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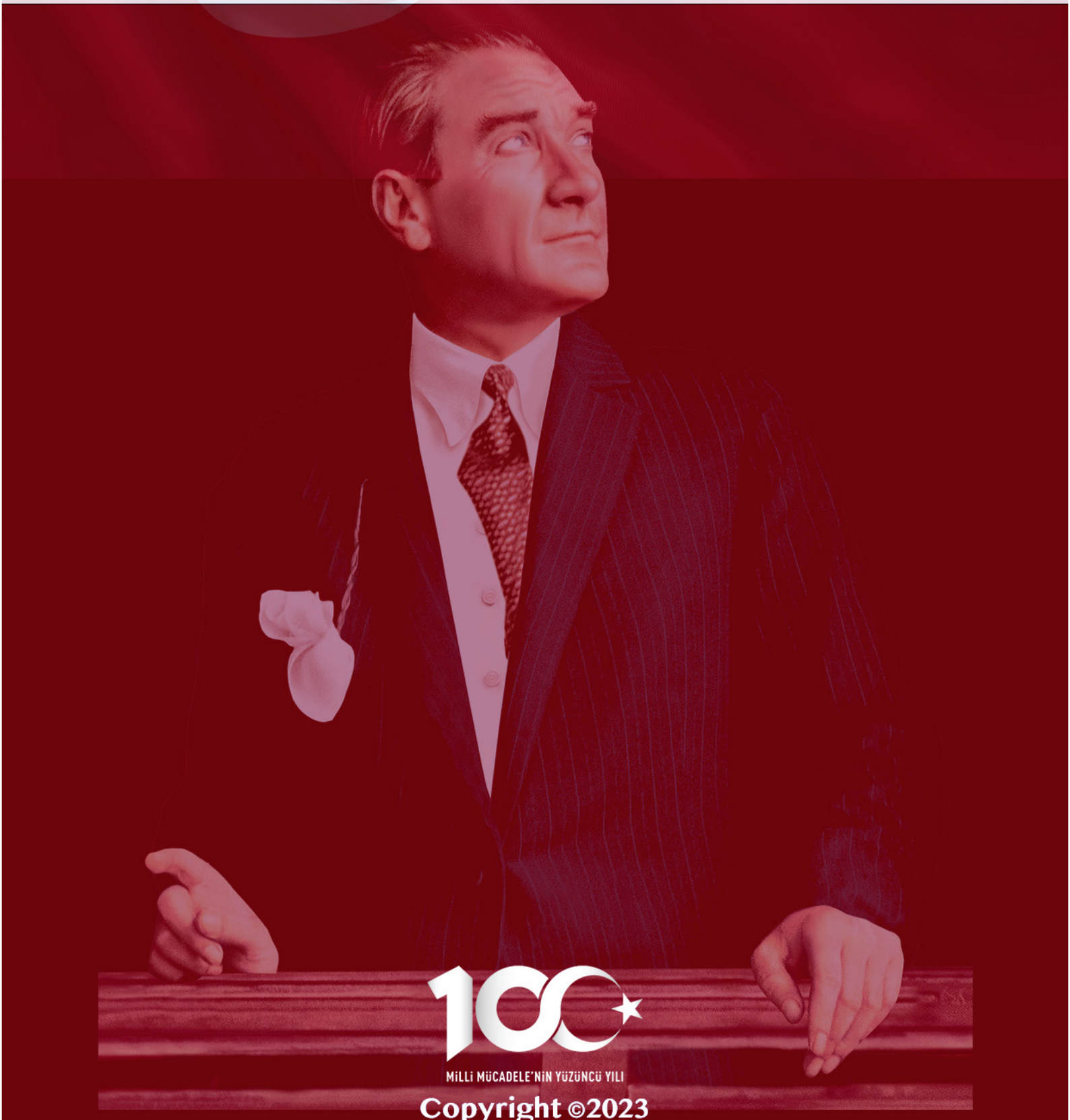

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Case Reports

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Internal Medicine

What do donor-specific antibody changes mean in kidney transplant patients?

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ABSTRACT

Background The role of immunological evaluation is significant in selecting a suitable donor to reduce post-transplant complications in kidney transplantation (KTx). It is unknown how often donor-specific antibody (DSA) positivity causes rejection or how often rejection will develop in patients who do not develop DSA positivity. We aimed to evaluate the relationship between the DSA changes and the KTx patients' biochemical parameters.

Material and Methods The study was a cross-sectional study evaluating 45 KTx patients. Demographic and clinical characteristics of the patients, pre-transplant DSA values, post-transplant DSA values, and biochemical parameters were retrospectively scanned from the hospital system. The patients' data were divided into three groups according to DSA changes.

Results DSA was negative in 21 (46%) patients and positive in 24 (54%) before transplantation. In the post-transplant follow-up, it was observed that the DSA value became positive in 7 patients and turned negative in 9 patients. Rejection developed in 22% of 9 patients whose DSA was positive before transplantation and turned negative after transplantation, and in 28% of 7 patients turned positive from negative. Estimated glomerular filtration rate (e-GFR) and creatinine levels in the post-transplant period were associated with the change in DSA. Also, e-GFR and neutrophil values were independently associated with rejection.

Conclusions Although DSA change affects kidney functions, we found that DSA positivity alone cannot predict rejection, and rejection may occur in the DSA-negative group. Neutrophil count and e-GFR changes were closely related to rejection. Therefore, DSA levels should be monitored regularly, but DSA change alone is insufficient for rejection evaluation.

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INTRODUCTION

Kidney transplantation (KTx) is the most effective treatment option for end-stage kidney disease. A successful kidney transplant improves the quality of life and significantly reduces mortality risk compared to dialysis treatment.[1,2] The role of immunological evaluation is significant in selecting a suitable donor before transplantation to reduce post-transplant complications.[3] As in all organ transplants, immunological problems in KTx have not been fully resolved yet. One of the most critical follow-up goals after KTx is to reduce the risk of antibody-mediated rejection. Sensitisation is the most vital immunological mechanism for rejection before and after transplantation.[4] The most critical risk factors for immunological sensitisation are incompatibility in human leukocyte antigen (HLA) and antibodies against these antigens. While reasons such as previous transplantation history, pregnancy, and blood transfusions are responsible for pre-transplant immunological sensitisation, the most critical risk factors for post-transplant immunological sensitisation are acute rejections, insufficient immunosuppression, and incompatibility observed in tissue antigens.[5,6]

Donor-specific antibodies (DSA) are anti-human leukocyte antigen antibodies formed against mismatched antigens in the donor. Many investigators have demonstrated the effects of DSAs on graft survival, including graft rejection and worse graft function. It has been shown that de-novo anti-HLA antibodies can develop even if the graft function is normal in KTx patients, which can predict graft dysfunction in long-term follow-up.[7,8] In addition, more metabolic side effects occur due to increased immunosuppressive therapy in patients with DSA positivity.[9-11]

It is unknown how often DSA positivity, which is an essential part of immunological follow-up in KTx, causes rejection or how often it will develop in patients who do not develop DSA positivity. We aimed to evaluate the relationship between the changes in DSA values measured before and after KTx and the clinical and biochemical parameters of the patients.

MATERIAL AND METHODS

The study was cross-sectional, and ethics committee approval was obtained from Konya Necmettin Erbakan University (Ethics Committee Number: 2019-2223). The data of 45 kTx patients (all transplants were from living donors and up to 4th-degree relatives) were scanned retrospectively, and medical records (including age, gender, transplantation dates, laboratory results, pre-transplantation induction therapy, and immunosuppressive treatment regimens in the follow-up periods) were recorded from our hospital system.

The patients ' DSA levels and biochemical tests DSA levels and biochemical tests of the patients when the kidney function tests stabilised after transplantation were recorded as pre-transplant values. Biochemical tests and DSA levels requested during the last control of the patients who completed at least three months of follow-up after kTx were recorded as post-transplant values. Patients were divided into three groups according to the changes in DSA status: Group 1: Patients with positive DSA levels; Group 2: Patients with negative DSA levels; and Group 3: Patients with stable DSA levels.

All biochemical analyses were undertaken in the Central Biochemistry Laboratory of our hospital. Serum creatinine was measured with the Jaffe Method. An automated clinical chemistry analyser measured serum C-reactive protein (CRP) levels with an immunoturbidimetric assay (Diasis Diagnostic System). Serum levels of calcium, phosphate, and intact parathyroid hormone (iPTH) were measured. iPTH was measured using the Elecsys PTH assay. For the 24-hour urinary proteinuria levels, total protein concentration levels were measured by a turbidometric assay using benzethonium chloride. The results were expressed as mg/L.

DSA measurements

DSA values before and after transplantation were studied using the Luminex method. For longitudinal analysis of DSA levels, bead assays were performed retrospectively (centralised analysis) to avoid influences of day-by-day variations in test results (test batches including samples from four to six patients each). Donor specificity was defined according to serological and/or low- or high-resolution donor/recipient HLA typing (HLA-A, -B, -Cw, -DR, -DQ, -DP on availability) provided by the local HLA lab. Test results were documented as mean fluorescence intensity (MFI) of the immunodominant DSA. An MFI threshold > 1,000 was considered positive.

Statistical analysis

Analytical and graphical methods were used to

evaluate the data regarding normal distribution, kurtosis values of analytical methods, Shapiro-Wilk test, and coefficient of variance. The histogram and detrended Q-Q plot graphs were assessed among the visual methods, and the normal distribution was decided. The Mann-Whitney U test was used as a non-parametric test to compare the non-normally distributed numerical variables between the two groups. The Kruskal Wallis Test was used to reach more than two groups. Fisher's exact test or Chi-square test was used to compare categorical variables. Binomial Logistic Regression, a Back-Step method, was used to independently assess the factors associated with rejection in those who showed rejection. If the p-value is less than 0.05, it is considered statistically significant. SPSS version 14.0 was used for statistical calculations.

RESULTS

Forty-five patients, 17 women (37.8%) and 28 men (62.2%), who had kidney transplants from living donors, were included in this study. The mean follow-up period of the patients was 27 ± 18 months, and the mean age was 43.36 ± 13.92 years. DSA was positive in 24 (53%) patients before transplantation and negative in 21 (47%) patients. In the post-transplant evaluation, DSA was positive in 22 patients and negative in 23 patients. In the follow-up of 7 patients whose DSA was negative before transplantation, their DSA became positive. In 9 patients whose previous DSA test was positive, DSA tests became negative in the follow-up. The patients were divided into three groups: decreased, stable and increased DSA levels. The data on the biochemical properties of the groups according to the DSA changes were presented in Table 1.

In this study, acute rejection developed in 7 of 45 patients (15.6%) during the follow-up period. All rejections were biopsy-proven, and the mean development time was 25 ± 19 months. While the group without rejection had higher estimated glomerular filtration rate (e-GFR) and calcium values, the serum urea, creatinine, phosphorus, white blood cell count, and neutrophil count were statistically higher in the group with rejection ($p < 0.05$) (Table 2). In this study, rejection developed in 22% of the patients whose DSA level was positive before transplantation and became negative after transplantation. The rejection rate was

Table 1. Comparison of laboratory change according to DSA change status

Changing Parameter	Total (n = 45) medium (min):(max)	Patients with decreased DSA (n = 12) medium (min):(max)	Patients with stable DSA (n = 15) medium (min):(max)	Patients with increased DSA (n = 18) medium (min):(max)	*p* value
eGFR (ml/min)	-9 (-96):(75)	5,5 (-57):(75)	-6 (-42):(27)	-20 (-96):(12)	**0.018**
Urea (mg/dl)	-13 (-56):(61)	-24 (-56):(7)	-14 (-53):(6)	-4,5 (-43):(61)	0.056
Creatinine (mg/dl)	0,1 (-0,4):(3)	-0,1 (-0,4):(1,5)	0,1 (-0,4):(0,9)	0,4 (-0,2):(3)	**0.009**
Sodium (mmol/L)	2 (-6):(8)	4,5 (-3):(8)	1 (-6):(5)	0 (-5):(4)	**0.008**
Potassium (mmol/L)	-0,5 (-1,4):(1,6)	-0,6 (-1,4):(-0,1)	-0,5 (-1,4):(-0,6)	-0,2 (-1,1):(1,6)	0.103
Calcium (mg/dl)	0,2 (-1,1):(1,9)	0,17(-0,2):(0,8)	0,2 (-0,4):(1,4)	0,2 (-1,1-1,9)	0.737
Phosphorus(mg/dl)	0,5 (-1,9):(1,7)	0,5 (-0,7):(1,7)	0,2 (-1,9):(1,4)	0,6 (-1,3):(1,6)	0.324
Albumine (mg/dl)	4 (-9):(15)	4 (-2):(12)	3 (-3):(15)	4 (-9):(11)	0.986
SGPT (u/L)	-5 (-58):(59)	-5 (-17):(29)	-5 (-17):(29)	-7,5 (-58):(59)	0.999
CRP (mg/L)	0,1 (-51,4):(33)	2,25(-10):(14,3)	0 (-51,4):(33)	-0,3 (-3):(29)	0.403
WBC (10^3 /uL)	-1,2 (-12,5):(4,5)	-3,6 (-2,1):(9,1)	-0,2 (-8,1):(4,5)	-1,5 (-12,5):(2,7)	0.139
Neutrophil (10^3/uL)	-1,8 (-11):(3,1)	-5 (-8,7):(1)	-1,2(-8,8):(2,8)	-2,9 (-11):(3,1)	0.228
Lympohcyte (10^3/L)	0,5 (-6,7):(4,3)	0,5 (-0,6):(2)	0,8 (-0,4):(3)	0,5 (-6,7):(3)	0.246
Hemoglobin (g/dL)	1,8 (-1,6):(5,7)	1,8 (-1,2):(5,3)	1,8 (-0,4):(4,8)	2 (-1,6):(5,7)	0.979
Platelet (10^3 /L)	1 (-202):(380)	-11 (-53):(139)	60 (-42):(380)	-14(-202):(128)	**0.027**
Proteinuria (gr/day)	-0,1 (-1):(3,6)	0,03 (-0,6):(1)	0,24 (-1):(0,1)	-0,1 (-0,5):(3,6)	**0.018**
Parathormone (ng/L)	0 (-831):(278)	-15 (-460):(67)	0 (-203):(128)	-0,5 (-831):(278)	0.819

eGFR: Estimated Glomeruler filtration rate, SGPT: serum glutamate pyruvate transaminase, CRP: C-reactive protein, WBC:White blood cell, Bold parameters indicate statistically significance

