 200	-	121	3.5	25	3
T2W (sagittal)	5500	100	200 x 200	-	123	3.5	23	2
DWI (axial)	4500	76	200 x 200	50.1000.1500	90	3	55	3
DCE (axial)	5.08	1.77	259 x 259	-	15	3.5	1	1

MRI, magnetic resonance imaging; TR, repetition time; TE, echo time; T2W, T2-weighted; T1W, T1 weighted; DWI, diffusion weighted imaging; FOV, field of view; DCE, dynamic contrast-enhanced; NSA, numbers of signals averaged.

patient data. There were no significant differences in mean age, prostate volume, PSA value, or lesion size between the groups ($P > 0.05$).

There was no evidence of PCa in 16 atypical nodules without DWI upgrade, classified as category 2. There were 36 atypical nodules with diffusion restriction (category 2 + 1), of which 1 (2.8%) had clinically insignificant PCa, and 2 (5.5%) had csPCa, respectively. Of the 12 nodules with a T2-weighted score of 3, 1 (8.3%) had clinically insignificant PCa and 3 (25%) had csPCa. The incidence of any PCa and csPCa was not significantly different between groups (Table 3). A representative patient was shown in Figure 2.

DISCUSSION

In PI-RADS v2, biopsies were mostly performed when the lesion score was 3 or higher.[6,7] The success of detecting clinically significant cancer in category 3 lesions varied significantly between studies.[8-10] The discrepancy in results is due to PI-RADS category 3 lesions demonstrating a lack of consensus among readers because of the ambiguous terminology employed in this classification, such as "obscured margins".[11-13] Therefore, some studies have proposed that the optimal threshold for targeted biopsy in TZ tumors should be ≥ 4.[14-16] In the updated PI-RADS v2. One, the term for an atypical nodule in the transition zone has been added.[3] Additionally, another important change in PI-RADS v2. One is the inclusion of DWI features in atypical nodules for upgrading to category 3 lesions.[3] Previous studies have shown that DWI plays an additional role to T2 scores of PI-RADS v2.[8,17] With this new approach, the performance of category ≥ 3 lesions in diagnosing csPCa has increased.[8]

DWI has also been a part of PI-RADS v2, where the category is upgraded from 3 to 4 when the DWI score is 5. The results of a study by Rosenkrantz et al.[18] even suggested that upgrading category 3 to 4 based on a DWI score of 4 may add value in detecting csPCa.

In our study, we compared the pathological results of DWI-upgraded atypical nodules (category 2 + 1), and conventional T2-weighted score 3 lesions. We found that the detection rates of any PCa and csPCa in DWI-upgraded lesions were 8.3% and 5.5%, respectively. In comparison, detection rates of any PCa and csPCa in conventional T2-weighted score 3 lesions were 33.3% and 25%, respectively. No statistically significant difference was found between the two groups. This could be due to the small number of patients in the study. Lim et al.[19] evaluated 104 patients with 109 lesions and reported that 28% of patients were diagnosed with any PCa and 8% were diagnosed with csPCa in DWI-upgraded lesions. In line with our study, there was also no significant difference in the detection of either any PCa or csPCa between groups.[19] In DWI-upgraded lesions, Byun et al.[20] found a significant improvement in the detection of csPCa and anyPCa. In their study, DWI-upgraded lesions were diagnosed with csPCa at a higher rate than the conventional T2-weighted-score-3 lesions.[20] In a prospective study with 1,238 eligible patients, Costa et al.[21] found that 6%

Table 2. Demographics and Clinical Variables

	Atypical nodules without DWI restriction (n=16)	DWI-upgraded atypical nodules (n=36)	T2-weighted MRI score 3 nodules (n=12)	*P*
Age	63 ± 9.8	66.6 ± 6.3	60.3 ± 7.5	0.157
Prostate volume	80.6 ± 26.2	93.9 ± 51.1	67.1 ± 35.3	0.209
PSA (ng/mL)	10.4 ± 5.4	13.6 ± 7.6	7.5 ± 3.3	0.071
Lesion size (mm)	8.6 ± 2.2	12.1 ± 5.1	10.1 ± 3.2	0.260
Pathology				
Benign	75.0 (12/16)	41.7 (15/36)	50.0 (6/12)	
Prostatitis	25.0 (4/16)	50.0 (18/36)	16.7 (2/12)	
ISUP grade 1	-	2.8 (1/36)	8.3 (1/12)	
ISUP grade 2 and 3	-	5.5 (2/36)	25.0 (3/12)	

Values are expressed as mean ± SD or percentage with numbers in parentheses. DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; ISUP, International Society of Urological Pathology.

Table 3. Rates of Any Prostate Cancer and Clinically Significant Prostate Cancer by Type of Nodules

	DWI-upgraded atypical nodules (n=36)	T2-weighted MRI score 3 nodules (n=12)	*P*
Pathology			
Any PCa	8.3 (3/36)	33.3 (4/12)	0.055
csPCa	5.5 (2/36)	25.0 (3/12)	0.092

Values are percentages with numbers in parentheses. DWI, diffusion weighted imaging; PCa, prostate cancer; csPCa, clinically significant PCa; MRI, magnetic resonance imaging.

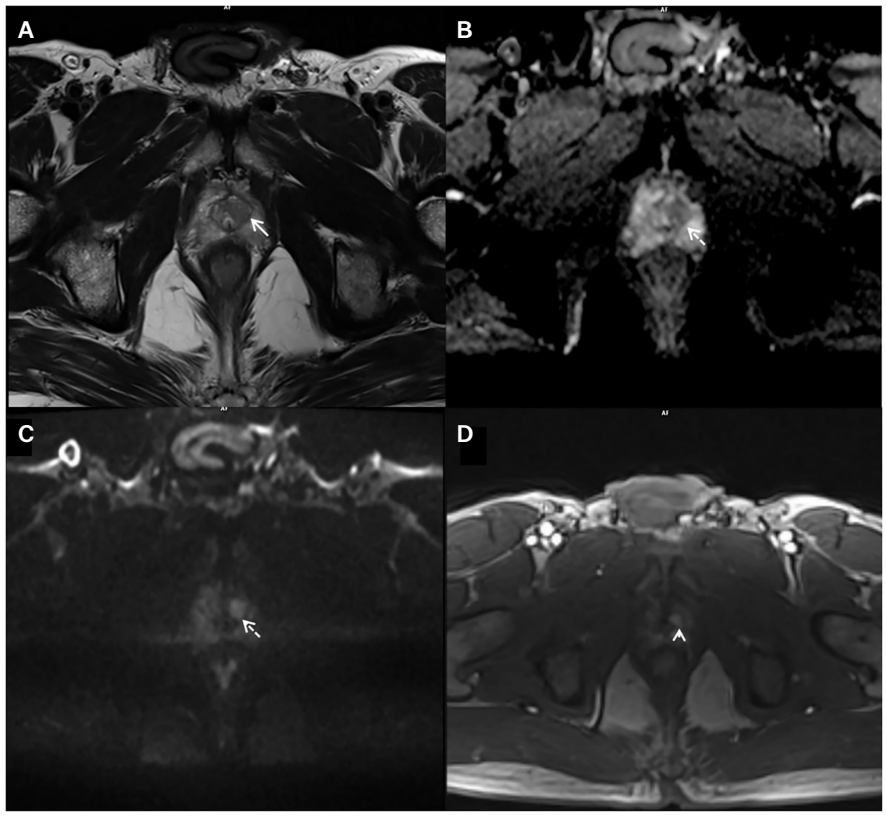

Figure 2. (A) Axial T2-weighted image shows a circumscribed hypointense atypical nodule in the anterior aspect of left apex transitional zone (arrow). (B) Apparent diffusion coefficient map shows marked hypointensity in the lesion compared to the background (dashed arrow) and (C) diffusion weighted images (DWI) (b-1500 s/mm^2) show marked hyperintensity in the lesion compared to the background (dashed arrow), respectively. (D) Dynamic contrast-enhanced image shows early contrast enhancement in the nodule (arrowhead) (T2 score: 2, DWI score: 4, dynamic contrast-MRI: positive, Prostate Imaging Reporting and Data System category 2 + 1).

MRI, magnetic resonance imaging.

of patients had DWI-upgraded lesions and 7% had conventional T2-weighted category 3 lesions. Clinically significant cancer was detected in 6% of 49 patients with DWI-upgraded lesions and in 11% of 61 patients with conventional T2-weighted category 3 lesions.[21] The rate of csPCa was not statistically different between groups.[21]

Consistent with the findings of Lim et al.[19], we found no evidence of PCa in atypical nodules without DWI upgrade. This may be due to the small number of atypical nodules without DWI upgrade in both studies.[19]

A recent meta-analysis found that the PCa detection rates for TZ DWI-upgraded and conventional T2-weighted score 3 lesions were 12% and 19%, respectively. There was a non-significant difference in PCa detection rates between the two groups. It was thought that it might also originate from the small sample size in studies.[22]

Study Limitations

There were some limitations of our present study. First, it was a retrospective study with a small number of patients and was carried out at a single institution. Moreover, only transrectal US/MRI fusion biopsies were included in the study. Accepted as a reference standard, transrectal US/MRI fusion biopsy may lead to mis-sampling or inadequate sampling. In addition, some patients may not have undergone biopsy due to variations in the management of PI-RADS 3 lesions.

In conclusion, no PCa was not detected in category 2 patients without DWI restriction. csPCa was detected in 5.5% of patients with DWI-upgraded atypical nodules and in 25% of patients with conventional T2-weighted score 3. There was no statistically significant difference between the two groups. The updates to TZ assessment in PI-RADS v2.1 may improve the detection rate of csPCa. However, prospective studies with larger patient groups are needed.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Selçuk University (approval no.: 2023/39, date: 17.01.2023)

Informed Consent: The ethics committee approved the waiver of informed consent due to the retrospective nature of the study. In addition, permission was obtained from the institution for the use of medical records and databases in this retrospective study.

Footnotes

Author Contributions

Concept Design – H.Ö., A.K., M.K., M.K.; Data Collection or Processing – H.Ö., B.B.A., U.A., E.A., M.K., M.K.; Analysis or Interpretation – H.Ö., B.B.A., U.A.; Literature Review – B.B.A., U.A., A.K.; Writing, Reviewing and Editing – H.Ö., B.B.A., U.A., E.A., M.K.

Declaration of Interests: The authors have no conflict of interest to declare.

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ABCResearch

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Research Article

The Rhomboid Fossa in Turkish Children: A Comprehensive Analysis of Chest CT

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ABSTRACT

Objective: This study aims to determine the incidence, dimensions and side distribution of excavated-type rhomboid fossa (RF) in the Turkish pediatric population.

Methods: Thoracic computed tomography scans of a total of 5985 pediatric patients performed between January 2016 and July 2024 were evaluated retrospectively. The presence of RF was evaluated by consensus by two radiologists on axial, coronal, and sagittal sections obtained in bone window settings. Size measurements were taken on coronal sections for transverse and craniocaudal diameters, and on sagittal sections for anteroposterior diameters. For statistical analysis, gender distribution was evaluated with the chi-square test, and size differences between sides were evaluated with an independent and paired t-tests. $P < 0.05$ was considered significant.

Results: The excavated type RF was detected in 2.77% (166 patients; 124 men, 42 women). It was significantly more common in men ($P < 0.001$). RF was most frequently seen bilaterally (56%), followed by the right side (25%) and the left side (19%) ($P < 0.001$). In bilateral cases, although there was no significant difference in the transverse dimension between the right and left diameters ($P = 0.572$), the anteroposterior ($P = 0.042$) and craniocaudal diameters ($P = 0.018$) were found to be significantly larger on the right side. In all patients, the anteroposterior ($P = 0.034$) and craniocaudal ($P = 0.025$) diameters of the right RF were significantly larger than the left RF. It was also shown that larger RFs were significantly associated with bilateral localization ($P < 0.001$).

Conclusion: This study is the first to reveal the incidence of excavated type RF in the Turkish pediatric population. Findings show that RF occurs bilaterally and more frequently on the right side, and is significantly more common in men. Additionally, it has been found that the size of the RF may be an effective factor in bilateral localization. Our study shows that RF is a criterion that can be used to ascertain gender.

Keywords: Children, CT, rhomboid fossa

INTRODUCTION

Unidentified human skeletal remains are located in several regions worldwide, including Türkiye. Skeletal remains are usable for identification, including sex, age, and size in forensic medicine.[1] They were used for sexual dimorphism assessment, including the pelvis, skull, upper and lower limb bones, sternum, patella foot bones, and clavicles.[2] Various parameters, such as length, mid-shaft circumference, sternal end, acromial end, and rhomboid fossa (RF), have been utilized to identify sex in anthropology and forensic sciences.[3]

The ligamentum costoclaviculare (LCC), or rhomboid, is inserted into the lower portion of the clavicle. On its insertion point, it can produce impressions, tuberosities, depressions, and a fossa, which is referred to as the RF in anatomical and anthropological research.[4] The LCC was initially characterized as comprising a single plane of fibers. The bilaminar structure was first formally described, with the anterior and posterior fiber layers reported to incline upward and outward.[5,6] The region of the robust LCC insertion attachment to the inferior surface at the proximal end of the clavicle occasionally contains excavations of irregular shape, varying depths, and are complete with sclerotic

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manifestations. These cavities, known as RF, should be regarded as variations of the LCC insertion. Such relationships have been identified in both children and adults of all genders; however, they occur more frequently in males, particularly young males.[7]

The excavated RF of the clavicle is an overlooked anatomical feature that may lead to diagnostic challenges. The untrained viewer may misinterpret specific anatomical features, such as the RF, as diseases ranging from mild fibrous dysplasia to chronic osteomyelitis. Its unilateral manifestation may be mistaken for a malignancy.[3]

As demonstrated by previous studies that assessed the correlation between the presence of the clavicular RF and sex,[8,9] the prevalence of the RF was significantly higher in males than in females in skeletons of diverse populations worldwide. In order to ascertain the sex of unidentified skeletons, Prado et al.[3] successfully investigated the presence of the RF in relation to the sex and age of individuals. The RF was more frequently associated with males than with females (63.6% of males and 2.9% of females' left clavicles).

The incidence and anthropological investigation of the clavicular RF in childhood, have never been reported in the Turkish population. Consequently, the aim of this study was to determine the prevalence, size, and side distribution of the excavated type RF in the Turkish population, specifically among individuals aged 0-18.

MATERIAL AND METHODS

The presented retrospective study was approved by the Biomedical Research Ethics Committee of Koç University with a reference number: 2024.311.IRB2.140, date: 24.09.2024 and was conducted in accordance with the Declaration of Helsinki. In compliance with our institution's protocol, written informed consent is acquired from all patients or their parents prior to computed tomography (CT) scans, encompassing permission to utilize images for research purposes.

We analyzed 5985 chest CT examinations of pediatric patients from January 2016 to July 2024 to identify the excavated type RFs. Chest CT scans were performed with 64-slice and 128-slice scanners (Somatom Definition AS and Somatom Definition Flash, Siemens Healthineers). The indications of chest CT were predominantly pneumonia, trauma, and oncological follow-up. The examinations were conducted during a single breath hold while in the supine posture, with arms elevated above the head. The thoracic cavity, from the superior aspect of the lungs to the inferior aspect of the posterior costophrenic sulci, was imaged with a collimation of 0.625 mm, parameters of 80-120 kVp and 20-150 mAs. The kVp and mAs were automatically selected. The application of contrast medium was varied according to the indication of the examination. The evaluation of clavicular RF was performed on the 1.5 mm thick axial bone window images, as well as sagittal and coronal reformat images.

The evaluation of the patients included in the study was performed by two radiologists with 5 (H.Ö.A.) and 11 (G.T.Y.) years of experience. After screening the patients, a consensus decision was made on patients who had RF. In these patients, RF size measurements were made in bone window settings on CT images. Measurements were made primarily on coronal reformatted sections, specifically assessing the transverse and craniocaudal dimensions. Then, anterior-posterior dimension measurements were made on the sagittal reformatted images (Figure 1, Figure 2 and Figure 3). All measurements were

MAIN POINTS

- Excavated-tip rhomboid fossa (RF) was detected in 2.77% of the Turkish pediatric population and was found significantly more common in males. This suggests that RF may serve as a useful anatomical marker in sex estimation.
- RFs were most frequently observed bilaterally (56%), followed by right-sided (25%) and left-sided (19%) occurrences. The right fossae were significantly larger in both anteroposterior and craniocaudal dimensions.
- Recognizing RF as a normal anatomical variant is important to avoid misdiagnosis in pediatric imaging. Moreover, it may provide valuable insights in forensic and anthropological assessments.

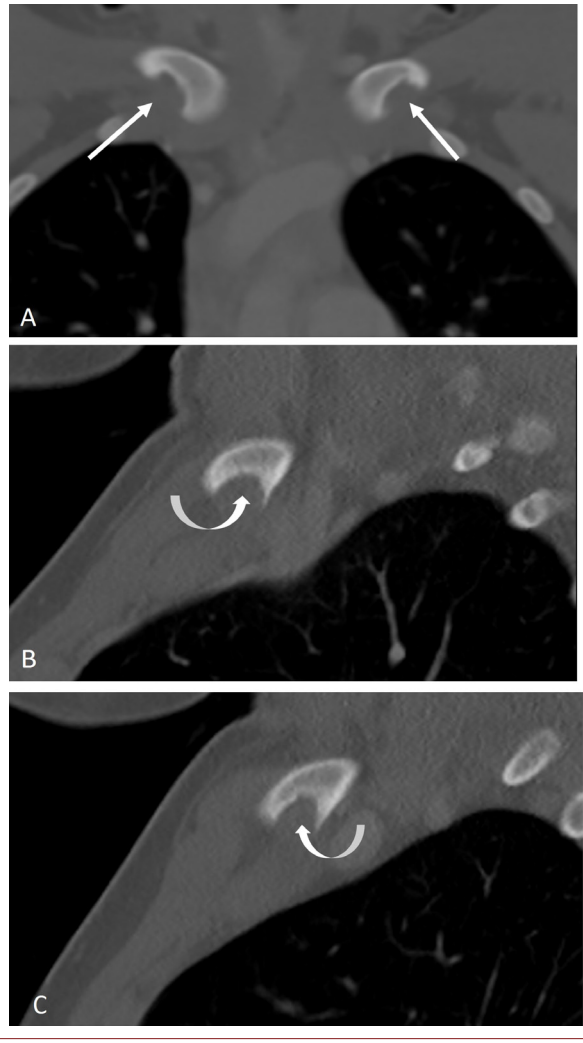

Figure 1. CT imaging of clavicula at the level of the sternoclavicular joint. (A) coronal reformat image; large bilateral excavated type of rhomboid fossa's (arrows). (B) and (C) sagittal reformat image; right and left excavated type RFs (curved arrows).

CT, computed tomography; RF, rhomboid fossa.

recorded through consensus among radiologists. In addition, the patients' ages, patients' gender, and the reasons for the CT examination were also noted.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 26.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were calculated for each RF diameter (transverse, anteroposterior, and craniocaudal), and mean values were noted for both right- and left-sided RF. The distribution of lesions by sex (male vs. female) was assessed using the chi-square test to determine statistical significance. For bilateral cases, paired t-tests were used to compare right and left lesion dimensions within the same patients. For overall comparisons across all patients including unilateral and bilateral cases, independent t-tests were applied to assess differences in the size of right and left RFs for each diameter separately. Additionally, all RF sizes from the right and left sides were combined, and an independent t-test was conducted to compare overall RF size distributions. *P* values below 0.05 were considered statistically significant.

RESULTS

Among 5985 pediatric patients, a total of 166 patients (124 males and 42 females) have an excavated type of RF (2.77%). To explore age-related differences in the incidence of excavated type RF, the study population was stratified into four age groups: 0-5 years (n=1490), 6-10 years (n=1525), 11-15 years (n=1510), and 16-18 years (n=1460). Excavated type RF was detected in 1.8% (27/1490) of patients in the 0-5 age group, 2.2% (33/1525) in the 6-10 age group, 3.1% (47/1510) in the 11-15 age group, and 4.1% (59/1460) in the 16-18 age group. Lesions were statistically more common in males, indicating a significant sex distribution difference ($P < 0.001$). Also, 36 patients (22%) had a history of malignancy, and CT examinations were performed for treatment response evaluation.

The excavated type of RFs was most commonly observed bilaterally in 93 patients (56%), followed by right-sided in 42 patients (25%) and left-sided in 31 patients (19%). The distribution of the type of excavated RF was statistically significant ($P < 0.001$) (Table 1).

Among unilateral localized excavated types of RF, the right-sided versions had larger mean diameters across all measured parameters. The mean transverse diameter was 10.21 mm for the right-sided excavated type of RF, and 9.04 mm for the left-sided excavated type of RF. The size difference between right-sided and left-sided excavated RF did not reach statistical significance ($P = 0.275$). The mean anteroposterior diameter was 3.87 mm for right-sided excavated type of RF and 3.18 mm for left-sided excavated type of RF; the difference between sizes was not statistically significant ($P = 0.075$). The mean craniocaudal diameter was 3.86 mm for right-sided

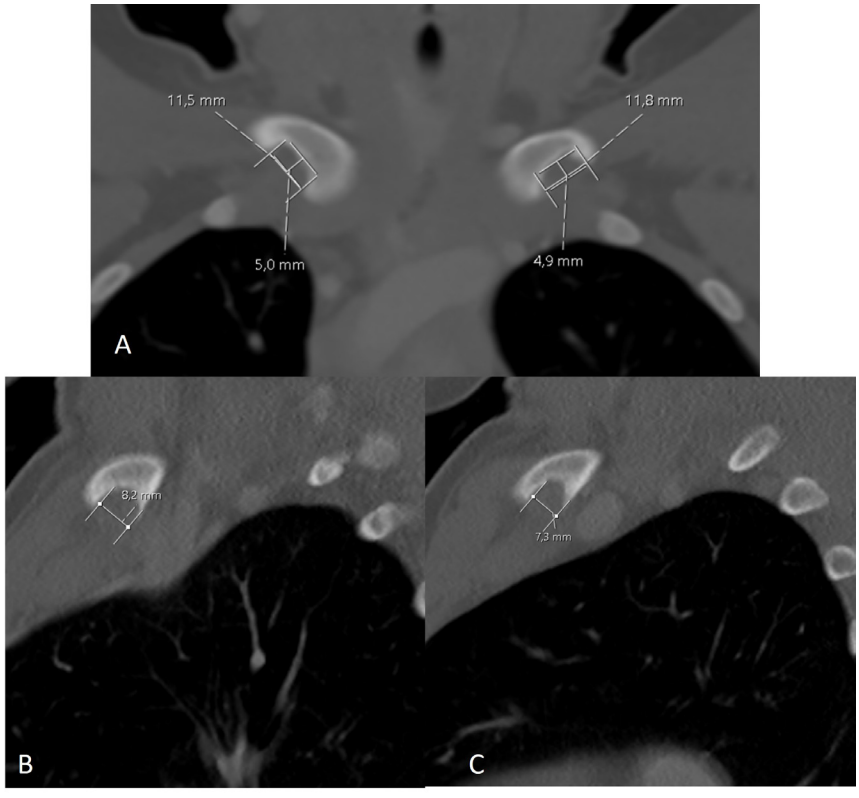

Figure 2. CT imaging of clavicula at the level of the sternoclavicular joint. (A) coronal reformat image and (B) and (C) sagittal reformat images; shows RF measurements.

CT, computed tomography; RF, rhomboid fossa.

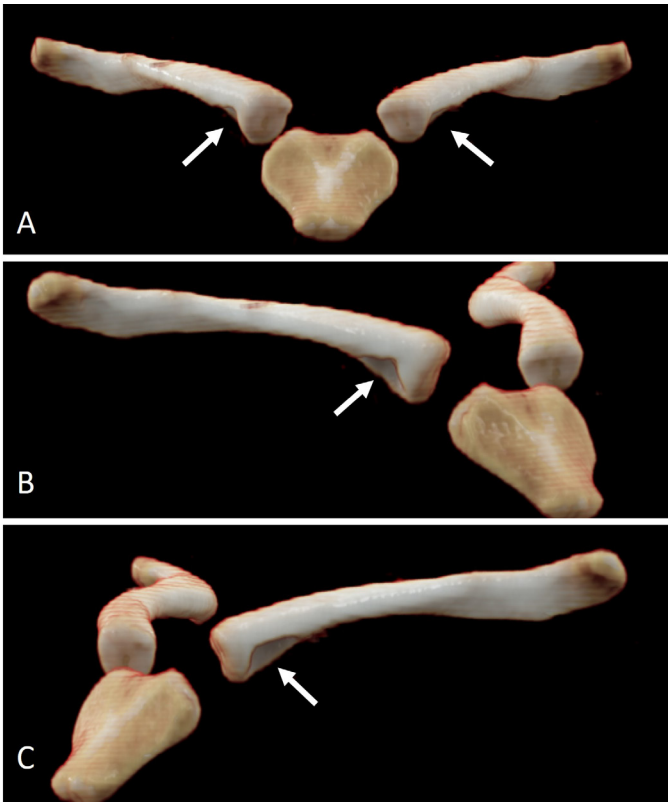

Figure 3. Computed tomography 3D (three dimensional) image, posterior-anterior and lateral projection; bilateral excavated type of RFs (arrows).

RFs, rhomboid fossas.

excavated RF and 3.32 mm for left-sided excavated RF, and the difference between the two groups was not significant (P = 0.109) (Table 1).

In cases with bilateral excavated type of RF, the comparison of right and left sizes showed no significant difference in the transverse diameters (P = 0.572). However, the anteroposterior (P = 0.042) and craniocaudal (P = 0.018) sizes were significantly larger on the right side, revealing an asymmetry between the two sides (Table 1).

In the evaluation of all right and left excavated type of RFs' sizes among all patients, including both unilateral and bilateral cases, right-sided RFs were significantly larger in the anteroposterior diameter (P = 0.034) and the craniocaudal diameter (P = 0.025). However, no significant difference was observed in the transverse diameter (P = 0.806). These findings show that the right-sided RF tends to be larger in the anteroposterior and craniocaudal diameters (Table 1).

The correlation between the excavated RF size type and the rate of bilateral localization was determined. The statistical analysis showed that larger RFs were significantly associated with bilateral localisation (P < 0.001), suggesting that fossa size may play a role in their distribution pattern.

DISCUSSION

The present study has demonstrated the incidence of the excavated type RF of the clavicles in the Turkish population for the first time. The excavated type RF was detected in 2.77% of 5985 pediatric patients in our study. This rate shows a lower incidence compared to other studies in the literature.

Table 1. Location, Sex and Size Distribution of Excavated Type RFs in Study Cohort

			Patient number/size	*P* value
Sex		Female	42 (25.3%)	**< 0.001**
		Male	124 (74.7%)	
Localization	Bilateral		93 (56%)	**< 0.001**
	Unilateral	Right	42 (25%)	
		Left	31 (19%)	
Unilateral RF	Transverse size	Right	10.21 mm	0.275
		Left	9.04 mm	
	Anteroposterior size	Right	3.87 mm	0.075
		Left	3.18 mm	
	Craniocaudal size	Right	3.86 mm	0.109
		Left	3.32 mm	
Bilateral RF	Transverse size	Right	10.41mm	0.572
		Left	10.59 mm	
	Anteroposterior size	Right	3.99 mm	**0.042**
		Left	4.62 mm	
	Craniocaudal size	Right	3.91 mm	**0.018**
		Left	3.52 mm	
All RF	Transverse size	Right	10.34 mm	0.806
		Left	10.2 mm	
	Anteroposterior size	Right	3.96 mm	**0.034**
		Left	3.51 mm	
	Craniocaudal size	Right	3.89 mm	**0.025**
		Left	3.47 mm	

RF, rhomboid fossa.

For example, Paraskevas et al.[10] detected excavated-type RF in 26.88% of 80 chest radiographs. Parsons'[9] study examined 183 adult English clavicles and reported that excavated-type RF incidence was 10%. However, the scope of our study is wider, and the results could be more reliable because the study includes 5985 pediatric patients and CT examinations. The low incidence rate obtained may be explained by the exclusive examination of the pediatric patient group. We believe that in this age group, excavated type RF may not yet be developed enough to have deeper fossae. This highlights the impact of age group differences on incidence. In support of this, our subgroup analysis revealed a slightly increased incidence in older children, particularly those aged 11-18 years, suggesting a potential influence of skeletal maturation on RF development.

In our study, excavated type RF, which was detected in 74.6% of male clavicles and 26.4% of female clavicles, showed a significant difference between sexes. Similarly, previous anthropological and anatomical studies have reported a significant association between the presence of excavated-type RF and male sex. Prado et al.[3] in a study of 209 Brazilian cadavers (107 men and 102 women, age range: 19-85 years), found the prevalence of RF to be 63.6% in men but only 2.9% in women. Additionally, in the examination of the skeletal collection compiled by William F. McCormick at the University of Tennessee (231 males and 113 females, age range: 10-92 years), the presence of RF in the left clavicle indicated male sex in 92.2% and female sex in 7.8%, while in the right clavicle, these rates were 81.7% for men and 18.3% for women.[4] In both studies, it is evident that RF was more common in men, consistent with our findings.

In our study, we found the occurrence of the condition bilaterally in 93 patients (56%), followed by right-sided in 42 patients (25%) and left-sided in 31 patients (19%). Similarly, in Prado et al.'s[3] study, the prevalence of bilateral RF in men was found to be 29%. In addition to that, it was shown that the prevalence of right and left sided RF was 18.7% and 15.9%, respectively.[3] Paraskevas et al.'s[10] study revealed that excavated type RF was more common on the right side than the left side in both male and female samples. In the same study, it has been stated that excavated type RF is more common on the right side in right-handed individuals and more common on the left side in left-handed individuals.[10] These findings indicate that the localization of excavated-type RF may vary in different populations and studies, but the tendency to occur bilaterally and be followed by occurrence on the right side is evident.

In our study, we also found that in cases of bilateral prevalence, excavated type RFs are usually asymmetric. A new and significant finding is that in cases with bilateral excavated type of RF, the comparison of right and left sizes showed no significant difference in the transverse, but the anteroposterior and craniocaudal sizes were significantly larger on the right side. This reveals asymmetry between the two sides. Also, the statistical analysis showed that larger RFs were significantly associated with bilateral localization, suggesting that fossa size may play a role in their distribution pattern. To the best of our knowledge, no such information is provided in the literature.

We are unable to make a definitive determination regarding the potential causes of excavated type RF, as we do not possess the necessary data on the occupations and sporting activities of the individual patients. However, in previous studies, the presence of RF in a two-year-old child (our earliest case with RF) renders physical overload insufficient to account for the RF.[9]

Our findings have potential clinical, forensic, and anthropological implications. Clinically, the excavated type RF may mimic pathological bone lesions on imaging, especially in pediatric patients, leading to diagnostic pitfalls if not properly recognized. In forensic and anthropological contexts, the presence and size of RF may aid in sex estimation and skeletal profiling. However, the generalizability of these findings may be limited due to ethnic, genetic, and developmental variability. Morphological variations in clavicles across populations should be considered when applying these results outside the Turkish pediatric cohort. Therefore, future multicenter studies involving diverse populations are warranted to validate and extend these observations.

Study Limitations

This study has several limitations. First, it is retrospective in nature. Although the overall CT dataset was large, the number of patients with excavated RF was limited. Additionally, a possible selection bias exists, as only pediatric patients who underwent chest CT examinations were included, which may not reflect the general population incidence of excavated RF. Another limitation is the absence of interobserver and intra observer agreement analysis for RF detection and measurement, which may affect the reproducibility and generalizability of our radiological assessments.

CONCLUSION

The findings of our study demonstrate that excavated type RF tends to be more common in the right clavicle, and the larger excavated type RF is significantly associated with bilateral occurrence, highlighting a potential influence of fossa size on distribution patterns. Our study proves, that the presence of an excavated type RF can be used as a qualitative criterion for the differentiation of sex in Turkish individuals. Furthermore, awareness of the excavated type RF in pediatric imaging is crucial, as it may mimic pathological conditions such as lytic lesions or chronic infection. Recognizing this anatomical variant can help radiologists avoid diagnostic pitfalls.

Ethics

Ethics Committee Approval: This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Biomedical Research Ethics Committee of Koç University with a reference number of 2024.311.IRB2.140, date: 24.09.2024.

Informed Consent: The study had retrospective design, no additional procedures were performed. Informed consent forms are obtained from each patient and/or their parents before the radiological examination in our institution as a clinical routine.

Footnotes

Author Contributions

Concept Design – G.T.Y., E.Ö.; Data Collection or Processing – G.T.Y., H.Ö.A., E.Ö.; Analysis or Interpretation – G.T.Y.; Literature Review – G.T.Y., H.Ö.A.; Writing, Reviewing and Editing – G.T.Y., H.Ö.A., E.Ö.

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Research Article

Correlation Between Neutrophil-to-Lymphocyte Ratio and Severity Scores in Septic Patients Presenting to Emergency Department

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ABSTRACT

Objective: Sepsis is a life-threatening condition caused by a dysregulated immune response to infection, leading to organ dysfunction and high mortality rates. Early identification is crucial but challenging, particularly in vulnerable populations. The neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential biomarker for assessing sepsis severity. This study evaluates the correlation between NLR and established severity scores, including Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment, to determine its usefulness in early risk assessment.

Methods: This prospective observational study was conducted in the emergency department of a tertiary care hospital, enrolling 64 patients based on predefined criteria. Data collection included medical history, physical examination, laboratory investigations, and radiological evaluations. Statistical analyses were performed using SPSS and R software, with significance set at $P < 0.05$.