Table 2. Comparison of biochemical parameters according to rejection status

Parameter		Total Median (IQR) or n (%)	Patient Without Rejection (n = 38) Median (IQR) or n (%)	Patient with Rejection (n = 7) Median (IQR) or n (%)	*p* value
Age		46(19-68)	46(19-68)	46(20-56)	0.549
Gender	Female	17(%37,8)	14(%36,8)	3(%42,9)	1.000
	Male	28(%62,2)	24(%63,2)	4(%57,1)	
Pre-Transplant DSA	Negative	21(%46,7)	18(%47,4)	3(%42,9)	1.000
	Pozitive	24(%53,3)	20(%52,6)	4(%57,1)	
DSA Change	Stable or Decreased	27(%60)	24(%63,2)	3(%42,9)	0.412
	Increased	18(%40)	14(%36,8)	4(%57,1)	
Tacrolimus At First	On Target	17(%37,8)	14(%36,8)	3(%42,9)	1.000
	Off Target	28(%62,2)	24(%63,2)	4(%57,1)	
Tacrolimus at Follow-up	On Target	29(%64,4)	24(%63,2)	5(%71,4)	1.000
	Off Target	16(%35,6)	14(%36,8)	2(%28,6)	
eGFR (ml/min)		63(13-205)	64(13-205)	36(27-62)	**0.001**
Urea (mg/dl)		41(20-111)	36(20-111)	59(36-92)	**0.016**
Creatinine (mg/dl)		1,2(0,5-4)	1,2(0,5-4)	1,8(1,3-2,6)	**0.002**
Calcium (mg/dl)		9,5(8,4-10,7)	9,5(8,4-10,7)	8,9(8,4-9,7)	**0.007**
Phosphorus (mg/dl)		3,2(1,3-4,4)	3,2(1,3-4,4)	3,8(2,9-4,1)	**0.037**
Albumıne (mg/dl)		44(29-51)	44(29-51)	45(42-47)	0.975
SGPT (u/L)		14(5-75)	15,5(5-63)	8(6,8-75)	0.316
CRP (mg/L)		2(0,3-35)	2(0,3-35)	4,5(0,4-31)	0.825
WBC (10^3 /uL)		7,1(3,1-16)	6,9(3,1-16)	10(6,6-10)	**0.042**
Neutrophil (10^3 /uL)		4,5(1,6-9,3)	4,2(1,6-9,3)	7(5-8,4)	**0.003**
Lympohcyte (10^3 /L)		1,7(0,4-6,3)	1,7(0,4-6,3)	1,5(0,6-3,4)	0.293
Hemoglobin (g/dL)		13,4(9,9-16,8)	13,6(9,9-16,8)	12,3(10,3-15,1)	0.259
Platelet (10^3 /L)		232(124-658)	235,5(124-658)	224(128-323)	0.398
Proteinuria (gr/day)		0,2(0,1-4,9)	0,2(0,1-4,9)	0,3(0,1-3,7)	0.307

eGFR: Estimated Glomeruler filtration rate, SGPT: serum glutamate pyruvate transaminase, CRP: C-reactive protein, WBC: White blood cell, Bold parameters indicate statistically significance

28% in the patient group whose DSA value was negative before and became positive after transplantation.

Binomial logistic regression analysis evaluated the factors associated with rejection ($p < 0.05$). The logistic regression model was statistically significant, $\chi^2(2) = 18.698$, $p < 0.001$. The model explained 58.7% (Nagelkerke R2) of the variation in rejection and correctly classified 91.1% of cases. e-GFR and neutrophil values at follow-up were independently associated with rejection. In follow-up, each unit increase in neutrophil value was associated with rejection by 2.13 fold; each unit decrease in follow-up e-GFR was associated with a 1.11-fold increased probability of rejection (Table 3).

DISCUSSION

In this study, we evaluated the DSA levels of the patients in the pre-transplant and post-transplant follow-up periods and the relationship between DSA, biochemical parameters, and rejection status. First, we showed that, as expected, post-transplant DSA change can affect kidney function. The second significant result was that DSA positivity alone was insufficient to predict rejection, and rejection was possible in the DSA-negative group. Finally, we found that the two most valuable criteria for predicting rejection were neutrophil count and e-GFR change.

The most important risk factors for immunological sensitisation are the incompatibility of HLA antigens

Table 3. Parameters Associated with Rejection

	Univariate Analysis			Multivariate Analysis		
	OR	%95 CI	*p-value*	OR	%95 CI	*p-value*
Calcium (mg/dl)	0,085	0,012-0,627	0,016			
Neuthrophil (10^3 /uL)	1,773	1,113-2,825	**0,016**	2,131	1,092-4,156	**0,026**
Creatinine (mg/dl)	4,333	1,015-18,49	0,048			
Urea (mg/dl)	1,044	1,002-1,088	0,041			
e-GFR (ml/min)	0,912	0,851-0,977	**0,009**	0,908	0,847-0,974	**0,007**
e-GFR Change (ml/min)	0,955	0,921-0,99	0,012			
Creatinine Change(mg/dl)	3,887	1,01-14,959	0,048			

Among the parameters that were found to be significant related to rejection in the univariate analysis, those with $p < 0.05$ were included in the multivariate analysis. Backward Stepwise method was used in logistic regression analysis ($\chi^2(2) = 18.698$, $p < 0.001$ Nagelkerke R Square = 0.587 and the final model (step 7) is shown in the table Abbreviations: OR = odds ratio CI = confidence interval, eGFR: Estimated glomeruler filtration rate, Bold parameters indicate statistically significance.

and antibodies against these antigens.[3] De novo anti-HLA antibodies can develop even if the graft function is normal in kTx patients, which can predict graft dysfunction in long-term follow-up.[5,6] It has long been known that anti-HLA antibodies are a risk factor for worse allograft outcomes before transplantation.[12,13] With the reporting of the relationship between de novo anti-HLA antibody formation and rejections after transplantation, the effects of newly developed anti-HLA antibodies on graft outcomes are now more clearly known.[7,14,15] Many studies found significant correlations between anti-HLA antibodies and acute rejection, several rejection attacks, chronic rejection, and decreased graft survival.[8,15,16] At the same time, donor-specific antibodies produced after transplantation were correlated with immunological complications and graft failure.[17,18] In addition, some studies draw attention to the strong relationship between non-donor-specific antibodies and rejection.[19,20] In this study, we didn't find a significant association between DSA positivity before transplantation or an increase in DSA titer in the post-transplantation period and the development of rejection. One of the most important reasons this association could not be demonstrated may be the inability to detect non-donor-specific antibody-induced rejections.

Contrary to the literature, our study had no significant relationship between DSA change and rejection. One reason may be the inability to differentiate C1q (+)/(–) DSA. In recent years, it has been shown that C1q (+) DSAs cause a higher risk of organ rejection and graft loss compared to C1q (–) DSA. In studies, C1q (+) DSAs have been shown to have significantly higher MFIs than C1q (–) DSAs, independent of rejection.[21,22] it was also revealed that more intense C4d accumulation and more frequent graft loss were observed in kidney biopsies in patients with C1q (+) DSA.

Not all individuals exposed to foreign HLA alloantigens are equally likely to be sensitised. Similarly, rejection does not develop in all patients with positive DSA levels or increased titers during follow-up. In our study, rejection developed in 4 (22%) of 18 patients whose DSA values increased during follow-up. In 14 (88%) patients, there was no significant change related to rejection. Only some individuals are equally susceptible, possibly due to the immunogenic difference of the antigens encountered and the differences in the immune response genes that are prone to form antibodies against foreign HLA antigens.[23] The absence of rejection in every sensitive individual can be explained by accommodation.[24]

One of the significant results of our study is the frequency of rejection in the DSA-negative patient group. Rejections due to HLA incompatibility in kTx are not only due to donor-specific class I and II antibodies. Rejections may also result from unclassifiable and non-donor-specific antibody responses.[18,25] The damaging effects of these antibodies, called non-DSA, on graft survival are equivalent to those of DSAs.20 In studies of patients who developed acute rejection, most had HLA antibodies.[26] However, it has been reported that 8-20% of patients did not develop HLA antibodies during acute rejection attacks.[27] Only DSA levels were considered in our study, and non-donor-specific antibodies were not considered. However, considering that non-donor-specific antibodies have the same effect on graft survival, the cumulative effect will be proportional to the level of DSA.[28] In our study, 42.9% of the patients who developed acute

rejection had negative DSA levels, and 57.1% were positive. The high rate of rejection was remarkable in the group with negative DSA. Our study's data also supports that antibodies other than DSA may be the reason for rejection.

When we examined the relationship between rejection and changes in biochemical parameters, we observed that changes in e-GFR and creatinine predict rejection. Since rejection is expected and biopsy is planned according to the change in e-GFR and creatinine, the most critical indicators that alert the clinician to rejection are still the changes in eGFR and creatinine values. Because creatinine levels will provide late information about developing kidney injury in clinical follow-up, many centres have recently been researching to predict both immunological damage and immune sensitisation with an earlier and better predictor. Monitoring anti-HLA antibodies after transplantation will be a suitable method for detecting chronic immune damage and early detection of rejection development in the long term. Decreased e-GFR value in the follow-ups in transplant outpatient clinics warns the clinician of rejection. This study found that a one-unit decrease in e-GFR during the follow-up period was associated with 1.11-fold increased rejection. As a result of our logistic regression analysis, each unit increase in neutrophil values during the follow-up period was found to be 2.13-fold associated with rejection. Microvascular inflammation accompanied by endothelial damage and inflammatory events dominated by neutrophils, especially in antibody-mediated rejections, are present in acute rejections.29-31 Considering the increase in neutrophils as a precursor of inflammation, the increased risk of rejection with an increase in neutrophils was already an expected finding.

Our study has three main limitations. First, the sample size was relatively small. Second, non-DSA antibodies were not investigated, and C1q (–) and (+) differentiation could not be made in patients with DSA positivity. Third, all of the patients enrolled in the study were Turkish. One should consider that our results cannot, therefore, be applied to all patients because of the differences between nationalities.

Despite all the studies, whether immunological monitoring can be performed on developing HLA antibodies in KTx patients is still unclear. Although the development of HLA antibodies is a risk for rejection, some patients may experience rejection without the development of antibodies, or the graft function may be normal despite the development of antibodies. For this reason, the titer, type, positivity time of the antibodies, and their relationship with the treatments should be investigated in more detail.

CONCLUSIONS

In conclusion, this study found that DSA change can affect kidney functions, and neutrophil count and e-GFR change are closely related to rejection. Therefore, DSA levels should be monitored regularly, but DSA change alone is insufficient for rejection evaluation. Further research on more valuable markers is also needed to predict the risk of rejection.

Highlights

•Post-transplant DSA change may affect kidney function.

•DSA positivity alone was insufficient to predict rejection.

•Rejection was possible in the DSA-negative group.

•The two most valuable criteria for predicting rejection were neutrophil count and e-GFR change.

Conflict of Interest

All authors declare that there is no conflict of interest in this study.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Necmettin Erbakan University, Meram School of Medicine, Konya, Turkey. (Decision number: 100, date: 27.12.2019).

Authors' Contribution

Study Conception: TA, KT,; Study Design: KT, TA, HÖ,; Literature Review: HÖ, TA,; Critical Review: KT,; Data Collection and/or Processing: HÖ, TA, İB,; Analysis and/or Data Interpretation: FS; Manuscript preparing: İB, TA.

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Maternal and Fetal Outcomes in Pregnant Women with Takayasu's Arteritis: Single Center Experience over Ten Years

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A B S T R A C T

Background This study aims to assess pregnant women's maternal and fetal outcomes with Takayasu's arteritis (TA).

Material and Methods The study comprised ten pregnant women at the time of diagnosis or afterwards among the 50 patients diagnosed with TA between 2003 and 2021. Twenty-one pregnancy outcomes of 10 patients were obtained from hospital records and telephonic interviews. Two pregnancies were excluded due to timing before diagnosis.