Results: Among 64 patients, 23 (35.9%) had a NLR of ≥ 8, while 41 (64.1%) had an NLR of < 8, with a mean of 7.57. Patients with NLR ≥ 8 were more likely to require vasopressor support ($P = 0.009$) and had significantly lower mean arterial pressure ($P = 0.027$) and systolic blood pressure ($P = 0.041$). Higher inflammatory markers were noted in the NLR ≥ 8 group. Strong correlations were found between NLR and APACHE ($r = 0.80$), and between NLR and procalcitonin ($r = 0.81$).

Conclusion: This study highlights the NLR as a crucial biomarker for sepsis severity in emergency department patients. Elevated NLR correlates with critical severity scores and poorer hemodynamic status. It also suggests that NLR can enhance diagnostic accuracy, aiding timely interventions and improving outcomes in critical care.

Keywords: Neutrophil-to-lymphocyte ratio, procalcitonin, sepsis, APACHE II, SOFA

INTRODUCTION

Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection.[1] Globally, sepsis affects an estimated 31.5 million individuals each year, with approximately 19.4 million progressing to septic shock and resulting in around 5.3 million deaths annually. In-hospital mortality rates for sepsis range from 17% to 26%.[2] The 2020 Global Burden of Sepsis study, conducted by the Institute for Health Metrics and Evaluation, reported 48.9 million incident cases in 2017, equating to 677.5 cases per 100.000 age-standardized population. Overall, sepsis accounted for 19.8% of global deaths, with 11.0 million fatalities in 2017.[3] In India alone, sepsis cases were estimated at 11.3 million, with 2.9 million sepsis-related deaths (297.7 per 100.000 population) in 2017.[4] These figures underscore the

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need for reliable and easily measurable biomarkers to facilitate early detection and risk assessment, particularly in low- and middle-income countries like India.[4]

Classic signs of infection and organ dysfunction, such as fever, productive cough, and dysuria, are commonly observed in sepsis. However, sepsis can also present with subtle or atypical symptoms, complicating diagnosis and delaying timely intervention.[5] Effective sepsis management relies on early and accurate identification of high-risk patients, often assessed through established scoring systems including the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA). Although widely used, these scoring systems are complex and may not always be feasible for rapid bedside assessment in emergency settings, creating a demand for simpler, more accessible tools in clinical practice.[6-9]

There is a growing need for simpler and more accessible tools to assess the severity of sepsis in clinical practice.[10] The inflammatory and immunological response plays a pivotal role in sepsis pathophysiology, driving efforts to identify reliable biomarkers that can enhance prognosis and guide management. While several biomarkers have been investigated, only a few are currently integrated into clinical practice.[11] Among these, the neutrophil-to-lymphocyte ratio (NLR), an easily calculable marker derived from a complete blood count, has garnered attention as a potential biomarker that reflects the immune dysregulation characteristic of sepsis. NLR has shown potential for predicting poor outcomes in various critical illnesses; however, its effectiveness as an independent predictor of mortality in sepsis, particularly in relation to the established severity scoring systems APACHE II and SOFA, remains underexplored. Hence, the present study aims to evaluate the association between NLR and APACHE II/SOFA scores in septic patients presenting to the emergency department (ED), with the objective of determining whether NLR can be used as a surrogate marker for disease severity and facilitate early risk assessment.

MAIN POINTS

- Elevated neutrophil-to-lymphocyte ratio (NLR) levels were associated with significantly higher C-reactive protein (P = 0.002), serum lactate (P < 0.001), and procalcitonin levels (P = 0.006), suggesting their role as a surrogate marker for systemic inflammation and sepsis severity.
- NLR showed a strong correlation with Acute Physiology and Chronic Health Evaluation II (r = 0.80) and Sequential Organ Failure Assessment scores (r = 0.74), highlighting its potential as a reliable biomarker for assessing illness severity in septic patients, with higher NLR values indicating worse clinical outcomes.
- The respiratory tract was identified as the most common infection source (53.1%), followed by urinary infections (21.9%) and gastrointestinal infections (15.6%), underscoring the need for targeted antimicrobial strategies in septic patients presenting to the emergency department.
- Given its strong correlation with key inflammatory and severity markers, NLR emerges as a cost-effective, readily available biomarker that can enhance early risk stratification, guide clinical decision-making, and improve sepsis management in emergency and critical care settings.

MATERIAL AND METHODS

This study was approved by the Institutional Ethics Committee-Biomedical Research and Scientific Committee of Indraprastha Apollo Hospitals (approval no.: 152-20120-201-230554, date: 30.06.2022). Also, a written informed consent was obtained from the patient for study participation.

This prospective observational study was conducted over a period of 20 months in the ED of a tertiary care hospital, involving a total of 64 patients. Inclusion criteria were established based on the quick SOFA scores for patients aged over 18 years, which required a respiratory rate of ≥ 22 breaths per minute, altered mental status, systolic blood pressure (SBP) of ≤ 100 mmHg, and a serum lactate level greater than 2 mmol/L. Exclusion criteria included pregnant women, individuals under 18 years, prior antibiotic use for more than 24 hours, haematological disorders, chronic inflammatory conditions, recent steroid use, and chemotherapy or radiotherapy within the last three months.

Each patient underwent a comprehensive assessment that included detailed history- taking, demographic information such as age, sex, special habits, substance abuse, co-morbid conditions, and past medical history. A comprehensive physical examination was performed, using techniques such as inspection, palpation, percussion, and auscultation, guided by the patient's reported symptoms. Laboratory assessments included essential tests, arterial and venous blood gas analysis, complete blood count, serum creatinine levels, urinalysis, liver function tests (which encompassed albumin, serum glutamic oxaloacetic transaminas, serum glutamic pyruvic transaminase, bilirubin, and international normalized ratio), blood glucose measurements, C-reactive protein (CRP), procalcitonin, and serum lactate. Cultures were collected from all suspected infectious biological fluids, and the NLR was derived from the complete blood count results. Radiological evaluations, including abdominal ultrasound, echocardiography, electrocardiography, and chest imaging (chest X-ray or non-contrast computed tomography chest), were also performed. The sepsis severity scores SOFA and APACHE II were calculated upon admission for each patient.

Statistical Analysis

Data management involved meticulous checking of collected data in case record forms for completeness and accuracy. Descriptive statistics for categorical data are expressed as numbers and percentages, while mean ± standard deviation is used to express continuous data based on normal distribution.

After appropriate data filtration, the datasheet was analyzed using SPSS statistical software version 22.0 and R version 3.2.0. Chi-square (χ^2) test for categorical data and Student t-test for quantitative variables were performed to compare the time taken to receive scan reports. The means of two or more groups were compared using analysis of variance to determine any significant differences. A *P* value ≤ 0.05 was deemed statistically significant.

RESULTS

Of the 64 patients, 23 (35.9%) had an NLR of ≥ 8, whereas 41 (64.1%) had an NLR of < 8. The NLR values demonstrated a wide range, with a minimum value of 2.19 and a maximum value of 17.5 (Table 1). The age distribution analysis revealed that among 23 patients with an NLR of ≥ 8, 39.13% were aged 56-65 years, 30.43% were aged 46-55 years, and 21.74% were aged 66-75 years. In contrast, among 41 patients with an NLR of < 8, 34.15% were in both the 46-55 year and 56-65 year age groups, while 8.70% were aged over 75 years (*P* = 0.358). Regarding gender distribution, the NLR ≥ 8 group included 52.17% males and 47.83% females, whereas the NLR < 8 group included 56.10% males and 43.90% females (*P* = 0.764). Additionally, 47.8% of patients in the NLR ≥ 8 group required vasopressor support, which was significantly higher than the 17.1% in the NLR < 8 group (*P* = 0.009) (Table 2).

Mean arterial pressure (MAP) was significantly lower in patients with an NLR of ≥ 8 (mean 62 mmHg) compared to those with an NLR of < 8 (mean 76 mmHg; *P* = 0.027). SBP also demonstrated a significant difference, with patients having an NLR of ≥ 8 exhibiting a mean SBP of 92 mmHg, whereas those with an NLR of < 8 had a mean SBP of 108 mmHg (*P* = 0.041). Although the diastolic blood pressure showed a trend towards significance (*P* = 0.08), it did not reach statistical significance. Laboratory assessments in the NLR ≥ 8 group indicated significantly elevated CRP levels (mean 41.30 mg/L vs. 22.24 mg/L; *P* = 0.002), serum lactate levels (mean 6.88 mmol/L vs. 3.66 mmol/L; *P* < 0.001), and serum procalcitonin levels (mean 16.47 ng/mL vs. 6.93 ng/mL; *P* = 0.006) as compared to those in the NLR < 8 (Table 3).

The median APACHE score among 21 patients with an NLR of ≥ 8 was 13 (range: 8-28), indicating a higher severity of illness compared to those with an NLR of < 8 (n=41), whose median APACHE score was 9 (range: 3-18). Similarly, the median SOFA score was significantly elevated in the ≥ 8 NLR group was 8 (range: 6-11) versus 4 (range: 2-9) for the < 8 NLR group (Table 4).

Regarding the source of infection, the majority of patients had respiratory infections, accounting for 53.1% (n=34) of the cohort. 21.9% (n=14) had urinary infections, while 15.6% (n=10) had gastrointestinal tract (GIT) infections (Table 5).

The NLR had a strong correlation with the APACHE score (*r* = 0.80), SOFA score (*r* = 0.74) and serum procalcitonin (PCT) levels (*r* = 0.81). Also, NLR showed a moderate correlation with serum lactate levels (*r* = 0.64), but a weaker correlation with CRP (*r* = 0.45) and white blood cell (WBC) count (*r* = 0.28) (Table 6).

DISCUSSION

This prospective observational study was conducted on 64 patients to evaluate the correlation between NLR and severity scores such as APACHE II and SOFA in septic patients presenting to the ED. In our study, the respiratory system was the most commonly affected, accounting for 53.1% of cases, followed by the urinary system (21.9%) and the GIT (15.6%, n=10). Our findings align with those of Rehman et al.[12] who reported pneumonia as the most common source of sepsis in 44.0% (n=74) of patients, followed by urinary tract infections (26.2%, n=44), soft tissue/skin infections (19%, n=32), and intra-abdominal infections (5.4%, n= 9), and central nervous system infections (4.8%, n=8). Similarly, Velissaris et al.[13] observed that the most frequent origins of sepsis were pulmonary (36.8%, n=42), urinary (23.6%, n=27), surgical (15.7%, n=18), abdominal (10.5%, n=12), cutaneous (7.14%, n=10), and unknown sources (4.3%, n=5).

We observed that patients with elevated NLR exhibited lower MAP and SBP, suggesting they may experience greater hemodynamic instability or severity of illness. Additionally, higher neutrophil counts and CRP levels were observed in patients with elevated NLR, indicating a more pronounced inflammatory response. This aligns with the understanding that

Table 1. The Quantitative Values of the Neutrophil-to-Lymphocyte Ratio Among Study Participants

Parameter	Value
NLR ≥ 8	23 (35.9%)
NLR < 8	41 (64.1%)
Minimum	2.19
Mean	7.57
Median	6.86
Maximum	17.5

NLR, neutrophil-to-lymphocyte ratio.

Table 2. Baseline and Clinical Characteristics of Participants

Parameters	NL ratio		Chi-square test	*P* value
	≥ 8 (n, %)	< 8 (n, %)		
Age (years)				
≤ 45	0 (0.00)	5 (12.20)	4.370	0.358
46-55	7 (30.43)	14 (34.15)		
56-65	9 (39.13)	14 (34.15)		
66-75	5 (21.74)	7 (17.07)		
> 75	2 (8.70)	1 (2.44)		
Gender				
Female	11 (47.83)	18 (43.90)	0.090	0.764
Male	12 (52.17)	23 (56.10)		
Vasopressor needed				
Yes	11 (47.8)	7 (17.1)	6.786	**0.009**
No	12 (52.2)	34 (82.9)		

NL, neutrophil-to-lymphocyte.

Table 3. Blood Pressure and Lab Investigations at the Time of Admission

	NL ratio		*P* value
Parameters	**≥ 8**	**< 8**	
Mean arterial pressure			
Mean	62	76	
Median (range)	67 (46-84)	79 (56-90)	**0.027**
Systolic blood pressure			
Mean	92	108	
Median (range)	98 (60-114)	110 (70-130)	**0.041**
Diastolic blood pressure			
Mean	62	66	
Median (range)	58 (40-72)	68 (52-88)	0.08
Serum total bilirubin			
Mean	1.41	1.57	
Median (range)	1.4 (0.8-3.2)	0.9 (0.7-2.6)	0.66
Serum creatinine			
Mean	1.64	1.13	
Median (range)	1.3 (0.5-5.3)	1.4 (0.4-3.44)	0.24
Platelet			
Mean	119100	122100	
Median (range)	115000 (26000-211.200)	128000 (26000-345.000)	0.10
Total leukocyte count			
Mean	19216	16378	
Median (range)	18300 (8000-30100)	15500 (11000-34000)	0.167
Neutrophil			
Mean	18626	11795	
Median (range)	17500 (7000-31700)	12100 (2600-31700)	**0.018**
Lymphocyte			
Mean	1721	1867	
Median (range)	1740 (840-2530)	2100 (680-2600)	0.855
C-reactive protein			
Mean	41.30	22.24	
Median (range)	26 (18-84)	14 (6-72)	**0.002**
Serum lactate			
Mean	6.88	3.66	
Median (range)	6.5 (3.9-14)	2.98 (1.8-11)	**< 0.001**
Serum procalcitonin			
Mean	16.47	6.93	
Median (range)	15.35 (11.65-34)	6.2 (5.5-26)	**0.006**

NL, neutrophil-to-lymphocyte.

Table 4. Disease Severity Score Among Participants

Parameters	NL ratio	
	≥ 8	< 8
APACHE score		
Median (range)	13 (8-28)	9 (3-8)
SOFA Scale		
Median (range)	8 (6-11)	4 (2-9)
Glasgow Coma Scale		
Median (range)	14 (4-15)	14 (3-15)

NL, neutrophil-to-lymphocyte; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Table 5. The Source of Infection Identified in the Participants

System	n	%
Respiratory	34	53.1
Urinary	14	21.9
GIT	10	15.6
Others	6	9.3
Total	64	100.0

GIT, gastrointestinal tract.

Table 6. Spearman's Correlation Between NLR and Other Parameters

Scale	Co-relation coefficient (r)
	NLR
APACHE	0.80
SOFA	0.74
Serum procalcitonin	0.81
Serum lactate	0.64
C-reactive protein	0.45
WBC count	0.28

NLR, neutrophil-to-lymphocyte; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

NLR serves as a marker of systemic inflammation. Moreover, serum lactate levels were significantly higher in the elevated NLR group, which may indicate tissue hypoperfusion or a more severe metabolic derangement commonly associated with critical illness. Elevated procalcitonin levels in this group further suggest an increased risk of bacterial infection and sepsis. In contrast, no significant differences were found in serum total bilirubin, serum creatinine levels, or platelet counts between the groups. These findings are consistent with those reported by Shalaby et al.[14], who reported significant differences in MAP, SBP, neutrophil levels, serum creatinine, and platelet count across NLR groups. Similarly, a study by Liang and Yu[15] indicated that levels of serum creatinine, inflammatory markers (CRP, PCT, NLR), PCT, and total bilirubin were significantly higher in patients with severe bloodstream infections and sepsis compared to those in the non-critical group ($P < 0.05$).

The findings of the present study indicate that patients in the elevated NLR group had a higher median APACHE score compared to those in the lower NLR group, suggesting a greater overall severity of illness. Similarly, the SOFA scores were significantly higher in the NLR ≥ 8 group, reflecting a more pronounced degree of organ dysfunction and systemic response to critical illness. In contrast, the Glasgow Coma Scale were comparable between the two groups, indicating no significant difference in neurological status. Shalaby et al.[14] reported those patients with severe sepsis or septic shock have significantly higher APACHE II score ($P = 0.001$) and higher SOFA score on admission ($P = 0.014$) in patients with NLR > 10 compared to the NLR < 10.

The Spearman's correlation analysis revealed a strong positive correlation between the NLR ratio and both the APACHE II score ($r = 0.80$) and SOFA score ($r = 0.74$), indicating that higher NLR ratios are associated with increased severity of illness and greater organ dysfunction. Serum PCT exhibited a similarly strong correlation with the NLR ratio ($r = 0.81$), underscoring its association with infection and inflammation markers. Serum lactate showed a moderate correlation ($r = 0.64$), while CRP ($r = 0.45$) and WBC count ($r = 0.28$) demonstrated weaker correlations, reflecting varying degrees of association between these parameters and the NLR ratio. These findings are consistent with Liang and Yu[15], who reported positive correlations of NLR, CRP, and PCT levels with disease severity in sepsis patients ($r = 0.468$, 0.456, and 0.670, respectively; $P < 0.001$). Similarly, Velissaris et al.[13] demonstrated that NLR was positively correlated with sepsis severity scores [(SOFA, $r = 0.497$, $P < 0.001$; APACHE II, $r = 0.411$, $P = 0.003$; Simplified Acute Physiology Score II (SAPS II), $r = 0.445$, $P = 0.001$)] and total WBC count ($r = 0.531$, $P < 0.001$).

Total WBC count also correlated with the SOFA, APACHE II, and SAPS II scores.[16] Drăgoescu et al.[16] found significant correlations between NLR and both presepsin ($r = 0.56$, $P < 0.001$) and the SOFA score ($r = 0.65$, $P < 0.001$), supporting the utility of NLR as a prognostic tool in sepsis, comparable to markers like presepsin and SOFA score.

Study Limitations

Several limitations of this study warrant consideration. As a single-centre observational study with a limited sample size, there is a potential for residual confounding, underscoring the necessity for future multicentre studies that incorporate larger sample sizes and a broader range of variables. The implementation of stringent exclusion criteria excluded patients with abnormal baseline WBC counts, which may have omitted individuals with significant comorbidities that could impact the study's findings. Additionally, the NLR was calculated without differentiating between lymphocyte subtypes, and intraday variations in cell counts were not accounted for, as only the initial measurement of the day was utilized.

CONCLUSION

This study emphasizes the NLR as an important biomarker for assessing sepsis severity in ED patients. Elevated NLR levels correlate strongly with critical severity scores like APACHE II and SOFA, reflecting the overall condition of septic patients. Higher NLR values are associated with poorer hemodynamic status, along with increased inflammatory markers such as CRP and PCT. The study also identifies the respiratory tract as the predominant source of infection, which has significant implications for clinical management. Furthermore, the strong correlation between NLR and serum PCT levels suggests that NLR could enhance diagnostic accuracy and prognostic assessments, thereby contributing to timely interventions aimed at reducing mortality in sepsis patients. Overall, NLR is presented as a cost-effective and readily available tool that may assist clinicians in quickly evaluating sepsis severity, guiding timely disposition, and improving patient outcomes in critical care settings. Future research should continue to explore the clinical implications of NLR alongside other inflammatory markers to refine its application in sepsis management.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee-Biomedical Research and Scientific Committee of Indraprastha Apollo Hospitals (approval no.: 152-20120-201-230554, date: 30.06.2022).

Informed Consent: A written informed consent was obtained from the patient for the study participation.

Footnotes

Author Contributions

Concept Design – R.A., R.P., U.P.; Data Collection or Processing – R.A., R.P., U.P.; Analysis or Interpretation – R.A., R.P.; Literature Review – U.P.; Writing, Reviewing and Editing – R.A.

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ABCResearch

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Research Article

C-reactive Protein/Albumin Ratio as a Predictor of Comorbidity in Migraine and Restless Legs Syndrome

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ABSTRACT

Objective: The C-reactive protein/albumin ratio (CAR) is a reliable biomarker in the assessment and monitoring of inflammation. In this study, we aimed to investigate CAR rates in migraine alone and migraine with restless legs syndrome (RLS) and their relationship with migraine frequency, severity, and disease duration.

Methods: A total of 210 patients included in the study were grouped as those with only migraine and those with migraine accompanied by RLS. Variables between the groups were interpreted using a t-test and a Mann-Whitney U analysis. The relationship between CAR and variables was analyzed in migraine patients with RLS using Spearman's rho correlation coefficient.

Results: In patients with migraines with RLS, disease duration (t=-2.496, P = 0.013) was prolonged, and attack frequency (t=-3.971, P < 0.001) significantly increased compared to patients with migraines without RLS. In migraine patients with RLS, the values of CAR (z=-3.396, P = 0.001) and CRP (z=-3.704, P < 0.001) were higher. High CAR values were found to be a risk factor for prolonged disease duration (r = 0.281, P = 0.030) and increased attack frequency (r = 0.260, P = 0.044) in migraine patients with RLS.

Conclusion: CAR levels were significantly higher in migraine patients with comorbid RLS compared to those with migraine alone, showing a positive correlation with disease duration and attack frequency. These findings suggest that CAR could serve as a valuable biomarker for identifying chronicity and RLS comorbidity in migraine patients.

Keywords: Migraine, restless legs syndrome, C-reactive protein/albumin ratio

INTRODUCTION

Migraine is a primary headache that affects 14% of adults worldwide and is the second leading cause of disability. It is characterized by severe, unilateral, and throbbing pain, often accompanied by nausea, phonophobia, photophobia, and vomiting.[1] The pathophysiology of migraine is believed to be associated with the activation of the trigeminovascular pathway, which innervates the dura mater and large cerebral arteries, resulting in neuropeptide release and subsequent neurogenic inflammation.[2] Neurogenic inflammation has been shown to be mediated by pro-inflammatory cytokines, second messengers, and chemokines released from activated central nervous system cells.[3]

Restless legs syndrome (RLS) is a common sensorimotor disorder marked by an uncontrollable urge to move the legs, affecting 4% to 29% of the general population.[4] The increased prevalence of RLS in various inflammatory and autoimmune diseases, such as diabetes, multiple sclerosis, kidney disease, and rheumatoid arthritis, suggests the potential role of inflammatory factors in its pathogenesis.[5] Previous studies have consistently demonstrated that the incidence of RLS is higher in migraine patients compared to the general population.[6] Moreover, both conditions predominantly affect women and

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share abnormalities in iron metabolism, the dopaminergic pathway, and the endogenous opioid system, prompting research into potential shared etiological mechanisms.[7]

C-reactive protein (CRP) is a molecule whose level increases in the blood in inflammatory and infectious conditions, and is frequently used in the prognosis and treatment of some diseases.[8] Albumin is a negative acute phase reactant plasma protein associated with disease severity and mortality, and it decreases in inflammation.[9] The C-reactive protein/albumin ratio (CAR) has recently been used as a reliable biomarker in evaluating and monitoring inflammation, especially in chronic processes.[10] Although the elevation of CRP and inflammatory cytokines in migraine and RLS has been shown separately, to our knowledge, there is no study in the literature investigating CAR rates in the co-occurrence of these diseases.[11,12] Therefore, in our study, we aimed to examine CAR rates in patients with migraine and those with both migraine and RLS, and their relationship with migraine frequency, severity, and disease duration.

MATERIAL AND METHODS

Study Design and Participants

This study retrospectively included 210 patients diagnosed with either migraine or migraine with RLS who applied to our hospital's neurology outpatient clinic between January 2021 and January 2024. Ethics committee approval number 247 was received from Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee for the study on 26.11.2024. While preparing the study, the planning was conducted in accordance with the rules of the Declaration of Helsinki. Since the study was retrospective, only verbal consent was obtained.

Inclusion criteria were a confirmed diagnosis of migraine and/or RLS, and the absence of chronic inflammatory diseases, neoplasms, immunodeficiencies, or chronic conditions such as diabetes mellitus, arterial hypertension, thyroid dysfunction, chronic kidney disease, liver disorders, and hematologic abnormalities. Patients were excluded if their data were unavailable, if they had a history of infection within the last month, if they were pregnant, or if they were under the age of 18.

Migraine diagnoses were made according to the International Classification of Headache Disorders, while RLS was diagnosed using established clinical criteria.[1,13] As a result, 150 patients with migraine alone and 60 patients with comorbid RLS were included in the study. Each patient's visual analog scale (VAS) score and Migraine Disability Assessment (MIDAS) score were recorded.[14] MIDAS is a questionnaire consisting of five items that assess headache-related disability; it categorizes patients into grades I to IV, with higher scores indicating more severe disability. If the total number of days lost by the patient in the last 3-month period is between 0-5, the MIDAS score is considered I; if the number of days lost is between 6-10, the MIDAS score is considered II; if the number of days lost is between 11-20, the MIDAS score is considered III; and if the number is 21 +, the MIDAS score is considered IV. The VAS is a widely used tool to measure pain intensity on a scale from 0 to 10.

Blood parameters, including hemoglobin, white blood cell count, ferritin, total iron-binding capacity (TIBC), CRP, and albumin levels, were retrospectively obtained from medical records. CAR value was obtained by dividing CRP (mg/dL) by albumin (g/dL). CAR = CRP (mg/dL)/albumin (g/dL).[10]

Statistical Analysis

Data from a total of 210 patients, including those with migraines and those with comorbid RLS, were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. For variables showing a normal distribution, the Independent Samples t-test was used to compare the migraine and migraine with RLS groups; for those not normally distributed, the Mann-Whitney U test was applied.

Categorical variables were analyzed using the Pearson chi-square test. The Kruskal-Wallis test was used to assess differences in CAR values across different grades of the MIDAS (Migraine Disability Assessment) questionnaire. In the subgroup of migraine patients with RLS, relationships between continuous variables such as CAR values, attack frequency, and disease duration were examined using Spearman's rho correlation coefficient. A P value of < 0.05 was considered statistically significant.

The power of the study was calculated using the G*Power version 3.1.9.7 software. The effect size was determined to be 2.03. Based on this effect size and a total sample size of 210 participants (150 in the migraine group and 60 in the migraine + RLS group), the statistical power of the study was calculated as 100% at the 0.05 significance level.

In addition, a receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the CAR in predicting the presence of RLS in migraine patients. The optimal cut-off point for CAR was determined using Youden's index. Sensitivity, specificity, and the area under the curve (AUC) were calculated to assess the discriminatory ability of CAR values between the two groups.

MAIN POINTS

- The C-reactive protein/albumin ratio (CAR) emerges as a biomarker of chronic inflammation in patients with migraine and restless legs syndrome (RLS).
- A high CAR value shows a positive correlation with attack frequency and disease duration.
- The comorbidity of migraine and RLS negatively affects the clinical course of migraine.

RESULTS

We analyzed a total of 210 patients, 150 with migraine and 60 with migraine with RLS. The mean age of migraine patients was 42.20 ± 10.59, and 76% (n=114) were female. The mean age

of the migraine with RLS group was 43.17 ± 10.18, and 81.7% (n=49) were female. No difference was found between the groups regarding aura, family history, and migraine severity (*P* = 0.767, *P* = 0.222, *P* = 0.156, respectively). Although MIDAS grade 1 (21.7%) was less common and grade 3 (16.7%) and 4 (25.0%) were more common in the migraine with RLS group, this did not create a statistically significant difference (*P* = 0.156). The duration of the disease (t=-2.496, *P* = 0.013) was significantly prolonged in individuals with migraine and RLS compared to those with only migraine. When evaluated in terms of attack frequency, a statistically significant increase was found in those with migraine with RLS (t=-3.971, *P* < 0.001). (Table 1)

When the groups were compared in terms of blood parameters, hemoglobin (z=-2.100, *P* = 0.036) and albumin (t =2.446, *P* = 0.015) values were found to be statistically significantly lower in the in the migraine with RLS group. CAR (z =-3.396, *P* = 0.001) and CRP (z=-3.704, *P* < 0.001) values were significantly higher in migraineurs with RLS than in those without. (Table 2)

Table 1. Demographic Characteristics of Patients by Groups

	Migraine (n=150)	**Migraine + RLS (n=60)**		
	n (%)	**n (%)**	**Chi-square**	***P***
Gender				
Female	114 (76.0)	49 (81.7)	0.792	0.373
Male	36 (24.0)	11(18.3)		
Aura				
No	125 (83.3)	51(85.0)	0.088	0.767
Yes	25 (16.7)	9 (15.0)		
Family history				
Yes	33 (22.0)	18 (30.0)	1.492	0.222
No	117 (78.0)	42 (70.0)		
MIDAS				
Grade 1	49 (32.7)	13 (21.7)		
Grade 2	60 (40.0)	22 (36.7)	5.222	0.156
Grade 3	13 (8.7)	10 (16.7)		
Grade 4	28 (18.7)	15 (25.0)		
	Mean ± SD	**Mean ± SD**	**t**	***P***
Duration of disease (month)	45.4 ± 30.2	59 ± 34.9	-2.496	**0.013**
Frequency (number/month)	5.23 ± 3.23	7.55 ± 4.14	-3.971	**< 0.001**
Age	42.20 ± 10.59	43.17 ± 10.18	-0.604	0.546
VAS	8.19 ± 1.28	8.50 ± 1.28	-1.565	0.119

Chi-square, Pearson chi-square test; t, Independent Samples t-test; *P* , *P* < 0.05; RLS, restless legs syndrome; MIDAS, Migraine Disability Assessment; VAS, visual analogue scale; SD, standard deviation.

Table 2. Biochemical Test Results and Differences by Groups

	Migraine (n=150)		**Migraine + RLS (n=60)**		**Statistical test**	***P***
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**		
Hb (g/dL)	13.49 ± 2.01	13.5 (4-17.9)	12.87 ± 1.89	13.05 (7-16.7)	-2.100z	**0.036**
WBC (×10³ µL)	7.29 ± 1.41		7.47 ± 1.39		-0.809t	0.419
Ferritin (ng/mL)	39.11 ± 42.03	22.2 (0.04-230)	34.19 ± 44.64	23 (1.2-310.4)	-0.723z	0.470
TIBC (ug/dL)	374.93 ± 59.54		387.48 ± 58.75		-1.386t	0.167
CRP (mg/L)	0.41 ± 0.72	0.2 (0-5.8)	0.56 ± 0.71	0.37 (0.04-4)	-3.396z	**0.001**
Albumin (g/dL)	3.87 ± 0.82		3.55 ± 0.92		2.446t	**0.015**
CAR	0.11 ± 0.21	0.05 (0-1.61)	0.18 ± 0.24	0.12 (0.01-1.38)	-3.704z	**< 0.001**

t, Independent Samples t-test; z, Mann-Whitney U test; *P*, *P* < 0.0; Hb, hemoglobin; WBC, white blood cell; TIBC, total iron binding capacity; CRP, C-reactive protein; CAR, C-reactive protein/albumin ratio; SD, standard deviation.

Table 3. Clinical Features and CAR Relationship in Migraine Patients with RLS

	CAR		Statistical test	*P*
	Mean ± SD	**Median (min-max)**		
Gender				
Female	0.19 ± 0.25	0.12 (0.01-1.38)	z=-0.603	0.547
Male	0.12 ± 0.11	0.11 (0.03-0.37)		
Aura				
No	0.20 ± 0.25	0.12 (0.01-1.38)	z=-1.120	0.263
Yes	0.10 ± 0.08	0.09 (0.01-0.22)		
Family history				
Yes	0.18 ± 0.19	0.08 (0.02-0.63)	z=-0.089	0.929
No	0.18 ± 0.25	0.13 (0.01-1.38)		
MIDAS				
Grade 1	0.05 ± 0.04	0.04 (0.01-0.17)		
Grade 2	0.09 ± 0.08	0.06 (0.01-0.33)	KW = 1.522	0.677
Grade 3	0.23 ± 0.15	0.17 (0.09-0.60)		
Grade 4	0.40 ± 0.35	0.24 (0.13-1.38)		
	r	***P***		
Age	0.106	0.420		
VAS	0.086	0.512		
Frequency (number/month)	0.260	**0.044**		
Duration of disease (month)	0.281	**0.030**		

z, Mann-Whitney U test; KW, Kruskal-Wallis H; r, Spearman's rho correlation coefficient; *P*, *P* < 0.05; MIDAS, Migraine Disability Assessment; VAS, visual analogue scale; CAR, C-reactive protein/albumin ratio; SD, standard deviation.

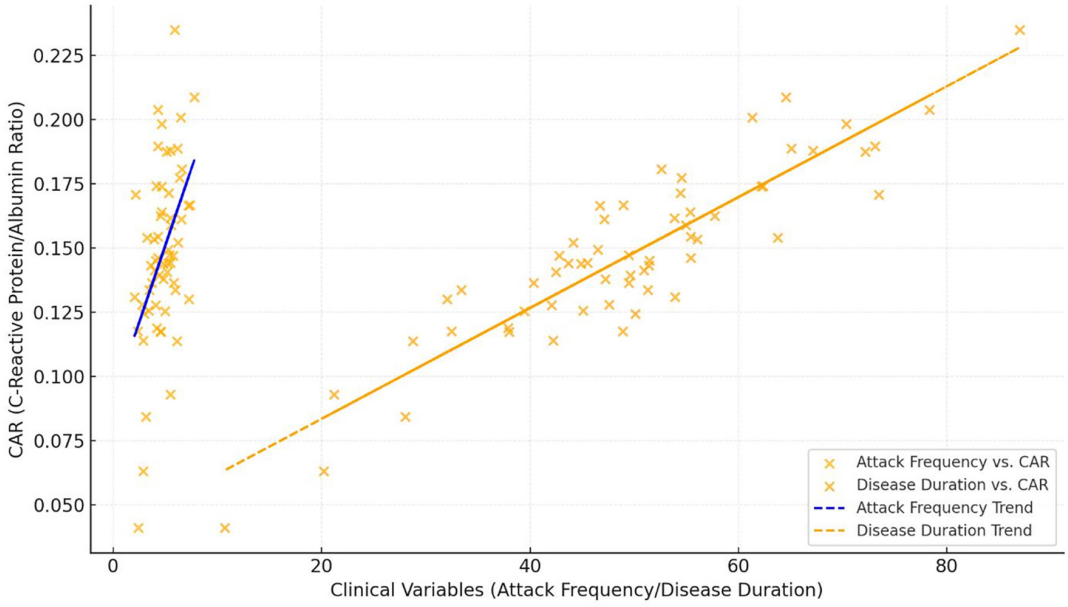

Figure 1. Chart of relationship between CAR values and attack frequency and disease duration in patients migraine with RLS.