Results Based on the angiographic classification, six patients had type 1, two had type 2b, and two had type 1+4 TA. 63.15% of pregnancies were planned, and the rheumatologist approved 42.10%. Live birth occurred in 16 (84.2%) of 19 pregnancies, three pregnancies (15.7%) resulted in abortion and two (10.5 %) of 19 pregnancies ended in neonatal death. In five (26.3%) of the 19 pregnancies, the disease was activated during pregnancy. Two neonatal deaths were from the two patients diagnosed with preeclampsia during pregnancy. Pre-existing hypertension and active disease are shared features of these two patients. After one year of follow-up, six pregnancies (31.5%) had active disease, and four (66.6%) had active disease both before and during pregnancy. While fetal data analysis revealed no congenital anomalies, four pregnancies resulted in low birth weight and intrauterine growth retardation (21.05%).

Conclusions The risk of developing preeclampsia and neonatal death should be considered, especially in TA patients with pre-existing hypertension who become pregnant during active disease.

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INTRODUCTION

Takayasu's arteritis (TA) is a rare systemic granulomatous vasculitis affecting large vessels.[1,2] It is most frequently seen in young females and has a male-to-female ratio of ¼. Age at onset is less than 30 in approximately 90% of patients.[1] As the disease mainly affects young women of childbearing age, pregnancy is more common than in other vasculitides.[2,3] Although it is a common disease in young women, it is relatively uncommon to be diagnosed during pregnancy.4 Diagnosis is often delayed due to the insidious onset of the disease and nonspecific initial symptoms.[3] However, obstetricians may be unfamiliar with diagnostic criteria, clinical activity evaluation, and management.[5]

While most pregnancies in women with TA are successful, they are predisposed to complications, particularly during the peripartum period.[2] New-onset arterial hypertension (HT), worsening of pre-existing chronic HT, preeclampsia, increased risk of arterial occlusion, development of an aortic aneurysm, heart failure, and cerebrovascular accident are critical complications for the mother.[6] Severe HT and preeclampsia affect 8% of the general population and 40% of TA patients.[2] Increased blood volume, cardiac load, and a continual inflammatory process in the vasculature may aggravate vascular lesions in a pregnant woman with TA.[7] Intrauterine growth retardation (IUGR), low birth weight (LBW), and even stenosis, which restricts regional blood flow and leads to fetal death, are all increased fetal risks compared to normal pregnancies.[6,8,9] In a systematic literature review of more than 200 pregnancies in women with TA, 20% of pregnancies were complicated by IUGR or LBW.10 Maternal and fetal complications are more likely to occur in those with severe maternal disease.[2] As a result, achieving optimal outcomes for mother and baby requires a focus on good management of this process.[11]

There is limited data to guide the management of vasculitis during pregnancy. It's important to discuss maternal and obstetric complications in TA patients due to disease activity and primary organ damage.1[1,12] Ideally, patients should have minimal disease activity for at least six months before conception, which should be maintained by drugs that can be used during pregnancy.[11,13] No systematic reports or guidelines exist on monitoring pregnant TA patients and their treatment before, during, and after pregnancy.[14] Unanswered questions include the risk factors for adverse obstetric outcomes and the effect of immunosuppressive drugs, aspirin, and antihypertensive medications on pregnancy outcomes.[15]

As a result, we summarised the data from 19 pregnancies of 10 patients complicated by TA to determine convenient and effective peri-pregnancy treatment measures and monitoring methods.

MATERIAL AND METHODS

Among the 50 patients we followed up with TA diagnosis between 2003 and 2021, 10 patients who were pregnant at the time of diagnosis or after that were included in the study. All patients were diagnosed using the American College of Rheumatology 1990 classification criteria.[16] This study was conducted with the approval of the Uludağ University Faculty of Medicine Clinical Research Ethics Committee, 2011-KAEK-26/332.

The data of 21 pregnancies of ten patients were evaluated retrospectively, and patients whose pregnancies were during or after TA diagnosis were included in the study. Patients were contacted by phone and asked about their pregnancy. Due to timing before diagnosis, two pregnancies were excluded. Nineteen pregnancies were evaluated.

The angiographic classification of TA was defined based on the classification proposed by Hata *et al* in 1996.[17] Patients with TA were also classified according to Ishikawa's severity criteria,[18] which include the following three groups: Group 1 (patients without complications), Group 2 (patients with one of the following complications: retinopathy, secondary HT, aortic regurgitation, or aortic or arterial aneurysm); Group 2 was further subdivided into severity classes 2a (not severe) and 2b (severe); and Group 3 (patients with two or more of the complications mentioned above).

Patient characteristics, disease severity (TA activity), maternal adverse events (new-onset arterial HT, worsening of pre-existing chronic HT, preeclampsia, eclampsia, hemolysis, elevated liver enzymes, low platelet [HELLP] syndrome), time (preterm delivery), and mode of delivery (caesarean section [C/sec], normal spontaneous vaginal delivery [NSVD]) and newborn outcomes (LBW, IUGR, neonatal intensive care unit [NICU], congenital anomaly, fetal death) were evaluated. LBW was defined as a birth weight of less than 2,500 g, while preterm delivery was defined as delivery before the 37th

week of pregnancy.[19] IUGR was defined as the fetus's weight being less than the 10th centile for gestational age.[20] In this study, we defined pregnancy morbidities as spontaneous abortion, therapeutic abortion, and fetal and maternal complications such as preterm birth, LBW, IUGR, congenital anomaly, NICU admission, preeclampsia or eclampsia, gestational HT, or gestational diabetes mellitus (DM).[21]

The World Health Organization (WHO) defines fetal death as the intrauterine death of a fetus, as a baby with no signs of life at or after 28 weeks of gestation for international comparison.[22] Neonatal death is defined as an infant death before 28 days of age.[23] Early neonatal deaths occur before the first seven days from birth, and late neonatal deaths occur between seven and 27 days of age. Postneonatal death is an infant death between 28 and 365 days of age.[23]

While determining the activation of our patients, we used the Indian Takayasu Clinical Activity Score 2010 (ITAS).[24] ITAS2010 with acute phase reactants (APR) (ITAS-A) was calculated by combining ITAS2010 with APR (either erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) as suggested by Misra *et al*.[24]

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences 26.0 (SPSS, Chicago, IL) program. Continuous variables were expressed as medians with interquartile ranges, whereas categorical variables were expressed as percentages. The distribution of variables was checked with the Kolmogorov-Smirnov test.

Table 1. General characteristics of the patients (n: 10).†

Age (years)	33.5 ± 6.04 – 34 (24:41)
Age of disease onset (years)	23.3 ± 5.43 – 23 (16:34)
Disease duration (years)	10.2 ± 5.9 – 9 (3:19)
BMI (kg/m^2)	25.8 ± 5.1 – 25.8 (17.8:35.2)
Diagnosed during pregnancy	
Yes	2 (20%)
No	8 (80%)
Angiographic classification at diagnosis	
I	6 (60%)
I+4	2 (20%)
2b	2 (20%)
Ishikawa classification at diagnosis	
I	7 (70%)
2a	1 (10%)
2b	2 (20%)
3	0
Activation of disease before pregnancy‡	
Remission	14 (73.6%)
Active	2 (10.5%)
Unknown	3 (15.7%)
Activation of disease during pregnancy‡	
Remission	12 (63.1%)
Active	5 (26.3%)
Unknown	2 (10.5%)
Activation of disease at 3 months post-pregnancy‡	
Remission	7 (36.8%)
Active	3 (15.7%)
Unknown	9 (47.3%)
Activation of disease one year after pregnancy‡	
Remission	10 (52.6%)
Active	6 (31.5%)
Unknown	3 (15.7%)

BMI: body mass index.

The values were expressed as n (%), mean ± standard deviation – median (interquartile range) and (minimum:maximum).

†Evaluation was made based on the course of 21 pregnancies, two of which occur before diagnosis (n: 19 pregnancies). ‡Evaluation was made on pregnancies.

RESULTS

Based on the angiographic classification, six patients had type 1, two had type 2b, and two had type 1 + 4 TA (Table 1). The mean gestational age was 29.5 ± 4.2 years (Table 2). 63.15% of pregnancies were planned, and the rheumatologist approved 42.10%.

Live birth occurred in 16 of 19 pregnancies (84.2%), and three (15.7%) resulted in abortion. There were three patients (30%) with chronic HT. Preeclampsia was seen in two of 19 pregnancies (10.5%) and two of 10 patients (20%). These two patients were diagnosed with TA during an investigation into preeclampsia during their pregnancy. Pregnancy outcomes of 19 pregnancies in 10 patients with TA were shown in Table 3. The mean gestational age at delivery of the

Table 2. Pregnancy and fetal data of patients (n: 10).

Total pregnancies†	19
Live births	16 (84.2%, 94.1%¥)
Age of delivery (years)	29.5 ± 4.2 – 30 (23:38)
Maternal age > 35 years at delivery	One patient and two pregnancies
Duration between diagnosis and pregnancy (months)	63.8 ± 48.7 – 48 (1:180)
Spontaneous abortion (= missed abortus)	1 (5.2%)
Therapeutic abortion	2 (10.5%)
Mode of delivery	
Normal spontaneous vaginal delivery	4 (21.05%)
Caesarean section	12 (63.1%)
Unknown	3 (15.7%)
Pregnancy plan	
Planned pregnancy	12 (63.15%)
Unplanned pregnancy	7 (36.8%)
Approval of the rheumatologist	
Has approval	8 (42.10%)
No approval	10 (52.6%)
Unknown	1 (5.2%)
Perinatal follow-ups	
Yes	14 (73.6%)
No	0
Unknown	5 (26.3%)
Fetal outcomes	
Birth weight (g)	2,742 ± 954 – 2,895 (530:4,100)
Gestation week	32.6 ± 11.5 – 38 (7:41)
Preterm birth < 37 weeks gestation‡	4 (25%)
Low birth weight	4 (21.05%)
Intrauterine growth retardation	4 (21.05%)
Neonatal death§	1 (5.2%)
Post neonatal death¶	1 (5.2%)
Intrauterine fetal death	0
Neonatal intensive care unit	2 (10.5%)
Congenital malformation	0
Maternal complications	
Chronic hypertension	3 (15.7%)
Preeclampsia	2 (10.5%)
Gestational diabetes mellitus	1 (5.2%)
Pregestational diabetes mellitus	0
Thyroid diseases∞	3 (15.7%)

The values were expressed as n (%), mean ± standard deviation – median (interquartile range) and (minimum: maximum).
†Evaluation was made based on the course of 21 pregnancies, two of which occurred before diagnosis (n: 19 pregnancy). ‡ Abortions were not included. § Neonatal death occurred in the sixth day of the birth = Early neonatal death. ¶ Postneonatal death occurred in the 240. day of the birth. ¥ If we exclude two therapeutic abortions. ∞ hypothyroidism, subacute thyroiditis, and toxic adenoma.

Table 3. Detailed pregnancy outcomes of 19 pregnancies in 10 patients with Takayasu's arteritis.

Patients	GPA	Classification Angiographic-Ishikawa		Comorbidities	Live birth	Age at delivery	Gestational age at delivery (or abortion) (week)	Birth weight (g)	Pregnancy morbidities	Mode of delivery	Disease activity of TA during pregnancy[µ]	Medication during pregnancy	Daily dose of steroid during pregnancy[‡]
1[†]-A	G5P3A2	I	2a	HT	Yes	24	26	530	Preeclampsia, postneonatal ex	C/sec	Active	No antihypertensive	No
1-B					No	27	9	N/A	Spontaneous abortion (=missed abortus)	N/A	Active	IFX, AZA, ASA, LT4	No
1-C					Yes	30	38+5	2,890	No	C/sec	Inactive	IFX, AZA, HCQ, ASA, LMWH, LT4, antihypertensive	No
1-D					Yes	31	38+3	2,900	No	C/sec	Inactive	AZA, HCQ, ASA, LMWH	5 mg
2-A	G3P2A1	IIb	1	None	Yes	27	39	3,750	No	C/sec	Inactive	No	5 mg
2-B					No	31	7	N/A	Therapeutic abortion	N/A	N/A	IFX	No
2-C					Yes	33	38	2750	No	C/sec	Inactive	TCZ (6 week), AZA, ASA	5-10 mg
3-A	G1P1A0	I	1	None	Yes	27	39	2,870	No	C/sec	Inactive	CZP, ASA	5-10 mg
4[†]-A	G2P2A0	IIb	1	None	Yes	32	40+5	4,100	Gestational DM	C/sec	Inactive	ADA, LT4	10 mg
5-A	G1P0A0	I	1	None	Yes	28	39	3,365	No	NSVD	Inactive	IFX, MMF	5 mg
6-A	G2P2A0	I	1	PsA	Yes	29	39	2,680	No	C/sec	Inactive	ADA	2.5-10 mg
6-B					Yes	31	40	2,980	No	C/sec	Inactive	No	5-10 mg
7-A	G3P2A1	I+ IV	2b	HT	Yes	34	32	960	Preeclampsia, neonatal ex	C/sec	Active	No antihypertensive	No
7-B					No	37	8	N/A	Therapeutic abortion	N/A	N/A	IFX, antihypertensive, ASA, LMWH, antithyroid	No
7-C					Yes	38	37	2,985	No	C/sec	Inactive	No	No
8-A	G1P1A0	I	1	None	Yes	24	39+5	3,580	No	NSVD	Inactive	MTX, HCQ	2.5-5mg
9-A	G2P1A0	III	I	None	Yes	23	35	2,030	Placental insufficiency	NSVD	Active	TCZ (4 week), LMWH	5-10 mg
9-B					Yes	24	38+5	3,450	No	NSVD	Inactive	ASA	10 mg
10-A	G1P1A0	I+IV	2b	HT, thalassemia	Yes	31	35+6	2,010	Oligohydramnios	C/sec	Active	AZA, HCQ, antihypertensive	30 mg

G: gravidity, P: parity, A: abortus, HT: hypertension, PsA: psoriatic arthritis, DM: diabetes mellitus, C/sec: caesarean section, NSVD: normal spontaneous vaginal delivery, ASA: acetylsalicylic acid, LT4: levothyroxine, LMWH: low-molecular-weight heparin, AZA: azathioprine, HCQ: hydroxychloroquine, MMF: mycophenolate mofetil, MTX: methotrexate, IFX: infliximab, TCZ: tocilizumab, CZP: certolizumab pegol, ADA: adalimumab, N/A: not available.

†1 and 4: Both patients had one pregnancy before diagnosis. µ: ITAS/ITAS.A was used to assess disease activity. ‡Prednisolone equivalent dose.

neonates was 32.6 ± 11.5 weeks. In four pregnancies (26.6%), preterm birth occurred before 37 weeks of gestation. Two of 19 pregnancies resulted in neonatal death (10.4%), and the need for NICU was also seen in these two pregnancies. No congenital malformations were observed, but LBW and IUGR were observed in four pregnancies (21.05%).

According to ITAS2010 and ITAS.A, the disease was active during pregnancy in five of the 19 pregnancies (26.3%) and four of 10 patients (40%) (Table 4). Six pregnancies (31.5%) were found to have active disease after one-year follow-up, and four (66.6%) had active disease both before and during pregnancy. When the patients were classified according to Ishikawa's severity criteria, only three were classified as class 2; three developed preeclampsia and oligohydramnios. Preeclampsia patients were in classes 2a and 2b. Another patient with oligohydramnios was found to be in 2b.

All patients except two used tumour necrosis factor-alpha (TNF-α) inhibitors before or during pregnancy. When the number of pregnancies was analysed, it was discovered that biologics were utilised before pregnancy in ten pregnancies (52.6%). However, the biological agent was only sustained in three out of ten pregnancies (30%). Regarding the interrupted biological agent, two of the remaining seven pregnancies used tocilizumab, and five used TNF-α inhibitors. Steroid use was found in 12 of 19 pregnancies (63.1%); the maximum dosage observed was 30 mg, which just one woman used. Only two patients did not receive any treatment, including conventional, biologic disease-modifying antirheumatic drugs (DMARDs) and steroids. These two patients were the two patients who were diagnosed with TA as a result of preeclampsia during pregnancy.

DISCUSSION

Handling pregnant patients with TA is frequently challenging due to the disease's cardiovascular and cerebrovascular complications and the lack of pregnancy-specific therapy guidelines.[25] Exacerbation of pre-existing HT and preeclampsia are the most common complications of TA in pregnancy.[26-28]

Table 4. Disease activity evaluation based on ITAS2010/ITAS.A scoring.

Patients	Disease activity pre-pregnancy		Disease activity during pregnancy		Disease activity in the three months after pregnancy		Disease activity one year after pregnancy	
	ITAS2010	ITAS.A	ITAS2010	ITAS.A	ITAS2010	ITAS.A	ITAS2010	ITAS.A
1-A	N/A	N/A	Active (4)	N/A	N/A	N/A	Active (8)	Active (11)
1-B	Inactive	Inactive	Active (2)	Active (5)	Active (3)	Active (5)	Inactive	Inactive
1-C	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
1-D	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	N/A	N/A
2-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Active (4)	Active (7)
2-B	Inactive	Inactive	N/A	N/A	Inactive	Inactive	Active (2)	Active (5)
2-C	Active (2)	Active (5)	Inactive	Inactive	Active (2)	Active (5)	Active (4)	Active (7)
3-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
4-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
5-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
6-A	Inactive	Inactive	Inactive	Inactive	N/A	N/A	Inactive	Inactive
6-B	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
7-A	N/A	N/A	Active (6)	N/A	Active (3)	N/A	Active (2)	Active (4)
7-B	Inactive	Inactive	N/A	N/A	N/A	N/A	Inactive	Inactive
7-C	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	N/A	N/A
8-A	Inactive	Inactive	Inactive	Inactive	Inactive	N/A	N/A	N/A
9-A	Active (2)	Active (5)	Active (2)	Active (5)	N/A	N/A	Inactive	Inactive
9-B	Inactive	Inactive	Inactive	Inactive	N/A	N/A	N/A	N/A
10-A	N/A	N/A	Active (4)	Active (6)	Inactive	Inactive	Active (3)	Inactive

ITAS2010: Indian Takayasu Clinical Activity Score 2010, ITAS.A: ITAS2010 with acute phase reactants, N/A: not available.

1-A and 7-A: The reason for being active was that the diagnosis was made during pregnancy. 1-B: spontaneous abortion, 2-B and 7-B: therapeutic abortion, 9-B: since the pregnancy was over, there was no three months or 1-year follow-up.

Infradiaphragmatic artery involvement, especially renal artery stenosis, appears to be the leading risk factor in most studies.[4,15,26-29] However, in a French cohort of 98 pregnant women, preeclampsia and IUGR-related renal artery involvement were not observed.[30] Similarly, two individuals with preeclampsia in our research had pre-existing HT and only one developed thickening of the renal artery wall.

While the rate of intrauterine fetal death is 1-2% in the general population, it is 4-5% in TA patients.1[0,15,30,31] There were no intrauterine deaths in our patients, and the live birth rates were similar to those in healthy women, totalling 84%-94% (if we exclude two therapeutic abortions).[15] However, two (10.4%) neonatal deaths from the two patients diagnosed with preeclampsia during pregnancy occurred in our research. One neonatal death on the sixth day of the birth was named ''early neonatal death'' due to severe intrauterine growth restriction and placental ischaemia due to preeclampsia. Also, one neonatal death occurred in the 240. day of the birth named ''postneonatal death'' preeclampsia-induced severe intrauterine growth restriction and placental ischaemia. These two patients had a shared history of pre-existing HT and active disease.

Patients with active or newly diagnosed vasculitis are more likely to experience disease flares, increasing their risk of premature delivery and miscarriage.26 A recent study noted that preterm deliveries occur in 17% of patients, with ranges in the literature between 4 and 30% and fetal loss between 8 and 30%.[14,25,30,32] Although the median gestational age at delivery was 38 weeks in our study, 25% of our cohort had preterm birth: two due to preeclampsia, one for suspected placental insufficiency, and one due to oligohydramnios. Moreover, as reported in the literature, all our patients had active disease during pregnancy.

Pre-pregnancy diagnosis and maintaining target blood pressure values with strict preconceptional disease control have improved successful pregnancy outcomes.[3,4,32,33] The fact that two neonatal deaths occurred in our study in these two patients diagnosed during pregnancy, and the disease remained active one year after pregnancy demonstrated the critical nature of pre-pregnancy diagnosis and disease remission, consistent with the literature.

It is challenging to assess disease activation during pregnancy. Angiography is not recommended during pregnancy due to the risk of fetal damage from the contrast material and radiation.9 ESR cannot be used for activity assessment as it may be elevated during pregnancy. CRP and colour Doppler ultrasound (US) are more appropriate for assessing pregnancy activity.[9,34] Conversely, CRP is not a TA-specific marker and can be affected by infection, trauma, and other factors. As pregnancy progresses, abdominal vascular US usage decreases, and operator-dependent errors rise.[9] We used ITAS-A to measure disease activation.

IUGR and LBW are the most frequently reported complications in newborns. Although previously reported rates ranged between 4% and 52%, this rate was found to be 20% in a literature review involving more than 400 pregnant women.[28] Bilateral renal artery involvement is the most significant risk factor.[15,30,32] Renin synthesis increases when the renal artery is obstructed, which would explain HT and reduced uteroplacental circulation that causes growth restriction.[33] IUGR and LBW occurred in 21.05 % of pregnancies and 40% of patients in our study. One of these patients had involvement of both renal arteries, while the other one had involvement of only one renal artery.

Vaginal delivery and epidural anaesthesia are preferred in pregnant women with TA. C/sec is recommended in pregnant women with stage 2b and 3 TA to prevent cardiac decompensation due to increased blood pressure during uterine contractions and cardiac output during labour.8 Again, obstetric reasons such as IUGR, prolonged labour, and decreased fetal heartbeats are the primary reasons for C/sec, which occurs at a rate of approximately 50%.[35-37] Concerns about the underlying disease accounted for 40% of the reasons for the C/sec one study.[38] In our study, it was observed that 63.1% of our patients had labour by C/sec. The high C/sec rate was considered a cause of concern among physicians related to TA.

Preconception counselling is vital for regulating cytotoxic drugs, folic acid replacement, and deciding the best time for pregnancy. The presence of chronic HT, vasculitis and active disease six months before conception are factors associated with poor pregnancy outcomes. Pregnancy should ideally be planned during the remission phase. Screening for blood pressure, renal function, cardiac status, and preeclampsia is crucial at regular prenatal visits. Fetal follow-up parameters should also be evaluated, including daily fetal kick count, gravidogram, serial fetal biometry, biophysical profile, and fetal Doppler US.[39]

As with preconception counselling, patients should be encouraged to have routine postpartum follow-up (3 months), as 20-40% of patients experience flares during this period.[26] In our study, postpartum disease activation was 15.7%. This rate, however, may not be reliable, given that 47.3% of patients did not return for follow-up over this period. Our study allowed us to self-critique and showed that we should be more cautious when advising patients on postpartum third-month follow-up.

Several limitations existed in our study. This study didn't have enough pregnancies to accurately represent all TA patients' pregnancy morbidity. The retrospective design requires caution in interpreting our study's findings. However, this study will help collect more clinical data for prospective studies on this rare condition. Additionally, one-year follow-up data on disease activation help examine disease progression.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Uludag University Faculty of Medicine Clinical Research Ethics Committee, approved this study (REC number: 2011-KAEK-26/332, date: 18.07.2019).

Authors' Contribution

Study Conception: BY, ED,YP,; Literature Review: BY, BNC, OS,; Critical Review: BY, BNC, OS, ED, YP,; Data Collection and/or Processing: BY, BNC,; Analysis and/or Data Interpretation: BY, BNC,; Manuscript preparing: BY.

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Earthquake disaster impact on health care of cancer patients: Single-centre experience

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ABSTRACT

Background The earthquakes in February 2023 in Turkey had a major impact on Turkey's health system, causing damage to hospitals and health centres in the affected areas. Cancer patients are one of the groups that are highly influenced by the disaster. The aim of this study was to evaluate some of the demographic and clinical characteristics of cancer patients who are getting health care in earthquake-affected areas.

Material and Methods Fifty cancer patients who lived in 11 cities of Turkey affected by the earthquake and were admitted to Gazi University Department of Medical Oncology after the earthquake between 15 February 2023 and 15 March 2023 were included in the study. Data such as demographic characteristics, cancer diagnosis, time of cancer treatment, and earthquake history were taken retrospectively from nationally-linked electronic records (E-nabız).

Results Breast cancer was the most common diagnosis of these patients. Most of the patients were taking active treatment (60%). Chemotherapy and hormonotherapy were the most common treatment modalities (20% and 18%, respectively). The median delay in the active treatment of 14 cancer patients was 24 days (2-60).

Conclusions The earthquake disaster has led to important impacts on cancer patients' care in most affected areas. The human, financial and medical resources should be improved. Especially if detailed nationally-linked electronic records are provided, cancer patients will not have difficulty seeking health care. This disaster should be an important stimulus for hospitals and healthcare systems to improve the care of patients during disasters.

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INTRODUCTION

After the earthquakes of 7.7 and 7.6 magnitudes on the Richter scale, originating from the Kahramanmaraş centre on February 2023, a large geographic area, including Turkey and also many countries such as Syria, Lebanon, Cyprus, Iraq and Israel, is affected. In Turkey, Kahramanmaraş, Hatay, Gaziantep, Malatya, Diyarbakır, Kilis, Şanlıurfa, Osmaniye, Adıyaman, Adana, Elazığ were among the most commonly affected cities.[1] The disaster affected many daily activities and systems, including the health care system.

The earthquakes had an impact on Turkey's health system. Some problems have been observed in the delivery of health services.[2] Cancer patients, who experience many economic and psychological difficulties during the treatment process, are one of the vulnerable groups that might be affected by the disaster. This patient population had several challenges and many needs during and after a disaster. They have encountered many physical traumas, such as amputations, fractures, dehydration, crush syndrome, and acute kidney injury. Furthermore, psychological traumas caused by the disaster, such as loss of life in family relatives and migration, were some of the difficulties experienced by cancer patients in the process. Komuro et al. [3] also showed that Patients diagnosed with cancer are at risk of exposure to intense short- and long-term psychological stress following a disaster. It was reported that patients had questions regarding interruption of their treatment and drug therapy.