CAR, C-reactive protein/albumin ratio; RLS, restless legs syndrome.

When clinical features of patients with RLS migraine were compared against CAR values, no differences were found regarding gender, aura, family history, and migraine severity (*P* and gt; 0.05). In the analyses performed using Spearman's rho correlation coefficient, a statistically significant, low-level positive correlation was found between attack frequency (r = 0.260, P = 0.044) and CAR, as well as between disease duration (r = 0.281, P= 0.030) and CAR. Accordingly, CAR values increased as attack frequency and disease duration increased in patients with RLS migraine (Table 3, Figure 1).

Additionally, a ROC curve analysis was performed to evaluate the diagnostic utility of the CAR value in distinguishing migraine patients with comorbid RLS from those without. The AUC ROC curve was found to be 0.650 (95% CI: 0.572-0.727, P = 0.001), indicating a fair discriminative capacity. To improve both clinical and statistical relevance, a revised cut-off value of 0.035 was selected, ensuring that specificity remained above 50%. At this threshold, the CAR value yielded a sensitivity of 53.3% and a specificity of 76.4%, with a Youden Index of 0.233. These updated findings suggest that CAR provides balanced diagnostic performance in identifying migraine patients with comorbid RLS, with moderate sensitivity and acceptable specificity (Table 4, Figure 2).

Table 4. ROC Cut-off Point for CAR in the Diagnosis of Migraine with Restless Legs Syndrome

Test	Cut-off point	Sensitivity (%)	Specitificity (%)	AUC
CAR	0.035	76.4	53.3	0.650

ROC, receiver operating characteristic; CAR, C-reactive protein/albumin ratio; AUC, area under the curve.

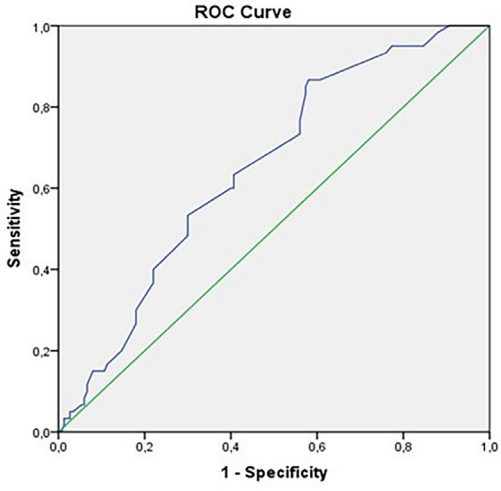

Figure 2. ROC curve for CAR in predicting migraine + RLS.

ROC, receiver operating characteristic; CAR, C-reactive protein/albumin ratio; RLS, restless legs syndrome.

DISCUSSION

We could not find a similar study in the existing literature showing the relationship between disease severity and CAR values, in patients with migraine and RLS. In this study, CAR values were higher in migraine patients with RLS compared to those with migraine alone. Our results showed that in migraine patients with RLS, high CAR values increase the risk of longer disease duration and more frequent attacks. Since high CAR values may reflect increased inflammation and a chronic disease course in migraine patients with comorbid RLS, we suggest that high CAR values could be used as a guiding biomarker for early identification of chronic migraine and for tailoring individualized preventive treatment strategies in this population. Supporting this, the ROC curve analysis demonstrated that CAR has moderate discriminative capacity in distinguishing migraine patients with and without RLS, with an area AUC of 0.650 (95% confidence interval: 0.572-0.727, P = 0.001). The optimal cut-off value for CAR was determined as 0.035, with a sensitivity of 76.4% and a specificity of 53.3%. These results suggest that CAR, while not highly specific, may be used as a sensitive screening biomarker for comorbid RLS in migraine patients.

Migraine and RLS impose a substantial burden on society due to their negative impact on quality of life and increased economic costs. Previous studies have shown both an increase in the prevalence of RLS in migraine patients compared to the healthy population and a greater likelihood that RLS accompanies migraine more often than it does other headaches.[15,16] Suzuki et al.[17] divided patients into two groups as migraine and migraine with RLS, for 7 years in their prospective study. As a result, they found significant sleep disturbances and increased MIDAS values in migraine patients with RLS compared to migraine patients without RLS. In our study, MIDAS grades 3 and 4 were higher in migraine patients with RLS compared to other migraineurs. However, this difference was not statistically significant. However, in another study comparing the relationship between chronic migraine and RLS, it was shown that RLS was associated with increased attack frequency and migraine severity.[18] Similarly, we found that attack frequency increased and disease duration was longer in migraine patients with RLS compared to migraineurs without RLS.

Sleep disturbances are known to exacerbate both the frequency and severity of migraine attacks. Patients with RLS frequently experience difficulty in initiating and maintaining sleep, which may contribute to an increase in pain perception, a reduction in pain thresholds, and impaired recovery following migraine episodes. This bidirectional interaction between RLS and migraine may explain the longer disease duration and more frequent attacks observed in patients with comorbid RLS. Supporting this, previous studies have shown that poor sleep quality is significantly associated with increased migraine severity and disability.[7,17]

Moreover, in another study, when patients were examined in terms of RLS, it was shown that the presence of migraine

significantly increased the severity of RLS.[19] These findings suggest that RLS comorbidity in migraine patients leads to increased disease severity and disability in both conditions. Understanding the shared pathophysiological processes is crucial for developing effective treatment strategies and preventing chronicity at an early stage.

Although the exact pathophysiology of RLS remains unclear, one emerging theory is brain iron deficiency, potentially caused by factors such as low peripheral iron or genetic predisposition.[4] An increase in the prevalence of RLS has been shown in the general population with iron deficiency anemia; furthermore, iron deficiency has also been associated with disease severity.[20] In our study, hemoglobin levels were low in migraine patients with RLS, but no difference was seen in ferritin and TIBC values between those with and without RLS. Similarly, Suzuki et al.[21] reported no association between RLS and serum iron or ferritin levels in migraine patients.

Chronic inflammation is characterized by elevated CRP levels and reduced albumin levels. The CAR value, which represents the ratio of these two parameters, is increasingly recognized as an indicator of inflammation and prognosis in various diseases.[23] Geng et al.[11], in a meta-analysis including 10 studies, showed that serum CRP values were increased in migraine patients compared to controls and associated this result with inflammation in migraine pathophysiology. Additionally, Sun et al.[24] reported that elevated serum CRP levels were not only associated with migraine presence but also correlated with greater migraine-related disability and severity, emphasizing its clinical relevance in the disease course. Furthermore, neurogenic inflammation characterized by neuropeptide release (such as calcitonin gene-related peptide, substance P), mast cell degranulation, vasodilation, and cytokine secretion has been increasingly recognized as a central mechanism in migraine pathogenesis.[24] In another recent study conducted on 235 migraine patients, no difference was found in CAR values between episodic and chronic migraine. In contrast, it was found to be significantly higher in patients with migraine attacks.[25] We found that CAR values were higher in migraineurs with RLS than in those without than in migraineurs. In addition, we showed that high CAR values in migraine patients with RLS are a risk factor for both prolonging the duration of the disease and increasing the frequency of attacks. We thought that increased CAR values in the combination of migraine and RLS, and the increase seen with prolonged disease indicate chronic inflammation in these patients. Our data suggest that increased CAR values in migraine patients may be a useful biomarker in understanding the chronicity of migraine and in developing RLS.

Study Limitations

The first limitation of our study was that it was a retrospective and single-institution study. Second, we excluded those with chronic diseases when determining our patient group, which significantly reduced the number of patients. For these reasons, we believe that larger and prospective studies would be useful to confirm our results. Another limitation of our study is the lack of data regarding body mass index (BMI). As elevated BMI has been associated with increased frequency and severity of both migraine and RLS, the absence of this parameter in our analysis may limit the interpretation of inflammatory mechanisms in this comorbidity.[15]

As a result, we showed that CAR values in migraine patients with RLS are higher than in migraineurs without RLS, and that high CAR values in these patients pose a risk for prolonged migraine duration and increased attack frequency. These data indicate that CAR may be a useful biomarker for determining the chronicity of the process and the development of RLS in migraine patients.

Ethics

Ethics Committee Approval: This study was approved by the Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (approval no.: 247, date: 26.11.2024).

Informed Consent: Since the study was retrospective, only verbal consent was obtained.

Conflict of Interest: The authors have no conflict of interest to declare.

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

Footnotes

Author Contributions

Concept Design – G.S., F.E.; Data Collection or Processing – G.S., M.A.; Analysis or Interpretation – G.S., F.E.; Literature Review – F.E., M.A.; Writing, Reviewing and Editing – G.S., F.E.

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Research Article

Detection of Pain Severity with the Full Cup Test in Knee Osteoarthritis and Its Relationship with Knee Function and Quality of Life

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ABSTRACT

Objective: The aim of this study was to evaluate pain severity using the Full Cup Test (FCT) in patients with knee osteoarthritis (OA) and its relationship with knee function and quality of life.

Methods: This multicenter, prospective, cross-sectional study was conducted between July 2024 and October 2024. Ethical approval was obtained from the University Non-Invasive Clinical Research Ethics Committee prior to the commencement of the study (2024-GOKAEK-248_105). All patients' demographic characteristics, general health data, and Kellgren-Lawrence staging were recorded. The following assessments were administered to all patients: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for evaluating knee pain and functionality; the Visual Analog Scale (VAS) and FCT for pain intensity at rest, and during movement; and the Short Form-36 (SF-36) for quality of life.

Results: A total of 108 participants (90% female; mean age: 57 years) were included. The majority were housewives, and approximately 25% were illiterate. FCT-rest scores demonstrated a strong correlation with VAS-rest and a weak negative correlation with the SF-36 bodily pain, vitality, and social functioning (SF) subscales ($P < 0.01$). FCT-motion scores were strongly correlated with VAS-motion, moderately positively correlated with WOMAC pain, stiffness, and total scores, and negatively correlated with SF-36 bodily pain, general health, mental health, and SF.

Conclusion: To our knowledge, this is the first study in the literature evaluating the utility of FCT in knee OA. FCT was found to be a valid, simple, and comprehensible tool for assessing pain in patients with knee OA. The results also demonstrated a meaningful association between FCT and both functional status and quality of life, indicating its broader clinical utility. Given its ease of use, FCT may be particularly beneficial in routine clinical practice, especially among elderly individuals and those with low educational attainment or cognitive decline.

Keywords: Full cup test, knee osteoarthritis, pain intensity, quality of life

INTRODUCTION

Knee osteoarthritis (OA) is a degenerative joint disease characterized by subchondral sclerosis, cartilage erosion, osteophyte formation, and both biochemical and morphological alterations in the synovial membrane of the articular cartilage.[1] It is the most prevalent joint disorder globally, affecting approximately 302 million individuals, and is a leading cause of physical disability, particularly among older adults.[2] The incidence and prevalence of chronic OA are steadily increasing in parallel with global population aging, making it a significant public health concern.[3] Additionally, around 25% of individuals over the age of 55 report at least one episode per year, and approximately 13% of elderly individuals have been diagnosed with knee OA for over seven years.[4] Risk factors for knee OA include advancing age, female sex, genetic predisposition, obesity, elevated bone mineral density, previous trauma, physical

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inactivity, certain occupational exposures, joint misalignment, ligamentous laxity, proprioceptive deficits, muscular weakness, and smoking.[5] Common clinical manifestations encompass morning stiffness, reduced joint range of motion, crepitus, joint instability, swelling, decreased muscle strength, fatigue, and pain. Radiological grading of knee OA is performed using the Kellgren-Lawrence (KL) classification system.

Despite its high prevalence, current treatments for knee OA primarily focus on symptom relief. These strategies include exercise, physiotherapy, assistive devices such as canes and splints, home modifications, self-management education programs, pharmacologic interventions, intra-articular injections, and surgical options like joint replacement.[6] The American College of Rheumatology highlights the importance of non-pharmacological approaches, such as weight reduction and aerobic exercise, in alleviating symptoms.[7]

Pain severity and treatment efficacy in knee OA are commonly assessed using patient-reported outcome measures. Frequently utilized tools include the Visual Analog Scale (VAS), Lower Extremity Functional Scale, Oxford Knee Scale, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[8] However, these instruments may pose challenges for older adults, particularly those with limited literacy or cognitive decline, as they contain complex or lengthy questions. A 2020 study from China demonstrated that increased age and decreased educational attainment were associated with greater difficulty in accurately assessing pain using standard scales.[9] These findings underscore the need for a simple, non-verbal, and easily applicable pain assessment tool tailored to this population.

The Full Cup Test (FCT), developed by Ergün et al.[10], was designed specifically to measure pain severity among patients with limited education. This method was initially applied in dental contexts to assess toothache and post-procedural pain.[11-13] FCT has since been utilized in evaluating musculoskeletal conditions. For example, a 2020 study assessing 43 patients, (74.4% female, mean age ~62) diagnosed with painful diabetic peripheral neuropathy via clinical examination and the Douleur Neuropathique 4 questionnaire found a strong correlation between VAS and FCT scores.[14] Similarly, in 69 electrodiagnostically confirmed carpal tunnel syndrome patients (87% female, mean age ~42), FCT scores were positively correlated with the Boston Carpal Tunnel Questionnaire (BCTQ) and with electrodiagnostic findings, indicating that FCT effectively reflects symptom severity.[15] In a 2022 study on 100 individuals with chronic low back pain (70% female, mean age ~56), FCT scores were significantly associated with VAS, the Oswestry Disability Index (ODI), and the Nottingham Health Profile, supporting its validity for both pain and functional evaluation.[16]

Despite the high prevalence of advanced age and low educational attainment among patients with knee OA, no previous study has examined the application of FCT in this population. This study aimed to evaluate pain severity using the FCT in individuals with OA and to investigate its relationship with knee function and quality of life.

MAIN POINTS

- To our knowledge, this is the first study to evaluate the Full Cup Test (FCT) in patients with knee osteoarthritis (OA).
- FCT was found to be a valid, simple, and comprehensible tool for assessing pain severity in knee OA.
- Beyond pain assessment, FCT also demonstrated significant associations with knee function and quality of life.
- Given its visual and intuitive format, FCT may be particularly useful in routine practice for older adults and patients with low literacy or cognitive limitations.

MATERIAL AND METHODS

Study Design

This multicenter, prospective cross-sectional study was undertaken between July 2024 and October 2024. Permission was obtained from the Yozgat Bozok University Non-Invasive Clinical Research Ethics Committee prior to the study (decision number: 2024-GOKAEK-248_105, date: 05.09.2024). Written and verbal informed consent was obtained from all patients. The study was conducted in accordance with the 1964 Helsinki Declaration.

Patients

Patients who applied to the city hospital and university hospital physical medicine and rehabilitation outpatient clinics for knee pain present for at least six months, received knee radiography, and were diagnosed with OA between July 2024 and October 2024, were included in the study. All the participants were aged 40 to 65 years. Patients with a history of malignancy, vasculitis, or neurological conditions that could influence pain perception; lumbar discopathy; those with a previous history of fracture or surgery in the knee area; or rheumatic diseases that may affect pain, such as rheumatoid arthritis, ankylosing spondylitis, or fibromyalgia were excluded from the study. All patients' personal information (age, gender, occupation, education), general health information [smoking and alcohol use, known chronic diseases, body mass index (BMI)], severity of knee pain, onset, and KL stage were recorded. The WOMAC, which evaluates pain and the functionality of the knee, the VAS rest, VAS motion, and FCT rest, FCT motion, which evaluate pain intensity, and the Short Form-36 (SF-36), which evaluates quality of life, were applied to all patients. The details of the implementation of the instruments are as follows:

The KL system was used to classify the radiographic severity of knee OA. There are four stages in total, from Stage 0 to Stage 4, and OA worsens as the stages progress. While there are no osteophytes and no narrowing of the joint space in Stage 0, there are prominent osteophytes in Stage 4, and the joint space is almost completely closed.

VAS for the Evaluation of Pain and Fatigue

For this evaluation, the patient is asked to mark his/her severity of pain and fatigue on a horizontal 10-cm line with number 0 on one end representing "no pain or no fatigue" and number 10 on the other end indicating "very severe pain or very severe fatigue".