As a result of the natural disaster, many cancer patients who might migrate from disaster areas to other regions throughout the process were re-evaluated and followed up in the treatment centres they applied to. In this case, nationally-linked electronic records and backup had become critical. In Turkey, at this point, the national electronic patient (E-Nabız) database, accessible all over the country, was significant for the healthcare continuum. The literature showed that disruption of cancer treatment can worsen patients' prognosis and survival outcomes.[4-6] A meta-analysis demonstrated that patients with a diagnosis of colorectal cancer who have a delay to adjuvant chemotherapy after surgery have worse survival outcomes.[7] Also, studies with prostate cancer patients and glioblastoma demonstrated poor survival outcomes after delay, interruption, and absence of treatments.5-8 In this study, we evaluated some demographic and clinical characteristics of cancer patients getting health care in earthquake-affected areas.

MATERIAL AND METHODS

Patient population

Cancer patients who lived in 11 cities of Turkey affected by the earthquake and were admitted to Gazi University Department of Medical Oncology after the earthquake between 15 February 2023 and 15 March 2023 were included in the study.

Data collection

We retrospectively searched the hospital electronic data system of the 3168 cancer patients admitted to Gazi University Department of Medical Oncology between 15 February 2023 to 15 March 2023. The 50 cancer patients with a history of being affected in earthquake disasters and adequate data were enrolled in the study. Their data, such as demographic characteristics, cancer diagnosis and stage, type of cancer treatment, and earthquake history, were taken from nationally-linked (E-Nabız) electronic records. The study was initiated with the ethics committee's approval (Date: 2023, Decision No: 479). All procedures were carried out according to the ethical rules and the principles of the Declaration of Helsinki.

Statistical analysis

The SPSS software version 23 was used during the data process. The variables are examined for normal distribution using visual and analytical methods (Kolmogorov–Smirnov or Shapiro–Wilk test). Descriptive analyses were performed using medians for non–normally distributed and ordinal variables. Categorical data such as gender, cancer diagnosis, histological subtype, stage of the disease, the types of treatment, the cities that patients came and the presence of injury were presented in counts and percentages.

RESULTS

A total of 50 cancer patients who were admitted to our clinic after the earthquake disaster with adequate data were included in this study. The median age of the patients were 56 (23-75) years. The demographic and clinical characteristics of the patients are shown in Table 1. Most of these patients were female (70%). Breast cancer was the most common diagnosis of these patients, and this diagnosis was followed

by gastrointestinal tract cancers, head and neck cancers and lung cancers. The most common histological breast cancer subtype was invasive ductal carcinoma (66.7%). Colon carcinoma (50%) was the most common gastrointestinal tract malignancy. Thirty-four per cent of the patients had stage IV disease on admission. When the to our clinic, most had ECOG (Eastern Cooperative Oncology Group) performance score 1 (Table 1). The laboratory findings revealed acute kidney injury in 2 patients. There were no patients with neutropenia. While twenty-eight patients (56%) had grade 1 anaemia, 7 had grade 2 anaemia.

Table 1. Demographic and clinical characteristics of the patient population (n: 50).

Age (years)	56 (23:75)
Female gender	35 (70)
Cancer diagnosis	
Breast	18 (36)
Gastrointestinal tract	8 (16)
Head and neck	7 (14)
Lung	6 (12)
Genitourinary system	3 (6)
Pancreas	3 (6)
Central nervous system	2 (4)
Hepatobiliary system	2 (4)
Gynecological	1 (2)
The city of Turkey that patients came from	
Hatay	13 (26)
Malatya	12 (24)
Gaziantep	6 (12)
Kahramanmaraş	5 (10)
Adıyaman	5 (10)
Adana	5 (10)
Diyarbakır	1 (2)
Elazığ	1 (2)
Osmaniye	1 (2)
Şanlıurfa	1 (2)
Presence of any injury after earthquake	
Staying under a dent	1 (2)
Crush syndrome	1 (2)
No	48 (96)
Type of active treatment	
Chemotherapy	10 (20)
Hormonotherapy	9 (18)
Targeted therapy	6 (12)
Immunotherapy	4 (8)
Chemoradiotherapy	1 (2)
No treatment	20 (40)
Tumor stage at diagnosis	
I	3 (6)
II	14 (28)
III	16 (32)
IV	17 (34)
ECOG performance score	
0	10 (20)
1	34 (68)
2	6 (12)

ECOG: Eastern Cooperative Oncology Group.
The values were expressed as n (%) and (minimum: maximum).

The cancer patients had been chiefly coming from Hatay and Malatya. One patient had stayed under a dent for 32 hours, fractured his foot, and suffered crush syndrome. One female patient with a cancer diagnosis also suffered from crush syndrome after earthquakes. These two patients were followed in the intensive care unit before being admitted to our hospital. Other patients were followed in outpatient clinics.

Most patients were taking active treatment (60%) during an earthquake. Chemotherapy and hormonotherapy were the most common treatment modalities (20% and 18%, respectively). Also, 18% of the patients took adjuvant therapy when admitted to our hospital. Fourteen patients were evaluated by radiodiagnostic methods during the follow-up period. One patient had a recurrent disease, and one had the disease in progression. Among the patients taking active treatment, no delay was recorded in 16 patients. The median delay in the active treatment of 14 cancer patients was 24 days (2-60). Furthermore, imaging and examination planning was delayed in only two patients not taking active medicine.

DISCUSSION

To the best of our knowledge, the current preliminary data is the first for evaluating some demographic and clinical characteristics of the cancer patients who lived in 11 cities of Turkey affected by the earthquake and were admitted to another clinic a month after the earthquake. We observed that the study population were taking mostly active treatment, and the median delay in active treatment of 14 cancer patients was 24 days (2-60) after the earthquake. Ozaki *et al.*[9] analysed 120 patients with breast cancer after the triple disaster in Fukushima, Japan, 2011. In this analysis, patients with ≥ 1-year delay increased statistically significantly after the disaster. Most of the patients were presented with late-stage disease (stages 3 and 4), associated with poor prognosis. In our study, we examined the patients for a month, so we could not evaluate the survival outcomes of the patients. Also, Jacqueline *et al.*[10] showed that after the earthquake in Mex-

ico, 6% of the cancer patients had difficulty getting health care and delay in treatment was seen. These findings show the earthquake's impact on access to cancer care. In addition, as soon as possible, the Turkish Society of Medical Oncology created a telephone on-duty medical oncologist list to support the doctors living in affected cities to support oncology patient care. After that, voluntary medical oncologists made rotations to affected cities to continue oncology patient care chemotherapy regimens.

In the literature, it was shown that delays in treatment modalities are associated with worse survival outcomes.[4-8] Our study has a short follow-up period for evaluating survival outcomes, but further studies with larger patient populations and more extended follow-up periods should be planned for analysing the survival outcomes.

Patients with chronic diseases like cancers may have many challenges and needs during disasters.[11] As well as cancer patients might have many economic and psychological problems during the process, they might also have many difficulties in their cancer care. Destroyed communication systems, damaged transport services and loss of functionality of many medical services can lead to disruption of medical services for cancer patients.[12] After the earthquake, outpatient and inpatient clinics, radiation oncology units, and pathology laboratories are all described in the medical literature about the delivery of oncology care. In addition, medication can be lost or left behind. Cancer patients, especially those who are socially isolated, elderly and those with insufficient knowledge of their medications, are at higher risk for a worse prognosis.[13,14]

Man *et al*.[12] emphasised that the healthcare infrastructures, the healthcare workforce, data dispersion, and patient relocation are among the problems that patients with cancer and healthcare givers face after a disaster. Especially lack of treatment history (past cycles, plans, staging details, histological diagnosis, and others), drug protocols, clinical trials, and research documents in cancer patients may be encountered during and after disasters.[15,16] Patients should accompany their treatment records.[11] In this case, national electronic databases of medical history reports of radiology, laboratory, and pathology can help physicians. In our practice, we had no difficulty getting information about the history of cancer treatment due to adequate and current nationally-linked electronic records (E-nabız). In addition, it is essential to educate cancer patients about their disease and treatment.

Porzio *et al*.[17] studied cancer patients in the region where three earthquakes occurred in Italy. The researchers maintained contact with patients through in-person visits or regular phone communication. Initially, the patients received continuous care, and it was observed that the rates of anxiolytic therapy, drug consumption, and patient compliance did not increase compared to the pre-earthquake period. However, among the cancer patients who had to evacuate the city but later returned, an increase in the frequency of post-traumatic stress disorder (PTSD) was observed. Furthermore, six months after the earthquake, an increase in the frequency of anxiety disorders, sleep disorders, and depression were reported among the cancer patients included in the study. Based on their findings, the authors suggested that patients exposed to earthquakes should be monitored for at least two years. Unfortunately, we cannot present similar data due to the limited duration of our study's follow-up period. Nonetheless, we are conducting close follow-ups and observation of 50 patients in our clinic.

Our study has some limitations. Firstly, the sample size is small because, especially in the study, we wanted to evaluate the cancer patients a month after the earthquake disaster. Also, we could not examine the survival outcomes of the patients due to the short follow-up period.

Continuity is essential in oncological care. Treatment schemas are individualised within specific periods. Also, it requires multidisciplinary management. It is known that earthquakes can be associated with worse outcomes for cancer patients. Disasters can cause psychological distress to both patients and caregivers. In conclusion, it is essential to formulate plans to support and help cancer patients in these difficult circumstances.

CONCLUSIONS

The earthquake has greatly impacted cancer patients' care in most affected areas. Health care for cancer patients must continue during and after a disaster. Healthcare systems of countries with a known high risk for disasters should consider the continuity of cancer patient care and establish referral systems. The human, financial and medical resources should

be provided. This disaster should be an essential stimulus for hospitals to improve the care of patients during disasters.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Gazi University, Ankara, Turkey. (Decision number: 07, date: 4.4.2023).

Authors' Contribution

Study Conception: OÜ, AÖ; Study Design: OÜ, NÖ, AÖ; Literature Review: OÜ, GS; Critical Review: OÜ, NÖ, AÖ; Data Collection and/or Processing: OÜ, GS,; Analysis and/or Data Interpretation: OÜ, OY; Manuscript preparing: OÜ, OY.

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The Frequency of Musculoskeletal Pain in Nurses Working in Internal Medicine Intensive Care Units and Related Factors

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ABSTRACT

Background The primary purpose of this study was to determine the frequency of musculoskeletal pain in nurses working in the internal medicine intensive care unit and to determine whether there were differences between nurses working in the internal medicine clinic. In addition, it was aimed to determine the individual and professional risk factors that will cause musculoskeletal pain in nurses working in the internal medicine intensive care unit.

Material and Methods After evaluating eligibility, 82 volunteer nurses, 36 working in the internal medicine intensive care unit and 46 working in the internal medicine clinic, were included in this single-centre, cross-sectional and descriptive study. The demographic characteristics of the participants, their regular exercise status and the factors related to their working conditions were determined by the questionnaire form created by the researchers.

Results Musculoskeletal pain was detected in 61.11% of internal medicine intensive care nurses. There was no statistical difference between the internal medicine intensive care and clinical nurses regarding musculoskeletal pain ($p > 0.05$). A statistically significant relationship was found between the situation of changing the patient's clothes and positioning the patient and the occurrence of musculoskeletal pain ($p < 0.001$). No significant relationship was found between internal medicine intensive care nurses' musculoskeletal pain and their demographic characteristics, regular exercise status and other working conditions ($p > 0.05$).

Conclusions Our study showed that nurses working in the internal medicine intensive care unit experienced a high rate of musculoskeletal pain. The study results will shed light on what kind of precautions nurses should take against work-related musculoskeletal pain.

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INTRODUCTION

The World Health Organization (WHO) has defined work-related musculoskeletal disorders as health problems of locomotor apparatus, i.e. muscles, tendons, the skeleton, cartilage, ligaments and nerves.[1] The incidence of work-related musculoskeletal disorders is high worldwide, and many risk factors depend on the nature of the work.[2]

Work-related musculoskeletal pain is a condition that requires global attention not only because of its individual health effects on workers but also because of its negative effects on countries' economies. In addition, the social problems created by this situation are also significant in terms of social dynamics. Over the past three decades, musculoskeletal disorders have emerged as the third leading cause of disability-adjusted life years among young adults globally.[3]

Work-related musculoskeletal disorders are common, especially among healthcare professionals in direct contact with patients, such as surgeons, nurses, and therapists.[4,5] The incidence of musculoskeletal pain is particularly high in nurses.[6] In a study conducted on 2,400 nurses related to musculoskeletal pain in Turkey, the 12-month prevalence was 79.5%.[7] It is thought that the quality of the work and working conditions of the nurses are related to the frequency of musculoskeletal pain.

Due to these individual and social problems caused by musculoskeletal pain in employees, it is critical to take early measures and to make necessary improvements in the work areas. This situation is more important in professions where work-related musculoskeletal pain is common, especially in nurses. The primary aim of this study was to determine the frequency of musculoskeletal pain in nurses working in the internal medicine intensive care unit and to determine whether there was a difference between nurses working in the internal medicine clinic. In addition, it was aimed to determine the individual and occupational risk factors that will cause musculoskeletal pain in nurses working in the internal medicine intensive care unit.

MATERIAL AND METHODS

The study protocol was approved by the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision number: 2011-KAEK-25 2023/08-02). The principles of the Declaration of Helsinki conducted the study. Consent was obtained from the participants who wanted to participate in the study voluntarily.

After evaluating eligibility, 82 volunteer nurses, 36 working in the internal medicine intensive care unit and 46 working in the internal medicine clinic, were included in this single-centre, cross-sectional and descriptive study. The participants were divided into two groups: nurses in the intensive care unit in group 1 (n: 36) and nurses in the clinic in group 2 (n: 46).

Participants who did not consent to participate in the study had a diagnosed inflammatory spine disease, had a congenital deformity that increased the risk of musculoskeletal pain, and had psychological, neurological and rheumatological disorders causing musculoskeletal pain were not included in the study. In addition, attention was paid to the fact that the participants included in the study had worked in the same department for at least one year and worked in their profession for at least one year. Finally, participants with chronic non-specific musculoskeletal pain before the study were excluded.

The data were obtained with a questionnaire developed by the researchers evaluating the nurses' socio-demographic characteristics, working conditions and musculoskeletal pain. Age, gender, body mass index (BMI, kg/m^2) and marital status of the nurses were recorded as socio-demographic data. In addition, questions about the working conditions of the nurses, the total working time in the same department, the type of shift they worked, their working positions during most of the daily working hours, whether they took part in changing patient clothes and took part in positioning the patient were recorded in the questionnaire data form. Apart from these, it was also questioned whether the participants did regular exercise (performing at least 150 minutes of moderate-intensity aerobic physical activity [e.g. walking] or 75 minutes of vigorous-intensity aerobic physical activity [e.g. running or jogging] throughout the week was defined as physically active)[8] and recorded in the questionnaire data form. Apart from these data, it was questioned whether the nurses had musculoskeletal pain at least once exceeding 24 hours in the last year, and if so, in which area.

Statistical analysis

The Shapiro-Wilk test assessed whether the variables follow a normal distribution. Continuous

Table 1. Comparison of demographic characteristics between study groups (n: 82).

	Nurses working in the internal medicine		*P*-value
	Intensive care unit (n: 36)	Clinic (n: 46)	
Age (years)	33.50 (24:52)	35 (25:55)	0.500[a]
Gender			> 0.99[b]
Female	32 (88.89%)	41 (89.13%)	
Male	4 (11.11%)	5 (10.87%)	
Marital status			0.589[c]
Married	24 (66.67%)	28 (60.87%)	
Single	12 (33.33%)	18 (39.13%)	
Body mass index (kg/m^2)	25.64 ± 3.22	25.32 ± 2.59	0.311[d]

Data were expressed as n (%) and median (minimum: maximum).
[a] Mann-Whitney U test, [b] Fisher's exact test, [c] Pearson chi-square test, [d] independent sample t-test

variables were presented as median (minimum: maximum) and mean ± standard deviation values. Categorical variables were reported as n (%). According to the normality test results, the Independent samples t-test or Mann-Whitney U test was used to compare the two groups. Pearson chi-square test, Fisher's exact test or Fisher-Freeman-Halton test was used for comparing categorical variables. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and p value < 0.05 was considered statistically significant.

RESULTS

A total of 82 nurses, 36 working in the internal medicine intensive care unit and 46 working in the internal medicine clinic, were included in the study. The median age of nurses working in the intensive

Table 2. Comparison of working conditions, regular exercise status and musculoskeletal pain status among study groups (n: 82).

	Nurses working in the internal medicine		*P* - value
	Intensive care unit (n: 36)	Clinic (n: 46)	
Total working time in the current department (years)	7.50 (1:20)	7 (1:22)	0.171[a]
Shift type			0.269[b]
Duty	18 (50%)	16 (34.78%)	
Daytime	5 (13.89%)	12 (26.09%)	
Variable	13 (36.11%)	18 (39.13%)	
Working position			0.063[b]
Mostly standing	33 (91.67%)	35 (76.09%)	
Mostly sitting	3 (8.33%)	11 (23.91%)	
Regular exercise status			0.780[b]
Yes	13 (36.11%)	18 (39.13%)	
No	23 (63.89%)	28 (60.87%)	
Taking part in changing patients' clothes			< 0.001[b]
Yes	29 (80.56%)	7 (15.22%)	
No	7 (19.44%)	39 (84.78%)	
Taking part in positioning the patient			< 0.001[b]
Yes	29 (80.56%)	7 (15.22%)	
No	7 (19.44%)	39 (84.78%)	
Musculoskeletal pain status			0.113[b]
Yes	22 (61.11%)	20 (43.48%)	
No	14 (38.89%)	26 (56.52%)	

Data were expressed as n (%) and median (minimum: maximum).
[a] Mann-Whitney U test, [b] Pearson chi-square test.

Table 3. Distribution of musculoskeletal pain in internal medicine intensive care nurses.

	Frequency
Musculoskeletal pain status	
Yes	22 (61.11%)
No	14 (38.89%)
Musculoskeletal pain area	
Spine pain	17 (77.27%)
Non-spine pain	5 (22.73%)
Total	22 (100%)
Spine pain area	
Low back pain	8 (47.06%)
Neck pain	4 (23.53%)
Back pain	5 (29.41%)
Total	17 (100%)
Non-spine pain area	
Hips and legs	2 (40%)
Shoulders	1 (20%)
Knees	1 (20%)
Wrists and hands	1 (20%)
Elbows	0
Ankles and feet	0
Total	5 (100%)

Data were expressed as n (%).

care unit was 33.50 (minimum: 24 – maximum: 52), while the median age of nurses working in the clinic was 35 (minimum: 25 – maximum: 55). A comparison of the demographic characteristics of the participants in Group 1 and Group 2 was given in Table 1. Variables such as age, gender, BMI and marital status were not different between the groups ($p > 0.05$).

The comparison of the working conditions, regular exercise and musculoskeletal pain status of the participants in Group 1 and Group 2 were shown in Table 2. There was no statistically significant difference between the regular exercise status of the participants in both groups ($p > 0.05$). Musculoskeletal pain occurring at least once in the last year and exceeding 24 hours was detected in 61.11% of the nurses in the internal medicine intensive care unit and 43.48% in the internal medicine clinic. Even though musculoskeletal pain was observed more frequently in nurses working in the internal medicine intensive care unit, no statistically significant difference was found between the two groups regarding musculoskeletal pain ($p > 0.05$). When both groups were compared regarding working conditions, it was determined that nurses working in the internal medicine intensive care unit were more involved in changing the patient's clothes and positioning the patient ($p < 0.001$).

The distribution of musculoskeletal pain of internal medicine intensive care nurses was given in Table 3. Our current study detected musculoskeletal pain in 61.11% of internal medicine intensive care nurses. Musculoskeletal pain mainly manifested itself as spine pain (77.27%). Low back pain (47.06%) was the most common pain area among spinal pain.

The relationship between musculoskeletal pain and demographic characteristics in internal medicine intensive care nurses was depicted in Table 4. According to the results of this study, there was no statistically significant relationship between musculoskeletal pain in internal medicine intensive care nurses and the demographic characteristics of the participants ($p > 0.05$).

The relationship between musculoskeletal pain, working conditions and exercise status in internal medicine intensive care nurses was given in Table 5. According to the results of the current study, a statistically significant relationship was found between the musculoskeletal pain in the internal medicine intensive care nurses and the situation of the nurses changing the patient's clothes and positioning

Table 4. The relationship between musculoskeletal pain and demographic characteristics in internal medicine intensive care nurses (n: 36).

	Musculoskeletal pain (n: 22)	No musculoskeletal pain (n: 14)	*P*-value
Age (years)	26 (29:48)	31 (24:52)	0.133[a]
Gender			> 0.99[b]
Female	19 (86.36%)	13 (92.86%)	
Male	3 (13.64%)	1 (7.14%)	
Marital status			0.471[b]
Married	16 (72.73%)	8 (57.14%)	
Single	6 (27.27%)	6 (42.86%)	
Body mass index (kg/m^2)	24.95 (19.50:30.20)	25.90 (23.30:34.90)	0.327[a]

Data were expressed as n (%) and median (minimum: maximum).
[a] Mann-Whitney U test, [b] Fisher's exact test.

Table 5. The relationship between musculoskeletal pain, working conditions, and exercise status in internal medicine intensive care nurses (n: 36).

	Musculoskeletal pain (n: 22)	No musculoskeletal pain (n: 14)	*P* - value
Total working time in the current department (years)	8.73 ± 3.56	8.21 ± 5.62	0.739[a]
Shift type			0.517[b]
Duty	11 (50%)	7 (50%)	
Daytime	2 (9.09%)	3 (21.43%)	
Variable	9 (40.91%)	4 (28.57%)	
Working position			0.051[c]
Mostly standing	22 (100%)	11 (78.57%)	
Mostly sitting	0	3 (21.43%)	
Regular exercise status			0.452[d]
Yes	9 (40.91%)	4 (28.57%)	
No	13 (59.09%)	10 (71.43%)	
Taking part in changing patients' clothes			< 0.001[c]
Yes	22 (100%)	7 (50%)	
No	0	7 (50%)	
Taking part in positioning the patient			< 0.001[c]
Yes	22 (100%)	7 (50%)	
No	0	7 (50%)	

Data were expressed as n (%) and mean ± standard deviation.
[a] independent sample t-test, [b] Fisher-Freeman-Halton test, [c] Fisher's exact test, [d] Pearson chi-square test.

the patient ($p < 0.001$). There was no significant relationship between musculoskeletal pain, other working conditions, and regular exercise status ($p > 0.05$).

DISCUSSION

In this study, 61.11% of nurses in the internal medicine intensive care unit had musculoskeletal pain. Although musculoskeletal pain was observed more frequently in internal medicine intensive care nurses than in the internal medicine clinic nurses, we did not find a statistically significant difference between the two groups. In addition, according to the results of the current study, a statistically significant relationship was found between musculoskeletal pain in internal medicine intensive care nurses and the situation of nurses changing the patient's clothes and positioning the patient. Again, we found no significant relationship between the other parameters examined in the current study and the occurrence of musculoskeletal pain in internal medicine intensive care nurses.

In a study on the prevalence of work-related musculoskeletal diseases, 300 nurses were included in the sample, and it was found that almost all nurses (97.3%) had complaints of work-related pain in the last 12 months.[9] In a study conducted in Nigeria, 90.7% were clinical nurses, and 118 nurses were included; 84.4% of the nurses who participated in the survey reported that they experienced work-related musculoskeletal pain at some point in their work life.[10] In the same study, the most common musculoskeletal pains of the participants were observed in the spine region and especially in the lower back.[10] In a study evaluating the prevalence and risk factors of work-related musculoskeletal disorders in intensive care unit nurses in China, musculoskeletal pain was observed in 97% of intensive care nurses within the last year.[11] In the same study, the most common pain was spine pain, especially low back pain.[11] The intensive care unit is a department that cares for relatively more severe patients. Compared to clinical patients, patients in intensive care units are generally less able to care for themselves and need more help from their caregivers. Nurses in the intensive care unit perform multiple procedures such as infusion, oral care and airway management daily. For many reasons, they take a more active role in patient care than nurses working in the clinic.[12-14] The overall 12-month prevalence of musculoskeletal pain among nurses worldwide is 40% to 85%. Considering the heavy working conditions of intensive care nurses, this rate may increase in nurses working in intensive care units.[15-20] In our study, 61.11% of the nurses working in the internal medicine intensive care unit and 43.48% of the nurses working in the internal medicine clinic had musculoskeletal pain lasting more than 24 hours in the last year. According to these results, although it is said that the prevalence determined in our study is less than

the literature, it is evident that it is compatible. In addition, in our study, musculoskeletal pain was more common in nurses working in the intensive care unit, similar to the literature. However, it was determined that working in the clinic or intensive care unit did not statistically increase the incidence of musculoskeletal pain in nurses. This difference is mainly due to the small sample size of our sample. In addition, since the participants evaluated the presence of musculoskeletal pain with the recall method, this method may be effective without a statistically significant difference between the two groups regarding musculoskeletal pain.

In general, the most common pain area in nurses with musculoskeletal pain is the spine. In addition, especially low back and back pain is observed more frequently in nurses with spine pain.[21-23] In a questionnaire study evaluating the frequency of musculoskeletal pain in nurses, 569 participants were included. 84.7% of the participants reported a high incidence of low back pain in the previous 12-month period. Low back pain was the most frequently reported body region for pain, followed by the neck, shoulders, and upper back.[24] In the current study, spinal pain was the most common musculoskeletal pain, with 77.27%, consistent with the literature. Low back pain (47.06%), back pain (29.41%) and neck pain (23.53%) are the most common spinal cord pains, respectively. In addition, non-spinal pain was observed less frequently in the current study, similar to the literature. Especially considering the working conditions of the nurses working in the intensive care unit, axial loading may be impaired because they stand more and take more responsibility in patient care. This can cause spinal pain. Our study also draws attention to these points with its results.

Our study found that the demographic characteristics and regular exercise status of the nurses working in the internal medicine intensive care unit were not associated with musculoskeletal pain. It was determined that among the working conditions of internal medicine intensive care nurses, taking part only in changing the patient's clothes and positioning the patient increased musculoskeletal pain. A study conducted among nurses in Italy determined that night shift work, insufficient education, frequent involvement in patient care, lack of equipment, work department, obesity, increased age, work-related stress and lack of physical activity increased the occurrence of low back pain.[25] In general, it is known that taking a primary role in patient care, such as bending, twisting, lifting heavy weights and performing strong movements, increases musculoskeletal pain in nurses. In addition, advanced age and being overweight are known as risk factors for musculoskeletal pain among nurses. Regular exercise is generally considered to be protective in terms of musculoskeletal pain.[26-31] Our results are not fully compatible with the literature because it is a single-centre and small sample size study. In addition, working conditions could be questioned in a limited way with the existing questionnaire. If more parameters were added, the working conditions could be examined more.