FCT: Patients were shown a picture of an empty glass and told that if their pain is very severe, the glass will be completely full, and if they have no pain, the glass will be completely empty. They were asked to draw a line on the glass with their fingers to show the severity of their pain. The FCT score was calculated using the formula "length of line (cm) / height of glass (cm) × 100". A Turkish validity study was conducted in chronic low back pain.[16]

WOMAC is a scale that enables the evaluation of functional disability due to OA in patients with knee OA. The scale consists of 24 questions and three main headings: pain, stiffness, and physical function. Each question is scored between 0 and 4 (0 = none, 4 = very severe). High WOMAC values indicate an increase in pain and stiffness and deterioration in physical function. A Turkish validity study was conducted by Tüzün et al.[17]

SF-36 is a scale that consists of 36 multiple-choice questions. The SF-36 measures eight domains of health-related quality of life, including physical functioning, role limitations due to physical health, bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems, and mental health (MH). In this scale, which examines eight dimensions of health-related quality of life, high scores indicate a better level of health, while low scores indicate deterioration in health.

Statistical Analysis

Power analysis was performed using G*Power version 3.1.9.4. For a correlation analysis assuming an assumed medium effect size ($r = 0.518$), an alpha of 0.05, and a power of 0.95, the required sample size was calculated to be 42 participants. Numerical variables with non-parametric distribution between the groups were compared with Mann-Whitney U tests. To determine the construct validity, Spearman's correlation coefficients were used to analyze the relationships between FCT and the VAS, WOMAC, and SF-36 scales, the correlation between FCT and VAS scores was illustrated with a simple scatterplot.

RESULTS

A total of 108 individuals, 90% female and with an average age of 57, were included in the study. Demographic and clinical characteristics of the individuals are presented in Table 1. The median age was 58 years. The majority of the participants were housewives, and approximately 25% were illiterate. The mean BMI was quite high at 31.80 kg/m^2 (Table 1). Most of the patients had bilateral knee pain. KL stage was stage 2 for almost half of the patients (Table 2). Pain, function, and daily life assessment scale scores are shown in Table 3.

Table 1. Demographic Characteristics of the Patients

Age (median-IQR)	58.0 (12.0)
Gender (n/%)	
Female	98 (90.7)
Male	10 (9.3)
Occupation (n/%)	
Housewife	92 (85.2)
Officer	9 (8.3)
Worker	3 (2.8)
Retired	4 (3.7)
Marital status (n/%)	
Married	99 (91.7)
Single	3 (2.8)
Widow	6 (5.6)
Education (n/%)	
Illiterate	28 (25.9)
Primary school	58 (53.7)
Secondary school	3 (2.8)
Highschool	15 (13.9)
University	4 (3.7)
Smoking (n/%)	16 (13.0)
BMI (mean ± SD)	31.80 ± 7.0

IQR, interquartile range; BMI, body mass index; SD, standard deviation.

FCT-rest showed a strong positive correlation with VAS-rest. A weak negative correlation was also observed between FCT-rest and SF-36 subdomains including BP, VT, and SF ($P < 0.01$). FCT-motion was strongly correlated with VAS-motion, and there was a fair positive correlation between FCT-motion and WOMAC-pain, stiffness, and total scores. Therefore, a fair negative correlation was found between FCT-motion and SF-36 BP, GH MH, and SF. The correlation of FCT and VAS scores with each other and WOMAC and SF-36 scale scores was presented in Table 4.

VAS-rest and FCT-rest scores did not significantly differ by gender, ($P = 0.566$ and $P = 0.756$, respectively), whereas VAS-motion and FCT-motion scores were significantly higher in females, ($P = 0.044$ and $P = 0.015$, respectively). VAS-rest, FCT-rest, VAS-motion, and motion scores were similar in illiterate and literate patient groups ($P = 0.470$, $P = 0.733$, $P = 0.059$ and $P = 0.075$). Similarly, VAS-rest, FCT-rest, VAS-motion, and motion scores were similar in the patient groups aged 0-60 years and greater than 60 years ($P = 0.622$, $P = 0.169$, $P = 0.610$, $P = 0.790$) (Table 4).

The correlation graphic between FCT-rest and VAS-rest scores was shown in Figure 1, and the correlation graphic between FCT-motion and VAS-motion scores was shown in Figure 2.

Table 2. Clinical Characteristics of the Patients

Systemic disease	
HT	40 (37.0)
DM	32 (29.6)
CAD	6 (5.6)
Other	4 (3.7)
Taking NSAIDs in the previous week for knee pain	93 (86.1)
Side of knee pain	
Right	7 (6.5)
Left	27 (25.0)
Bilateral	74 (68.5)
Duration of pain	36.0 (48.0)
Kellgren-Lawrence stage (right knee)	
Stage	
2	48 (43.5)
3	57 (50.7)
4	3 (2.8)
Kellgren-Lawrence stage (left knee)	
Stage	
1	2 (1.9)
2	48 (44.4)
3	55 (50.9)
4	3 (2.8)

HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; NSAID, non-steroidal anti-inflammatory drug.

Table 3. Pain and Daily Life Assessment Scale Scores

	Median-IQR or mean and SD
VAS-rest	6.0 (1.5)
FCT-rest	62.5 (17.5)
VAS-motion	7.0 (2.0)
FCT-motion	72. (17.5)
WOMAC-pain	12.0 (5.0)
WOMAC-stiffness	4.0 (2.0)
WOMAC-functional	43.34 ± 13.71
WOMAC-total	57.73 ± 23.13
SF-36 physical function	25.0 (20.0)
SF-36 role physical	0.0 (0.0)
SF-36 bodily pain	22.5 (12.5)
SF-36 general health	29.79 ± 17.91
SF-36 vitality	33.86 ± 17.10
SF-36 social functioning	37.5 (25.0)
SF-36 role emotional	0.0 (0.0)
SF-36 mental health	48.47 (15.17)

IQR, interquartile range; SD, standard deviation; VAS, visual analog scale; FCT, functional cup test; SF-36, short form-36; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

DISCUSSION

A total of 108 individuals, 90% of whom were female with a mean age of 57 years, were included in this study. The majority were housewives, and approximately 25% were illiterate. FCT-rest was strongly correlated with VAS-rest, while weak negative correlations were observed between FCT-rest and SF-36 subdomains: BP, VT, and SF ($P < 0.01$). FCT-motion was strongly correlated with VAS-motion, moderately positively correlated with WOMAC-pain, stiffness, and total scores, and moderately negatively correlated with SF-36 subdomains including BP, GH, MH, and SF.

The demographic findings of this study are consistent with the literature, indicating that knee OA is more prevalent among women (90.7%) and that the average age of affected individuals is around 57 years.[5,18] Similar to previous reports,[19,20] most participants in our study were housewives and a significant proportion (25.9%) were illiterate. The mean BMI was elevated at 31.80 kg/m^2, aligning with prior studies.[21,22] Moreover, bilateral knee pain was common, and nearly half of the patients were classified as KL stage 2, corroborating previous findings.[23,24]

Previous studies have established that low educational attainment is associated with increased pain severity in knee OA.[25-27] In a study involving 114 patients with low education and without dementia who reported headache or rheumatologic pain, 21.4% were unable to comprehend the VAS, whereas all patients successfully completed the FCT, with no significant difference found between VAS and FCT scores.[10] In another study from 2020, 43 patients (74.4% female, mean age ~62) with painful diabetic peripheral neuropathy were assessed using both VAS and FCT, among them, 76.7% had low education levels. A strong correlation was observed between VAS and FCT, and no significant relationship was found between education level and FCT scores.[14]

In a 2020 study of patients with electro diagnostically confirmed carpal tunnel syndrome (mean age ~42, 87% female), 50.72% had five or fewer years of education. FCT scores showed significant correlations with the Symptom Severity Scale, a BCTQ subscale, and were reported to be easy to understand among patients with low literacy levels.[15] Similarly, a 2022 study on chronic low back pain (70% female, mean age ~56) revealed that 17% of participants were illiterate. FCT scores were higher among illiterate patients, though not statistically different from VAS scores, suggesting FCT's suitability in this population.[16] In our study, 25.9% of patients were illiterate, and while FCT scores tended to be higher in this group, the difference was not statistically significant. This finding may reflect that using a visual and intuitive scale like the FCT allows for better self-expression of pain.

FCT has also been employed to assess pain severity in dental and oral/maxillofacial surgery settings, in addition to musculoskeletal disorders.[11-13] In a 2016 study in Iraq, postoperative dental pain was evaluated using five scales including FCT, and FCT was reported as the easiest and fastest to use.[11] A 2018 review from Thailand examining ten different pain measurement tools concluded that FCT was particularly applicable and reliable for assessing acute pain.[28] Similarly, a

Table 4. Correlation Analysis of FCT, VAS, WOMAC and SF-36 Scales

		FCT-rest	FCT-motion	VAS-rest	VAS-motion
VAS-rest	Rho	**0.806**	**0.504**	1.000	**0.496**
	P	**< 0.001****	**< 0.001****	.	**< 0.001****
FCT-rest	Rho	1.000	0.420	0.806	425
	P	.	< 0.001**	< 0.001**	< 0.001**
VAS-motion	Rho	**0.425**	**0.970**	**0.496**	1.000
	P	**< 0.001****	**< 0.001****	**< 0.001****	.
FCT-motion	Rho	0.420	1.000	0.504	970
	P	< 0.001**	.	< 0.001**	< 0.001**
WOMAC-pain	Rho	0.166	**0.542**	**0.283**	**0.529**
	P	0.101	**< 0.001****	**< 0.01****	**< 0.001****
WOMAC-stiffness	Rho	0.065	**0.431**	0.163	0.**426**
	P	0.525	**< 0.001****	0.108	**< 0.001****
WOMAC-functional	Rho	0.090	**0.450****	**0.255**	**0.450**
	P	0.375	**<0.001**	**0.011***	< 0.001**
WOMAC-total	Rho	0.141	**0.560**	**0.301**	**0.555**
	P	0.165	**< 0.001****	**< 0.01****	**< 0.001****
SF-36 physical function	Rho	-0.017	-0.295	-0.150	**-0.297**
	P	0.869	< 0.01*	0.138	**< 0.01****
SF-36 role physical	Rho	-0.023	-0.211	-0.112	-0.242
	P	0.823	0.028*	0.270	0.011*
SF-36 bodily pain	Rho	**-0.240**	**-0.563**	-0.395	-0.560
	P	**0.017***	< 0.001**	< 0.001**	< 0.001**
SF-36 general health	Rho	-0.083	**-0.323**	-0.194	**0.307**
	P	0.415	**< 0.001****	0.054	**< 0.01****
SF-36 vitality	Rho	**-0.235**	-0.367	**-0.305**	**-0.368**
	P	**0.019***	< 0.001**	**< 0.01****	**< 0.001****
SF-36 social functioning	Rho	**-0.263**	**-0.501**	**-0.351**	**-0.477**
	P	**< 0.01****	**< 0.001****	**< 0.001****	**< 0.001****
SF-36 role emotional	Rho	-0.111	-0.134	0.012	-0.176
	P	0.274	0.166	0.908	0.068
SF-36 mental health	Rho	-0.139	**-0.277**	**-0.211**	**-0.263**
	P	0.242	**< 0.01****	**0.036***	**< 0.01***

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed). VAS, visual analog scale; FCT, functional cup test; SF-36, short form-36; WOMAC: Western Ontario and McMaster Universities Arthritis Index; Rho P, Spearman's rank correlation coefficient.

2018 Malaysian study comparing FCT, VAS, and the numerical rating scale for postoperative dental pain found that FCT was the second most user-friendly scale after the numerical rating scale.[12] In our study involving patients with knee pain (90.7% female, mean age 57, age range 40-65), FCT was strongly correlated with VAS, consistent with these findings.

Although FCT is frequently compared with VAS, which primarily assesses pain severity, few studies have examined its relationship with functional status or quality of life. Two studies evaluated the association between FCT and functional capacity, while only one investigated its relationship with quality of life. In the 2020 carpal tunnel syndrome study, FCT was significantly correlated with the Symptom Severity and Functional Status subscales of BCTQ.[15] In a 2022 study on patients with chronic low back pain (mean age 56, 70% female), FCT scores were significantly associated with VAS, the ODI, and the Nottingham Health Profile.[16] Similarly, our study demonstrated significant associations between FCT and VAS, WOMAC, and SF-36, supporting its validity in assessing not only pain intensity but also functional limitations and quality of life in patients with knee OA. The demographic profile of our cohort, particularly the high female-to-male ratio, parallels previous studies and may reflect the higher prevalence of obesity and OA among women, as compared to men, as well as the prevalence of low back pain.

Study Limitations

This study has several limitations. First, mood disorders such as sleep disturbances, anxiety, and depression, which are known to influence pain perception and quality of life, were not evaluated. Second, the cross-sectional design limits the ability to infer causal relationships between the FCT and clinical outcomes. Third, although the study included a diverse group

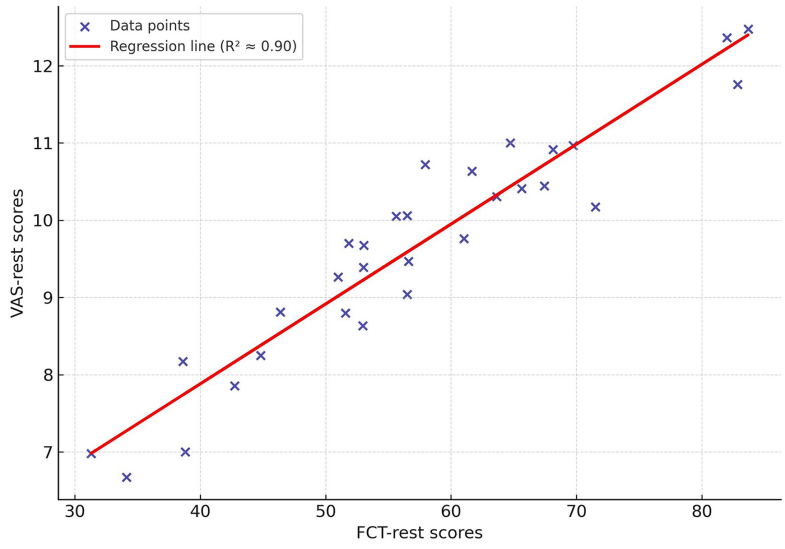

Figure 1. Correlation between FCT-rest and VAS-rest scores.

FCT, functional cup test; VAS, visual analog scale.

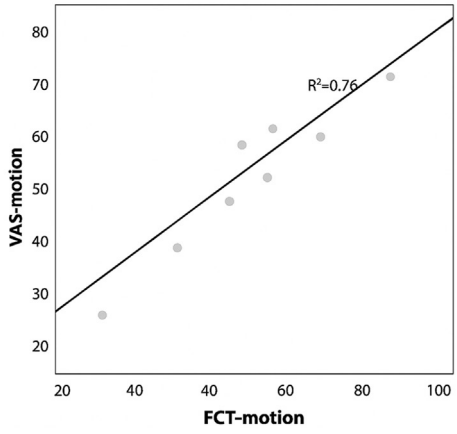

Figure 2. Correlation graphic between FCT-motion and VAS-motion scores-1.

FCT, functional cup test; VAS, visual analog scale.

in terms of literacy, the sample was predominantly female, which may limit the generalizability of the findings to male populations. Lastly, although FCT was correlated with well-established measures, its test-retest reliability and sensitivity to change over time were not assessed. Future longitudinal and multicenter studies are needed to confirm these findings and evaluate the responsiveness of FCT to clinical changes.

CONCLUSION

To our knowledge, this is the first study in the literature to evaluate the utility of the FCT in patients with OA. The findings suggest that FCT is a valid, simple, and comprehensible tool for assessing pain severity in this population. Importantly, FCT was not only associated with pain intensity but also demonstrated meaningful correlations with knee function and quality of life. Given its intuitive format and visual nature, FCT may be particularly beneficial in routine clinical practice for older adults and individuals with low literacy or cognitive limitations where traditional scales like VAS may be less applicable. Future studies should further examine its responsiveness to clinical change over time.

Ethics

Ethics Committee Approval: The study protocol was approved by Yozgat Bozok University Non-Invasive Clinical Research Ethics Committee with decision number 2024-GOKAEK-248_105, date: 05.09.2024.

Informed Consent: Written and verbal informed consent was obtained from all patients.

Footnotes

Author Contributions

Concept Design - G.D.K., E.Ş.B.; Data Collection and/or Processing - G.D.K., E.Ş.B.; Analysis and/or Interpretation - G.D.K., E.Ş.B.; Literature Search - G.D.K., E.Ş.B.; Writing, Reviewing and Editing - G.D.K., E.Ş.B.

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Case Report

Imaging-Guided Diagnosis of Malignant Pericardial Involvement in an HIV-Positive Patient with Non-Hodgkin's Lymphoma

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ABSTRACT

Malignant pericardial involvement is a rare manifestation of non-Hodgkin's lymphoma (NHL), particularly in immunocompromised individuals. In human immunodeficiency virus (HIV)-positive patients, this condition is especially uncommon and presents diagnostic challenges. Radiologic imaging is essential for early detection and management. An 80-year-old HIV-positive man with chronic kidney disease and a history of NHL presented with progressive dyspnea and a productive cough. Imaging revealed a large pericardial effusion with tamponade physiology. Urgent echocardiography-guided pericardiocentesis drained serosanguineous fluid. Chest computed tomography (CT) demonstrated diffuse nodular pericardial thickening and mediastinal lymphadenopathy, raising suspicion for malignant pericardial disease. Cytologic analysis confirmed diffuse large B-cell lymphoma. A pericardial catheter was placed for recurrent effusion management. Although initially stabilized, the patient developed tumor lysis syndrome and septic shock, and care was transitioned to hospice. Malignant pericardial effusion as an initial presentation of NHL in HIV-positive patients is rare. Differential diagnoses include opportunistic infections, Kaposi's sarcoma, and primary pericardial malignancies. Multimodal imaging, especially echocardiography and CT, plays a crucial role in diagnosing, guiding emergent interventions, and informing treatment planning. This case highlights the importance of integrating imaging with clinical findings to manage complex presentations in immunocompromised populations.

Keywords: CT, echocardiography, HIV, non-Hogkin's Lymphoma, pericardial effusion, PET-CT

INTRODUCTION

Malignant pericardial effusion is a rare clinical entity, particularly as an initial manifestation of non-Hodgkin's lymphoma (NHL).[1] In immunocompromised patients, such as those with human immunodeficiency virus (HIV), this presentation is exceedingly uncommon and poses significant diagnostic challenges. The buildup of fluid within the pericardial sac, known as pericardial effusion, is often linked to a poor prognosis and can result in severe complications, including cardiac tamponade, hemodynamic instability, and fatal outcomes.[2,3] Hence, early and accurate diagnosis through radiologic imaging is essential to guide clinical decision-making and optimize patient outcomes.

This case report details a unique presentation of malignant pericardial effusion with nodular pericardial thickening in an HIV-positive patient, emphasizing the diagnostic and therapeutic contributions of radiologic imaging.

CASE PRESENTATION

Informed consent was obtained from the patient for the publication of this case report, including the use of relevant clinical and imaging data.

The patient is an 80-year-old male with a significant medical history, including HIV and receiving highly active antiretroviral

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therapy (ART), hypertension, solitary kidney (status post gunshot wound with right nephrectomy), chronic kidney disease secondary to focal segmental glomerulosclerosis, NHL, and a history of cardiac tamponade requiring drainage.

He presented with a 4-day history of progressive shortness of breath, productive cough with white-yellow sputum, and generalized weakness. Physical examination revealed shallow breathing, increased work of breathing, diffuse coarse breath sounds, generalized abdominal tenderness, and bilateral lower extremity edema.

In the emergency department, the patient was tachypneic and hypoxemic, requiring supplemental oxygen. Laboratory findings were significant for normocytic anemia and elevated creatinine (3.3 mg/dL). A transthoracic echocardiogram (TTE) was performed urgently and revealed a large pericardial effusion with echocardiographic signs of cardiac tamponade. Based on these findings, emergent pericardiocentesis was performed, yielding serosanguinous fluid. Cytologic analysis of the pericardial fluid confirmed malignant cells consistent with NHL.

Following the procedure, a chest computed tomography (CT) was obtained during the oncology consultation, which demonstrated diffuse circumferential nodular thickening of the pericardium and mediastinal lymphadenopathy. These findings supported the diagnosis of diffuse large B-cell lymphoma with malignant pericardial involvement. The patient subsequently underwent pericardial catheter placement for recurrent effusion management. Despite initial stabilization, his condition progressively declined due to tumor lysis syndrome and septic shock. After multidisciplinary discussions and alignment with the patient's goals of care, he was transitioned to palliative care and discharged to hospice.

Initial imaging revealed moderate cardiomegaly, a large pericardial effusion with echocardiographic signs of cardiac tamponade, pulmonary venous hypertension, and trace pleural effusion (Figure 1a and 1b).

Follow-up chest CT showed diffuse circumferential high-attenuation nodular thickening of the pericardium with diffuse mediastinal and hilar lymphadenopathy (Figure 1c and 1d). Differential considerations included primary effusion lymphoma secondary to Human Herpesvirus 8. Additional possibilities included metastatic disease or primary pericardial mesothelioma. Imaging also revealed small bilateral pleural effusion with associated compressive atelectasis of the adjacent lung parenchyma.

MAIN POINTS

- Malignant pericardial effusion is an uncommon initial manifestation of non-Hodgkin's lymphoma, especially in immunocompromised patients such as those with human immunodeficiency virus. Early recognition is critical to prevent life-threatening complications like cardiac tamponade.
- Imaging modalities such as echocardiography, computed tomography, and fluorodeoxyglucose positron emission tomography/computed tomography play a central role in diagnosing pericardial involvement in lymphoma. These tools aid in detecting pericardial effusion, guiding pericardiocentesis, and differentiating between infectious and malignant causes.
- The management of malignant pericardial effusion requires collaboration between oncology, cardiology, infectious disease specialists, and palliative care teams. This ensures appropriate intervention strategies, including pericardiocentesis, catheter placement, chemotherapy, and symptom-directed palliative care.

DISCUSSION

Malignant pericardial involvement as a presenting manifestation of NHL is rare, with limited cases reported in the literature. Malignancies affecting the pericardium typically manifest as pericardial effusion or constrictive pericarditis, though these presentations are usually late-stage secondary developments.[4]

In patients with HIV/acquired immunodeficiency syndrome (AIDS), the incidence of pericardial effusion is notably higher, and when present, it should raise suspicion for underlying malignancies, including lymphoma. The immunocompromised state associated with HIV complicates both the diagnosis and treatment of such malignancies, as evidenced by cases where pericardial effusion was the first indication of disseminated lymphoma in AIDS patients.[5]

Moreover, patients with HIV come with diagnostic challenges due to atypical presentations of cardiac involvement. For instance, cardiac lymphomas in HIV-positive patients may present with vague symptoms, complicating the diagnostic process.[6] Additionally, there are diverse etiologies of pericardial effusions in HIV patients, including opportunistic infections such as tuberculosis, bacterial infections, and malignancies such as lymphoma and Kaposi's sarcoma. This diversity necessitates comprehensive diagnostic evaluations to determine the exact cause.[7]

Radiologic imaging was pivotal in identifying the pericardial effusion and nodular thickening, guiding emergent management, and suggesting an underlying malignancy. TTE is often the first-line imaging modality for detecting pericardial effusions.[8] Particularly echocardiography and CT aid in planning pericardiocentesis or biopsy by identifying optimal access points and evaluating procedural risks. In addition, follow-up imaging, especially with positron emission tomography (PET)-CT or magnetic resonance imaging, is essential for assessing response to chemotherapy and ART in HIV-associated NHL.

F-FDG PET/CT is a highly effective imaging modality for the initial staging of lymphoma and for assessing early treatment responses, enabling tailored management for individual patients. However, its use in post-treatment surveillance is not recommended due to a substantial risk of false-positive findings. Specifically in HIV-positive patients, this risk is exacerbated by opportunistic infections that can mimic lymphoma on PET imaging. Additionally, the recurrence of lymphoma is more common in HIV-positive individuals; factors contributing to this increased recurrence include larger tumor burden at diagnosis,

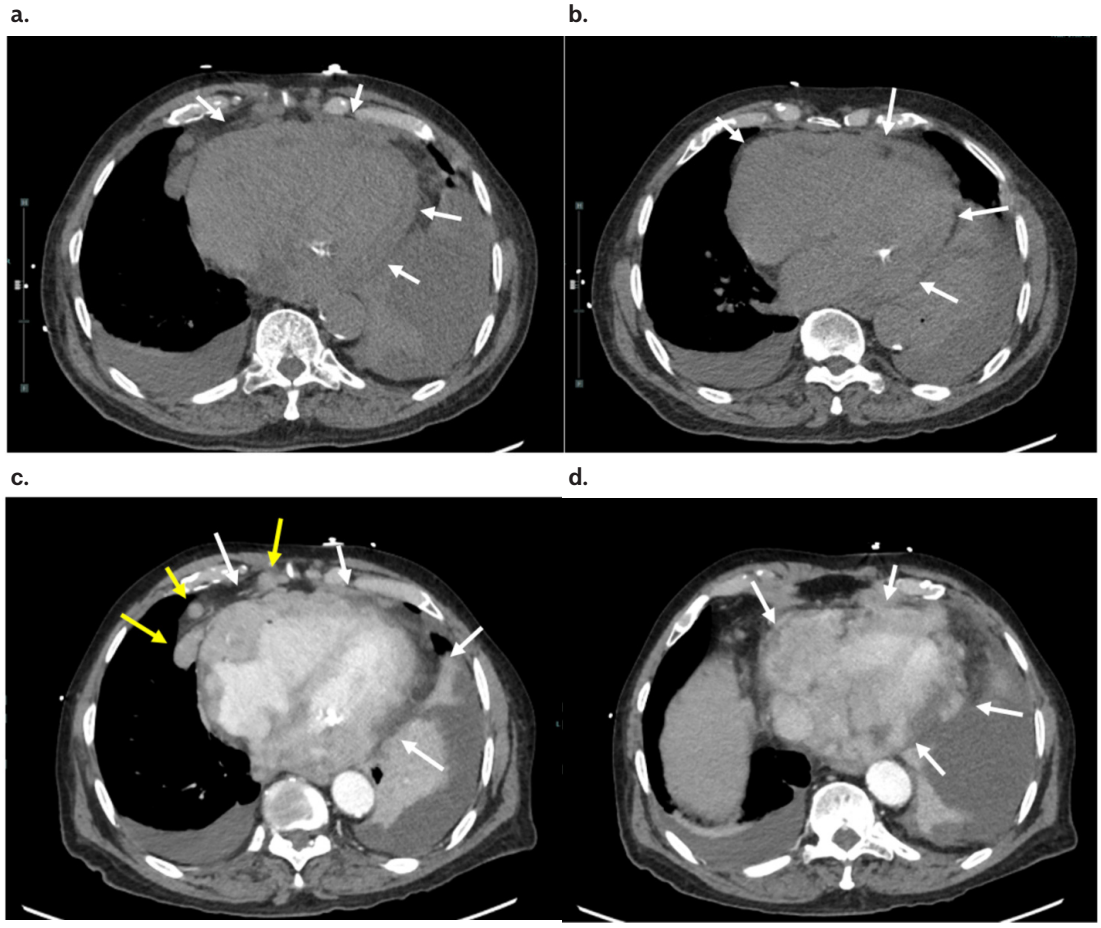

Figure 1. (a, b) Axial non-contrast CT images demonstrate a high-attenuation pericardial thickening (arrows), concerning for hemopericardium or pericardial infiltration, bilateral pleural effusion and left lower lobe compression atelectasis. **(c, d)** Axial post-contrast chest CT images show nodular, contrast-enhancing thickening of the pericardium (arrows), suggestive of malignant infiltration, enlarged pericardial lymph nodes (yellow arrows), consistent with lymphomatous involvement.

CT, computed tomography.

ongoing immune dysfunction, and less-than-optimal therapy in this patient population.[9] As a result, imaging strategies should be carefully aligned with the patient's clinical symptoms and the level of suspicion for disease recurrence.

This case demonstrates the diagnostic and therapeutic challenges of malignant pericardial effusion in an HIV-positive patient. Radiology played a central role in identifying the effusion, suggesting malignancy, and guiding emergent interventions. This report highlights the importance of a multidisciplinary approach to managing rare and life-threatening presentations of malignancy.

The rarity of malignant pericardial effusion as an initial presentation of lymphoma underscores the importance of maintaining a broad differential diagnosis in immunocompromised patients presenting with cardiopulmonary symptoms. Early recognition and management are crucial to prevent life-threatening complications such as cardiac tamponade.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case report, including the use of relevant clinical and imaging data.

Footnotes

Author Contributions

Concept Design – M.N.D., D.O-T.; Data Collection or Processing – M.N.D., D.O-T.; Analysis or Interpretation – M.N.D.; Literature Review – M.N.D.; Writing, Reviewing and Editing – M.N.D.

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ABCResearch

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Review

The Role of Imaging Methods in the Diagnosis and Treatment of Idiopathic Granulomatous Mastitis

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ABSTRACT

Idiopathic granulomatous mastitis (IGM) is an uncommon chronic inflammatory disease of the breast with an unclear etiology that mostly impacts young women. Its incidence is higher in the Middle East and Asian countries, particularly in Türkiye. Clinical signs such as mass, fistula formation, swelling, and radiographic abnormalities such as lymph node enlargement, abscess, calcifications, localized or widespread asymmetric density, and hypoechoic lesions may result in a misdiagnosis of malignancy or infection. There are no imaging findings that distinguish between IGM and breast cancer in any imaging method; in most cases, imaging tests like ultrasonography, magnetic resonance imaging, or mammography reveal non-specific characteristics, leading to biopsy. Histological assessment is used to reach a conclusive diagnosis of IGM. Common medical treatments include systemic steroid treatment (oral corticosteroid), local steroid treatment (local steroid injection in breast,), antibiotics, immunosuppressive drugs (methotrexate, etc.), and monoclonal antibodies. Abscess drainage and surgical excision are further alternatives. Although the conclusive diagnosis of IGM is made histologically, imaging methods have a significant impact in evaluating the number, location, their size, abscess development, and the likelihood of intervention, stability or change in lesions, and response to treatment in patients with confirmed diagnosis. In addition, radiology and interventional radiology units guide clinicians in the timely diagnosis of the disease and play an important role in local steroid injection, which is used effectively in its treatment.

Keywords: Idiopathic granulomatous mastitis, ultrasonography, magnetic resonance imaging, mammography, diagnosis, treatment

INTRODUCTION

Idiopathic granulomatous mastitis (IGM), also known as lobular granulomatous mastitis, is an uncommon chronic inflammatory disease of the breast with an unclear etiology. The average age of patients at presentation is between 32 and 35 years, a condition that primarily affects young women.[1-3] The most commonly recognized hypothesis is hypersensitivity, or autoimmune reaction, although the etiology remains unknown.[4] IGM is characterized by chronic non-necrotizing lobulocentric granulomatous inflammation around lobules and ducts, with a prolonged course of recurrent disease. IGM is mostly a disease that affects young women who are of reproductive age, and its frequency is higher in Middle Eastern and Asian countries, particularly Türkiye. This suggests that the disease's origin results from both environmental factors and genetic etiology.[5,6]

The misinterpretation of cancer or infection may result from clinical signs such as swelling, mass, and fistula development, as well as radiographic abnormalities such, lymph node enlargement, abscess, calcifications, isolated or widespread asymmetric density, and hypoechoic lesions.[7] Although IGM is not cancerous, it can be extremely resistant to treatment and locally aggressive, which can have a major negative impact on a patient's quality of life and result in cosmetic issues.[8]

There are no imaging findings that distinguish between IGM and breast cancer in any modality. Imaging tests like ultrasonography, magnetic resonance imaging (MRI), or

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mammography reveal non-specific characteristics, leading to biopsy.[7,9] There are some non-specific features of imaging in mastitis to confirm mastitis, assess the degree of the lesion, and determine the efficacy of conservative treatment. The extent of the lesion and the type of drainage required can be determined using ultrasound (US).[10]

A final diagnosis of IGM is made by histological investigation. Common characteristics of IGM include the presence of neutrophils, lobulocentric granulomatous inflammation, non-caseating granulomas, giant cells, and epithelioid histiocytes.[11]

Imaging of IGM

IGM is often aggressive and has characteristics of infected mastitis or inflammatory breast cancer. IGM diagnosis can be challenging and typically takes time. Before making an IGM diagnosis, cancer and all other probable causes of mastitis must be ruled out.[12] The appearance of imaging varies according to the amount of inflammation, the timing of radiographic evaluation, and the potential for previous intervention.[13] Even though US and mammography are often sufficient for imaging granulomatous mastitis, MR imaging can be useful for assessing advanced, aggressive, or refractory illness.[12]

Mammography

IGM is often a disease of reproductive age; therefore, mammography sensitivity reduces because the breast tissue pattern is dense in women of this age range.[14] IGM's mammography findings are non-specific, with varying imaging features. Examination of the literature suggests that focal asymmetry is the most common finding on mammograms. Especially in the presence of extremely dense or heterogeneous breasts, there are no imaging findings on mammography.[12,15-17] In some studies, studies have stated that global asymmetry or asymmetric dense breast parenchyma, is a less common appearance of granulomatous mastitis.[18,19] Mammographic findings in IGM include thickening of the skin, a solitary mass or multiple masses, nipple and skin recession, and axillary lymphadenopathy.[13,15,19] IGM is not generally associated with calcifications, and this condition is rarely reported.[12] (Figure 1)

MAIN POINTS

- Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory disease of the breast, of unclear etiology, which mostly impacts young women.
- Common medical treatments include steroid therapy, antibiotics, immunosuppressive drugs, and monoclonal antibodies. Alternatives include surgical excision and abscess drainage.
- While histopathology is the final diagnostic method for IGM, imaging methods have a significant impact in evaluating the number and location of lesions, size of lesions, abscess development, and the likelihood of intervention, stability or change in lesions, and response to treatment in patients with confirmed diagnosis.