There were some limitations of the current study. First, the fact that it was a single-centre study limits the generalizability of the study. Secondly, the small sample size was also a significant limitation. In addition, other limitations were that it was a study based on the subjective evaluation of the participants and the collection of study data using questionnaires without observation. Finally, pain was determined only by questioning, and scales were not used; it was difficult to generalise the results.

CONCLUSIONS

As a result, it was shown in our study that musculoskeletal pain was at a high rate in nurses working in the internal medicine intensive care unit and that the pain most commonly originated from the spine region. In addition, it has been shown that the involvement of nurses in changing the patient's clothes and positioning the patient increases musculoskeletal pain. Our study results will shed light on what measures should be taken for occupational diseases related to the musculoskeletal system in nurses. These results will be a guide for institutions and managers in the prevention of work-related diseases. In addition, our results will help nurses, among the occupational groups experiencing the most common musculoskeletal pain, in the early detection and treatment of pain.

Conflict of Interest

The author(s) declared no potential conflicts of interest concerning this article's research, authorship, and/or publication.

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Ethical Approval

The study protocol was approved by the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision number: 2011-KAEK-25 2023/08-02).

Authors' Contribution

Study conception: ACE, UE; Study design: ACE, UE; Supervision: ACE, UE; Materials: ACE; Data collection and/or processing: ACE; Analysis and/or data interpretation: ACE, UE; Literature review: ACE, UE; Critical review: ACE, UE; Manuscript preparing: ACE, UE.

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Urology

Delayed cystoscopy follow-up of non-muscle invasive bladder cancer during the COVID-19 pandemic may increase recurrence rates but not progression rates

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ABSTRACT

Background This study aimed to investigate whether there is a difference in recurrence and progression rate before and after the pandemic in patients who applied for bladder cancer and/or were followed-up-treatment-operated in the urology clinic during the pandemic.

Material and Methods A total of 116 non-muscle invasive bladder cancer (NMIBC) patients with delayed cystoscopy and 90 control patients with timely cystoscopy were included in the study between June and July 2020. Demographic data of the patients were recorded. Recurrences and progression scores were calculated and grouped according to these scores. The cystoscopy delay time was calculated from the planned cystoscopy time to the performed cystoscopy time. The recurrence and progression status of the patients were recorded, and a comparison was made between the two groups.

Results The median age was 63.6 years (interquartile range [IQR] 35–85) in the delayed cystoscopy group and 67.3 (25-87) in the control group. In the delayed cystoscopy group, 29 (25%) patients had tumour recurrence on follow-up cystoscopy, and 3 (10.34%) patients had tumour progression on subsequent TUR-BT. The mean cystoscopy delay time is 89.27 ± 27.35 days. As a result of the chi-square analysis performed on the group with 10-17 recurrence points found a statistically significant relationship between the experimental and control groups (χ^2 =5 .792; p = .016; $p < 0.05$). As a result of the chi-square analysis between the experimental and control groups according to the progression score groups, no statistically significant correlation was found between the experimental and control groups ($p > 0.05$).

Conclusions In this study, we reported that superficial bladder cancers with low recurrence scores could wait 3-6 months, but delaying 3-6 months in cases with a recurrence score of 10 or more increases the recurrence rate.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2, shortly named coronavirus disease 2019 (COVID-19), caused by a beta coronavirus, was declared a pandemic by the World Health Organization in March 2020, affecting millions of individuals worldwide.[1] It is predicted that the second wave or other similar pandemics may occur. Treatment of other diseases was postponed for a certain period due to the exceeding capacity of the health system against the risk of transmission. In response, professional organisations suggested re-prioritizing surgical cases, especially to avoid delays in the diagnosis and treatment of cancer patients.[2]

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide.[3] Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, carcinoma in situ [CIS]) or submucosa (stage T1).[4] This is called non-muscle invasive bladder cancer (NMIBC). NMIBC has a high probability of recurrence and progression. The recurrence and progression rates at five-year follow-ups were 78% and 45%, respectively.[5] Uro-oncologists worldwide have been troubled during the COVID-19 era, as it is well known that delays in managing bladder cancer can have deleterious effects.[6] It is essential to achieve the management of bladder cancer in such kinds of pandemic diseases. We aimed to investigate whether there is a difference in recurrence and progression rate before and after the pandemic in patients who applied for bladder cancer and/or were followed-up-treatment-operated in the urology clinic during the pandemic.

MATERIAL AND METHODS

Here, we presented a multicenter study with the contribution of Urology Clinics. Ethics committee approval of the study was obtained (HNEAH-KAEK 2020/139), and written consent was obtained from all patients. One hundred and sixteen patients with NMIBC bladder cancer who underwent delayed cystoscopy and TUR-T between June and July 2020 were included in the study whose cystoscopy was postponed due to the pandemic. Also, 90 NMIBC patients who underwent timely control cystoscopies were included as a control group. Patients with muscle-invasive bladder cancer, patients not yet diagnosed with bladder cancer, patients with residual tumours in their first operation, and patients who did not accept participation were excluded from the study. Delays starting from the scheduled date of cystoscopy

Table 1. Weighting used to calculate disease recurrence and progression scores.

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥8	6	6
Tumor diameter		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence/year	2	2
>1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total Score	0-17	0-23

CIS: carcinoma in situ.

according to the EAU follow-up protocol were recorded as "cystoscopy delay time." The definition of recurrence was characterised by the presence of a tumour on follow-up cystoscopy. TUR-computed tomography (CT) was planned under general or spinal anaesthesia when recurrence was detected, and the pathological features of the tumour were noted. Transurethral resection of the tumours was performed with the bipolar resectoscope with three urologists with at least five years of experience, and the pathologic specimens were evaluated by two uro-pathologist.

The recurrence and progression scores of these 116 cases were determined in the EAU 2020 Guideline's NMIBC (TaT1 and CIS) section.5 To predict short- and long-term risks of bladder cancer recurrence and progression in patients, the EORTC Genito-Urinary Cancer Group developed a scoring system and risk tables. The scoring system was based on the six most significant clinical and pathological factors: the number and diameter of tumours, prior recurrence rate, category (ta, T1) of tumours, concurrent CIS, and grade of tumours. The total recurrence and progression scores ranged between 0-17 and 0-23, respectively (Table 1).

Statistical analysis

Guideline values were compared statistically with the data in our study. The data analysis was done with IBM SPSS 25, and the frequency and percentage values of the variables were given. The differences between variables were analysed using the chi-square test. A p - value of < 0.05 was considered statistically significant in the study.

RESULTS

The median age was 63.6 years (interquartile range [IQR] 35-85) in the delayed cystoscopy group and 67.3 (25-87) in the control group. The initial pathology of 73 (62.9%) patients was Ta, and 43 (37.1%) was T1. In the delayed cystoscopy group, 29 (25%) patients had tumour recurrence on follow-up cystoscopy, and 3 (10.34%) patients had tumour progression on subsequent TUR-BT. The mean cystoscopy delay time was 89.27 ± 27.35 days. Demographic characteristics were shown in Table 2.

There was no recurrence of 13 patients who scored 0 points, 8 (15.1%) recurrence of 53 patients who scored 1 to 4, 11 (28.9%) recurrence of 38 patients who scored 5 to 9, 10 (83.3%) recurrence of 12 patients who scored 10 to 17 occurred. Eight patients who scored 10 -17 had T1 tumours, 1 had Ta high-grade CIS, and 1 Had TaG1 5 cm tumour. As a result of the chi-square analysis between the experimental and control groups regarding recurrence scores, no correlation was found between the experimental and control groups regarding the scores of recurrence 0, recurrence 1-4, and recurrence 5-9 ($p < 0.05$). As a result of the chi-square analysis performed in the group with 10-17 recurrence points, a statistically significant relationship was found between the experimental and control groups ($\chi^2 = 5.792$; $p = 0.016$; $p < 0.05$) (Table 3).

The progression score was shown in Table 3. There was no progression of 13 patients who scored 0 points, 1 (2.38%) progression of 41 patients who scored 2 to 6, 1 (3.33%) progression of 38 patients who scored 7 to 13, 1 (3.33%) progression of 31 patients who scored 14 to 23 occurred. As a result of the chi-square analysis between the experimental and control groups according to the progression score groups, no statistically significant correlation was found between the experimental and control groups for progression 0, progression 2-6, progression 7-13, and progression 14-23 scores ($p > 0.05$).

DISCUSSION

At the end of this study, we found that the recurrence rates increased in the patient group with a high recurrence score for cystoscopy delay, but it did not show any change in the progression rates.

COVID-19 has developed into a worldwide health problem affecting millions of individuals and has created many problems for patients who have bladder cancer in receiving care. There is no informationabout

Table 2. Demographic characteristics of the patients.

	Delayed cystoscopy group	Control group
Age (years)	63.6 (35-85)	67.3 (25-87)
Gender (male/female)	105/11	73/17
Initial pathology		
Ta	73 (62.9%)	50 (55.6%)
T1	43 (37.1%)	40 (44.4%)

Table 3. Comparison of recurrence rates of groups according to recurrence scores.

	Delayed cystoscopy group	Control group	*P* - value
Recurrence score 0			1.000
–	13	14	
+	0	0	
Recurrence score 1-4			0.591
–	45	19	
+	8	3	
Recurrence score 5-9			0.702
–	27	27	
+	11	9	
Recurrence score 10-17			0.016
–	2	11	
+	10	7	

the direct effect of COVID-19 and stress factors on the formation or progression of bladder cancer. It becomes an important issue to check our routine in managing bladder cancer. Long-term BC-specific mortality rates are around 1-2%, and active surveillance for recurrent low- and intermediate-risk NMIBCs is an important management option.[7,8] Marcq *et al*.[9] reported the role of active surveillance in low-grade non-muscle invasive bladder cancer (NMIBC) (Ta, T1a, < 1 cm, < 5 lesions) revealed a 15% upgrading and 10% upstaging at a median follow-up of 32 months. According to a combined analysis of 2,596 patients from seven EORTC Trials, the number of tumours, tumour size, and the prior recurrence rate are the most important prognostic factors for recurrence rate, T category, grade, and the presence of CIS for progression rate.[5] Due to the very low recurrence and progression rates of NMIBC, active surveillance protocols have been tried to be developed. In a study in which 186 NMIBC patients were followed for a median of 72 months, progression was detected in only 2%.[10] In another study, no muscle invasion progression was observed in the follow-up of 122 patients.[11] In light of these findings, although it was reported that the cystoscopy interval could be opened in NMIBC follow-ups, in our study, it was found that there was a significant increase in recurrence rates, especially when the cystoscopies of patients with high recurrence scores were delayed.

In the literature, it is reported that it is safe to defer cystoscopy and transurethral resection of bladder tumour (TURBT) for recurrence in patients with known low-grade NMIBC bladder tumours during the COVID-19 pandemic.[6,12,13] A recent multicenter study determined that delaying the cystoscopy for more than three months resulted in a 4.8-fold increase in tumour recurrence and a 6.7-fold increase in progression.[14] In our study, we observed that a delay of 3-6 months would not cause trouble in the NMIBC group with a recurrence score of 9 or less, in line with the literature.

Table 4. Comparison of progression rates of groups according to progression scores.

	Delayed cystoscopy group	Control group	*P*-value
Progression score 0			1.000
–	13	14	
+	0	0	
Progression score 2-6			0.695
–	40	18	
+	1	0	
Progression score 7-13			0.508
–	30	30	
+	1	0	
Progression score 14-23			0.737
–	30	27	
+	1	1	

We found that the delay in the cystoscopy suture had a significant effect on recurrence in the risky group with a recurrence score of 10-17. It was determined that there was no difference in the groups with recurrence scores between 0,1-4 and 5-9, but there was a statistically significant difference between the rates we obtained from the study and the rates determined in the Guideline in the group with a recurrence score between 10-17. There was no statistically significant difference between the progression rate in our study and the guideline ($p > 0.05$) (Table 4). Progression rates are consistent with our study, literature, and guideline rates.

The limitation of this study is that it was conducted with a limited number of cases and in a limited time. Another limitation of the study is that cancer-specific and overall survival could not be evaluated due to these patients' lack of long-term follow-up.

CONCLUSIONS

A prevailing consensus within the literature substantiates the admissible deferment of the treatment and subsequent surveillance of NMIBC by a span of 3 to 6 months, particularly in the context of exigent circumstances such as the COVID-19 pandemic or similar periods. This study presents noteworthy findings, indicating that NMIBC instances characterised by diminished recurrence scores may endure the postponement of 3 to 6 months with discernible prudence. Nonetheless, it is imperative to state that the deferment of a similar duration in cases where the recurrence score reaches or surpasses 10 shows a marked escalation in the recurrence rate, thereby underscoring the imperative of judicious clinical discretion in such scenarios.