US

Ultrasound is useful for assessing patients whose mammograms are normal but have palpable lesions on physical examination, although ultrasound findings of IGM may vary. The most common manifestation reported is a large mass with irregular borders, hypoechoic, and heterogeneous internal structure, with tubular extensions.[12,15,19,20] Posterior acoustic features can vary greatly, including both shadowing and enhancement.[12,15,17,21] Almost all lesions have a parallel orientation.[22] Doppler imaging shows that lesions and the surrounding breast parenchyma have increased internal blood flow.[13] In advanced disease, fluid collections or abscesses may occur.[12,15] (Figure 2) Other ultrasound findings include axillary adenopathy, subcutaneous fat obliteration, edema and skin thickness.[12,15,19]

A relatively new technique, Shear Wave Elastography (SWE), is a sonography-based imaging method used to assess tissue stiffness, and its usage area is gradually increasing. In patients with IGM, tissue rigidity increases in SWE, which can cause IGM to be confused with malignant lesions. Evaluation with SWE has primarily focused on distinguishing IGM from malignant lesions. SWE has high specificity and sensitivity in differentiating IGM from breast cancer with a lower shear wave velocity value and a lower SWE score. Current publications have revealed that elastography is utilized not only for diagnosis but also to evaluate the success of treatment.[6,23,24] The Tsukuba scoring system is a classification system developed by Itoh et al.[25] that evaluates SWE features. This scoring system states that a score of 1 to 3 indicates benign, whereas a score of 4 to 5 indicates a possible cancer.[25,26] (Figure 2)

MRI

MRI is a useful imaging method in addition to ultrasound and mammography in the evaluation of patients, and the findings in MRI vary depending on the severity of inflammation.[15,19,27] The most frequently identified findings on MRI are heterogeneous enhancing mass (or masses) or ring-shaped enhancing lesions. MRI may also show associated segmental or regional non-mass enhancement (NME). Some small lesions with confluency or well-defined margins, T2 hyperintensity, and rim enhancement at MR imaging have been assumed to be microabscesses (Figure 3). In serious disease, larger fluid collections can be identified interspersed with abnormal enhancement, with or without sinus tracts, that extend to the skin surface. NME without an accompanying mass is also prevalent, and NME with IGM has a more segmental distribution than a regional one. Diffuse NME is rarely encountered. Additional MRI findings include nipple retraction, nipple and/or skin thickening, axillary lymphadenopathy, sinus tracts, and parenchymal distortion. Although most examples include progressive or plateau patterns of enhancement, the enhancement kinetic aspects are non-specific. There is a small number of studies that demonstrate lesion enhancing patterns of plateau or washout.[12,15,19,20,27,28] Due to the variety in enhancement kinetic characteristics, MRI cannot consistently distinguish IGM from inflammatory breast cancer.[29] Importantly, MRI may be useful in following challenging cases treated with conservative therapy, documenting relapse, and assessing disease progression over time.[12]

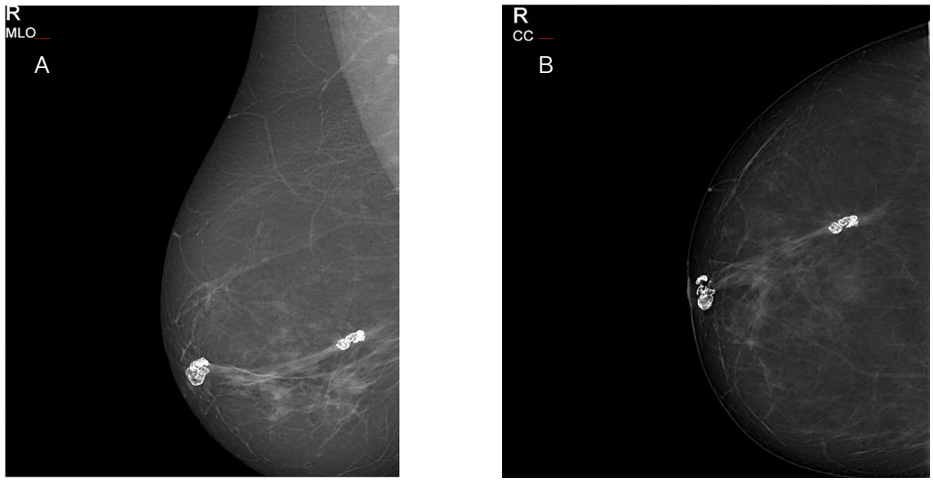

Figure 1. IGM in a 38-year-old woman with a painful mass of 4 weeks' duration in the retroareolar and outer region of the right breast. A and B: MLO (**A**) and CC (**B**) digital mammography images show coarse heterogeneous calcifications in the retroareolar and outer-middle region of the right breast, a rare finding of IGM.

IGM, idiopathic granulomatous mastitis; MLO, mediolateral oblique; CC, craniocaudal.

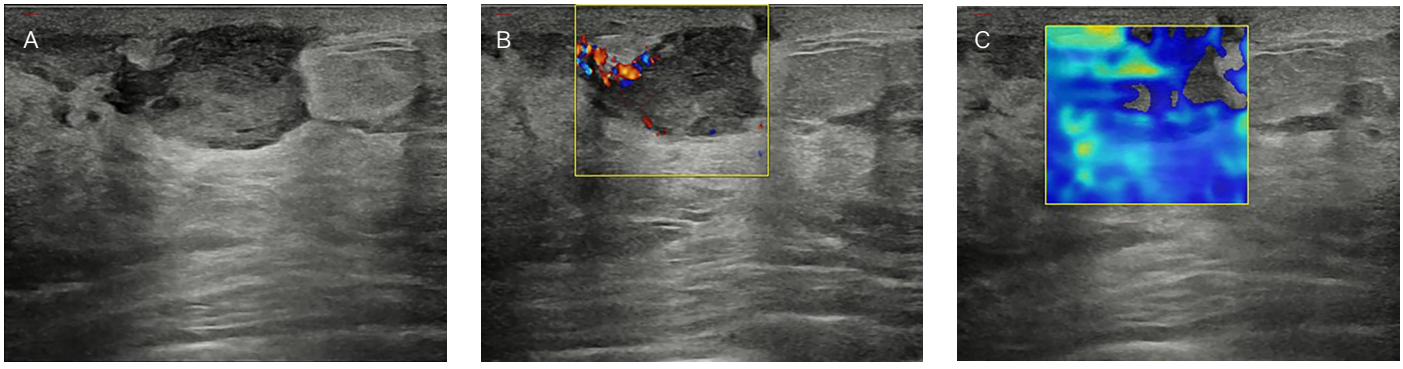

Figure 2. 28-year-old woman who presented with a tender, rapidly growing left-breast mass. Antibiotic treatment trials were unsuccessful. Abscess aspirations yielded sterile cultures and no malignancy. Pathology result was reported as IGM. (**A**) and (**B**) Ultrasound images obtained at the 2-o'clock to 6-o'clock position in the left breast for shows a complex mass with solid and cystic components and internal vascularity. The mass was believed to represent surrounding inflammation and/or granulation tissue associated with abscess formation. (**C**) Elastographic examinations show that the elasticity value of the lesion is in the benign category according to the Tsukuba scoring system.

Treatment of IGM

Once diagnosed, optimal treatments are urgently required to manage IGM.[30] The disease's long natural history and recurrence complicate decisions about how to treat and follow up. There has been a shift toward combination medical therapies, with or without surgery, to manage long-term and recurrent cases.[31] Common medical treatments include steroid therapy, antibiotics, immunosuppressive drugs (methotrexate, etc.), and monoclonal antibodies.[1]

Although antibiotics are also used in the treatment, this is questionable, as a direct causal relationship between bacterial infiltration and IGM has not been determined. The use of antibiotics is decided based on available microbiological data, and the selected agents are directed against gram-positive organisms.[32]

Abscess drainage and surgical excision are among the treatment options.[1] Surgery has unfortunate cosmetic effects, a prolonged scar healing process, and a high relapse rate. As a result, systemic steroids have been the most commonly used treatment for IGM.[33,34]

Systemic steroid therapy is the mainstay treatment for IGM and has been successful in up to 75% of patients.[18] However, long-term use of steroids can cause well-known, potentially serious side effects such as weight gain, impaired glucose tolerance, osteoporosis, peptic ulcers, Cushing's syndrome, and even mental disorders. For this reason, the duration of treatment should be adjusted according to the response of the disease, and the dose of steroids used in treatment should be as low as possible.[9,35,36]

Topical corticosteroids may be used adjunctively to prevent skin breakdown and control skin symptoms. In recent years,

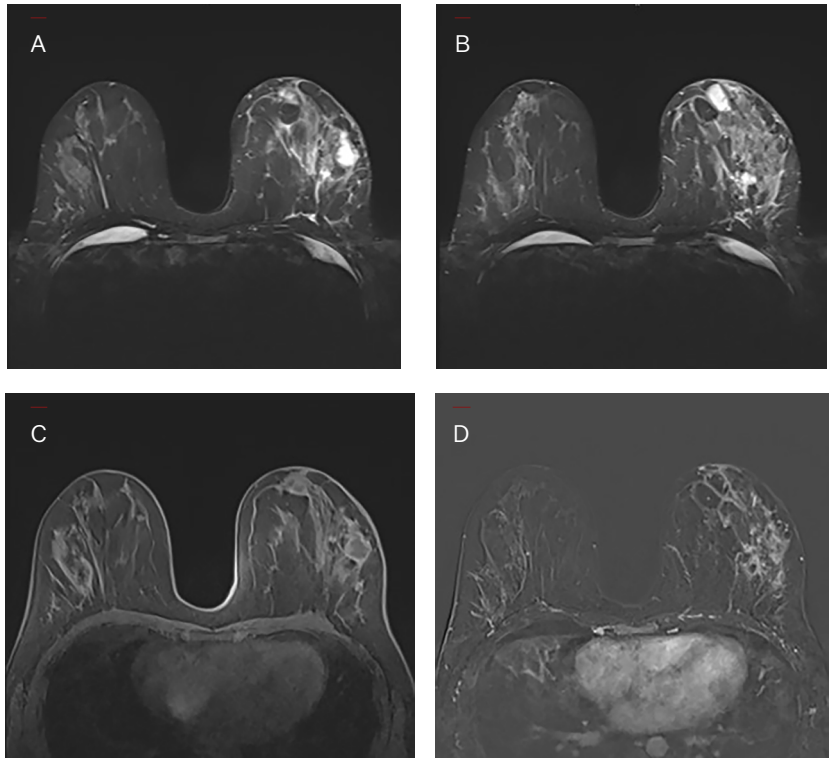

Figure 3. MRI in a 26-year-old female patient who complained of pain and swelling in the left breast and whose pathology result was reported as IGM. (**A**) and (**B**) On axial T2-weighted fat-saturated images, cystic lesions are observed in the retroareolar area and outer middle quadrant of the left breast. (**C**) In the gadolinium-based contrast material-enhanced axial T1-weighted fat-saturated image, there are lesions suggestive of a wall-enhanced abscess in the retroareolar plane and outer middle quadrant of the left breast. (**D**) In the gadolinium-based contrast material-enhanced axial T1-weighted fat-saturated subtraction image, irregular parenchymal contrast enhancements are observed in the outer quadrants of the left breast.

MRI, magnetic resonance imaging; IGM, Idiopathic granulomatous mastitis.

intralesional steroid injection has also emerged as a novel therapeutic approach. Topical corticosteroids, and intralesional corticosteroid injections may be used primarily to treat IGM patients who are experiencing systemic corticosteroid side effects or skin changes. The combination of intralesional and topical steroids may help decrease the likelihood of adverse effects such as atrophy, bruising, and the development of sterile abscesses while also extending the interval between intralesional steroid injections.[6,35,37-39]

Steroids and immunosuppressants have a similar mechanism of action on IGM. The most commonly used immunosuppressive agent is methotrexate. However, its use is limited due to side effects such as pulmonary fibrosis, bone marrow suppression, hepatic and nephrotoxic damage.[35,40]

CONCLUSION

IGM is a rare, benign chronic inflammatory breast disease for which the exact causes and recommended treatment approaches are not well defined. Imaging findings of IGM are not specific. It has features that often overlap with inflammatory breast cancer and other inflammatory breast diseases. Given the non-specific imaging findings of IGM, diagnosis is often based on the presence of specific histopathological findings and exclusion of other causes of inflammatory breast disease. Because of the substantial clinical and radiographic overlap with breast cancer, a histologic diagnosis requires a tissue sample. Corticosteroids, immunomodulatory medications, and antibiotics are among the medicinal therapies available. Surgery is often saved for situations where medical therapy is ineffective and the condition continues to worsen. In patients with histologically confirmed IGM, imaging methods play an important role in evaluating the multiplicity and location of lesions, lesion size, abscess formation and the possibility of intervention, lesion stability or change, and the response to treatment. In addition, radiology and interventional radiology units guide clinicians in the timely diagnosis and play an important role in local steroid injection, which is used effectively in its treatment.

Ethics

Informed Consent: N/A.

Footnotes

Author Contributions

Concept Design – H.A., S.A., M.K.; Data Collection and/or Processing – H.A., S.A.; Analysis and/or Interpretation – H.A., M.K.; Literature Review – H.A., S.A.; Writing, Reviewing and Editing – H.A., S.A., M.K.

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ABCResearch

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Letter to the Editor

Risk Factors and Preventive Approaches in Early Onset Osteoarthritis

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To the Editor,

I read with interest the review entitled 'Disorders Leading to Early-Onset Osteoarthritis: Orthopedic Considerations and Insights', and I would like to thank the authors for their valuable contribution to this topic, which is of great importance for physicians interested in the musculoskeletal system. The review comprehensively discusses the genetic and orthopaedic factors that play a role in the development of early-onset osteoarthritis (EOA).[1] Osteoarthritis is a disease that decreases the quality of life of individuals by negatively affecting joint health, and it often requires surgical intervention.[2] A multidisciplinary approach is required to prevent EOA and slow down its progression, especially in patient groups at risk. In this context, attention should be drawn to the importance of preventive and early interventions from the perspective of a physiatrist.

Obesity and weight control: Overweight and obesity are among the most important modifiable risk factors for osteoarthritis. Obesity may accelerate cartilage degeneration by increasing mechanical loading on the joint. In addition, it may accelerate the progression of the disease by triggering systemic inflammation. Therefore, promoting healthy nutrition and regular physical activity from childhood onwards may reduce the development of osteoarthritis in adulthood. Individuals who achieve weight control through diet and exercise are likely to have milder osteoarthritis symptoms.[3]

Prevention of joint injuries: Traumatic joint injuries, especially anterior cruciate ligament and meniscal tears, are strong risk factors for the development of osteoarthritis. Programmes including neuromuscular control and strengthening exercises should be implemented to prevent such injuries in athletes and physically active individuals. Exercises, especially those that increase knee stability, have been shown to be effective in the prevention of sports injuries.[4]

Muscle strength and biomechanical corrections: Muscle weakness can impair joint stability and accelerate the development of osteoarthritis. Muscle strengthening programmes and appropriate biomechanical alignments (postural corrections for the knee and hip joint) can maintain joint health. Maintaining proper posture and gait mechanics can reduce the risk of developing osteoarthritis in the long term by reducing abnormal loads on the joints.[3]

Physical activity and exercise: Regular physical activity is critical for maintaining joint health and slowing disease progression. While low-impact exercises (such as swimming, cycling, yoga) support joint health, activities that may cause heavy loading should be avoided. Individualised exercise programmes should be implemented to maintain range of motion and strengthen muscle function.[5]

Controlling inflammation: Chronic inflammation can accelerate joint degeneration. Healthy nutrition, anti-inflammatory diets and physical therapy applications, (cold-hot applications, electrotherapy) aimed at reducing inflammation in the early period may be effective. In addition, pharmacological and non-pharmacological approaches to reduce inflammation should be evaluated individually.[3]

Early diagnosis and intervention: Identifying clinical symptoms and risk factors in the early stages of osteoarthritis can slow the progression of the disease. For early diagnosis in individuals at risk, it may be useful to monitor joint health with non-invasive methods such as regular controls, ultrasound, and magnetic resonance imaging.

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Adopting a multidisciplinary approach for patient groups who can be diagnosed with early osteoarthritis will protect joint health in the long term and reduce the need for surgery.

Yours sincerely,

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