Highlights

•**What's known:** NMIBC has a high probability of recurrence and progression. The recurrence and progression rates at five-year follow-ups were 78% and 45%, respectively.

•**What's new:** NMIBC bladder cancers with low recurrence scores can wait 3-6 months, but delaying 3-6 months in cases with a recurrence score of 10 or more increases the recurrence rate.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Haydarpaşa Training and Research Hospital, İstanbul, Turkey. (Decision number: HNEAH-KAEK 20207139-22902, date: 13.07.2020).

Authors' Contribution

Study Conception: YB; Study Design: YB, AÇ; Literature Review: YB, AÇ; Critical Review: YB, AÇ; Data Collection and/or Processing: YB, AÇ,; Analysis and/or Data Interpretation: YB, AÇ; Manuscript preparing: YB, AÇ.

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Nephrology

An underestimated old friend: serum protein electrophoresis in the differential diagnosis of glomerulopathies

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ABSTRACT

Background Serum protein electrophoresis (SPEP) is an easy test separating serum proteins based on their physical and chemical properties. Although it is frequently used in the differential diagnosis of multiple myeloma and various chronic inflammatory diseases, its value in the etiologic classification of glomerular diseases has yet to be studied.

Material and Methods We retrospectively reviewed the medical records of patients who underwent renal biopsy from 2008 to 2016 at our institution. We excluded patients who can not be classified as primary (PGn) or secondary glomerulonephritis (SGn). Univariate and multivariate logistic regression analyses were performed for the prediction of SGn.

Results Four hundred thirty-two patients were included in the study. Of those, 57.9% had PGn. Rheumatological diseases, malignancies, and infections were the most common etiologic causes of SGn, accounting for nearly 75%. Univariate analysis revealed that alpha-1 (α1), gamma (Ɣ), and albumin fractions significantly differ between PGn and SGn groups. ROC curve analysis determined the cut-off value of (α1*Ɣ)/albumin ratio as 1.48. Multivariate analysis revealed that total serum protein and (α1*Ɣ)/albumin ratio were significantly independent predictors for SGn ($p = 0.020$ and $p < 0.001$, respectively).

Conclusions A ratio generated by multiplying α1 and Ɣ and dividing by albumin from SPEP, an easy, reliable, and cheap test, may help clinicians differentiate between PGn and SGn after validation in more extensive prospective studies.

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INTRODUCTION

Glomerular disease is a heterogeneous group of disorders affecting the functions of the glomeruli with various mechanisms.[1] Clinical manifestations of glomerular diseases vary from asymptomatic urinary abnormalities to life-threatening renal and extrarenal organ dysfunctions.[2] Although glomerular diseases are rare, considering each histopathologic type as a specific disorder, they constitute roughly 10% of patients receiving renal replacement therapy, according to the European Renal Association Registry Annual Report 2021.[3]

Serum protein electrophoresis (SPEP) is an easy and reliable laboratory technique for separating serum proteins into fractions based on their physical features, such as charge, shape, and molecular weight. Protein fractions in SPEP are as follows: albumin and alpha-1 globulin (α1), alpha-2 globulin (α2), beta globulin (β), and gamma globulin (Ɣ). Although the diagnostic instruments develop and improve over time, SPEP is still frequently preferred by clinicians, particularly since the second half of the 20th century.[4] In clinical practice, SPEP is a convenient laboratory test for differential diagnoses and follow-ups of numerous diseases.[5,6] Also, protein fractions in SPEP are reported to alter in various renal diseases.[7] However, there is no recommendation for its use in the differential diagnosis of glomerular diseases other than multiple myeloma.

Various classifications of glomerular diseases were proposed based on aetiology, histology, and pathogenesis.[8,9] According to the aetiology, glomerular diseases are classified as primary and secondary glomerular diseases.[10,11] Secondary glomerulonephritis (SGn) represents glomerular dysfunction secondary to an identifiable underlying or systemic cause. Although the differential diagnosis of primary and secondary glomerular disease is crucial for applying appropriate therapy to the patient, this classification sometimes becomes challenging in clinical practice despite recent biomarkers.[12,13] The etiological causes of histopathologically confirmed secondary glomerulonephritis are mostly rheumatological diseases, amyloidosis, infections, and malignancies.[14,15] These disorders are accompanied by monoclonal gammopathies or marked by chronic inflammation, causing characteristic changes in SPEP. Therefore, in the present study, we investigated the predictive value of SPEP for classifying glomerular diseases as primary glomerulonephritis (PGn) or SGn.

MATERIAL AND METHODS

We reviewed the electronic medical records of the patients who underwent renal biopsies between January 2008 and November 2016 in the Department of Nephrology Bursa Uludag University. The study was in accordance with the 1964 Declaration of Helsinki. The clinical research ethics committee of Bursa

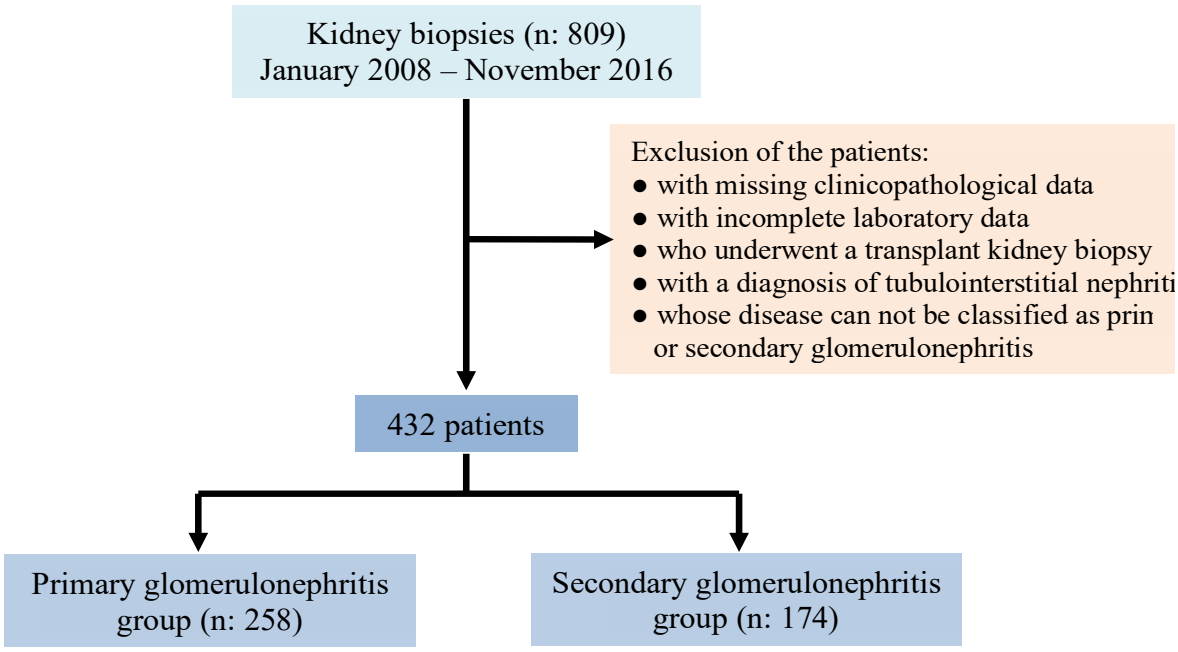

Figure 1. Flow chart of patient selection and study design.

Uludag University Faculty of Medicine approved the study (Approval number: 2017-14/30). We extracted the participants' demographic features, comorbidities, clinical manifestations, laboratory findings at admission, pathological results, treatments, and clinical courses. SPEP results and graphs at the time of admission were accessed from patient files or electronic medical records of our centre.

Figure 1 displayed the patient's flow chart. The patients were classified as PGn and SGn by two experienced nephrologists, evaluating their laboratory and histopathological findings and clinical courses. Histopathologic features of mesangial proliferation, tubulointerstitial polymorphonuclear inflammation, crescents in light microscopy, mesangial and/or diffuse staining in immunofluorescence microscopy, monoclonal light chain staining were considered a secondary aetiology. Patients with membranous glomerulonephritis (MGN) were considered primary MGN whose histopathologic features were consistent with typical findings and positive phospholipase A2 receptor (PLAR2) antibody. MGN patients with mesangial proliferation in their biopsy and negative anti-PLA2R were typed as secondary MGN. Patients with histopathological findings of amyloidosis, cast nephropathy, and monoclonal gammopathy of renal significance were also classified as SGn. We excluded patients with incomplete clinicopathological and lab-

Table 1. Clinicopathological characteristics of the patients (n: 432).

Parameters	Values
Age (years)	43.1 (14.0:84.0)
Gender (Male)	246 (56.9)
Serum urea (mg/dL)	43.0 (10.0:277.0)
Serum creatinine (mg/dL)	1.1 (0.2:13.6)
24-h urine protein (g/day)	4.5 (0.0:49.8)
Indications for biopsy	
Nephrotic syndrome	180 (41.6)
Nephritic syndrome	148 (34.3)
Isolated non-nephrotic proteinuria	96 (22.2)
Isolated glomerular hematuria	8 (1.9)
Histopathological diagnosis	
Primary glomerulonephritides	258 (59.7)
MGN	84 (19.4)
FSGS	77 (17.8)
IgA nephropathy	46 (10.7)
MPGN	25 (5.8)
MCD	24 (5.6)
Fibrillary GN	2 (0.4)
Secondary glomerulonephritides	174 (40.3)
AA amyloidosis	42 (9.7)
AL amyloidosis	6 (1.4)
Lupus nephropathy	34 (7.9)
Crescentic GN	25 (5.8)
MGN	10 (2.3)
FSGS	15 (3.5)
MPGN	12 (2.8)
Diabetic nephropathy	8 (1.8)
Hypertensive nephropathy	5 (1.2)
IgA nephropathy	4 (0.9)
MGRS	5 (1.2)
Cast nephropathy	3 (0.7)
Thrombotic microangiopathy	3 (0.7)
MCD	1 (0.2)
Fibrillary GN	1 (0.2)

MGN: membranous glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis; MCD: minimal change disease, GN: glomerulonephritis, MGRS: monoclonal gammopathy of renal significance.
The values were expressed as n (%) or median (minimum: maximum).

oratory data, those who underwent transplant kidney biopsy, and those who cannot be classified as PGn or SGn.

Statistical analysis

Statistical analyses were conducted operating SPSS, version 28.0 (IBM, NY, USA). Descriptive statistics were presented as percentages for categorical variables and mean with standard deviation or median with ranges according to the distribution of variables for continuous variables. Student t-test or Mann–Whitney U test for continuous variables and Pearson's Chi-squared test for categorical variables were used to compare the variables between groups. The optimal cut-off point for α1*Ɣ/albumin ratio was determined using receiver operating characteristic (ROC) curve analysis. Enter method was employed for multivariate binary logistic regression analysis, including factors with a *p* - value below 0.20 in univariate analysis. A *p* - value of 0.05 was set for statistical significance.

RESULTS

A total of 432 patients (43.1 [14.0-84.0] years old, 56.9% male) were enrolled in our study. Demographic and clinicopathological characteristics were shown in Table 1. The leading cause of kidney biopsy was nephrotic syndrome (41.6%), followed by nephritic syndrome. Approximately 60% of the cases were patients with PGn, and 174 had SGn. The most common histopathological diagnosis was MGN in PGn, accounting for 32.6% of PGn cases, and amyloidosis (11.1%) in SGn. The etiological causes of SGn were presented in Table 2. Approximately half of the patients with SGn (49.4%) had rheumatological diseases, and systemic lupus erythematosus was the leading aetiology. Malignancy and infection were common for the following reasons. Nine patients were included in the SGn group due to clinicopathological and laboratory findings (mostly amyloidosis patients), but etiological reasons could not be revealed.

Clinical and laboratory parameters of PGn and SGn were compared in Table 3. Female patients were more common in the SGn group than in the PGn group. Haemoglobin level, 24-hour urine protein and serum total cholesterol, complement 3 (C3) and complement 4 (C4) levels were significantly higher in patients with PGn. Conversely, serum urea, creatinine, total protein, C-reactive protein, and immunoglobulin G levels were significantly higher in the SGn group than in the PGn group. Analysis of protein fractions in SPEP revealed that the percentage of albumin was significantly higher in patients with PGn. However, α1 and Ɣ percentages were significantly higher in patients with SGn.

We calculated the (α1*Ɣ)/albumin ratio ([% of α1 fraction multiplied by % of Ɣ fraction] divided by % of albumin fraction) using SPEP fractions, which differed significantly between PGn and SGn to determine the value of SPEP in distinguishing PGn and SGn. Figure 2A demonstrated the Box-and-whisker plot showing (α1*Ɣ)/albumin ratio in PGn and SGn groups. Figure 2B showed the ROC curve of (α1*Ɣ)/albumin ratio, taking the presence of SGn as the endpoint of interest. In ROC curve analysis, the cut-off value for (α1*Ɣ)/albumin ratio was determined as ≥ 1.48 (AUC: 0.680, sensitivity: 70.7%, specificity: 61.2%, $p < 0.001$).

The results of binary logistic regression analysis were exhibited in Table 4. Multivariate analysis revealed that serum total protein level (odds ratio [OR], 1.768; 95% confidence interval [CI], 1.093-2.861; *p* =

Table 2. Etiological causes of secondary glomerulonephritides (n: 174).

Etiological reasons	Frequency
Systemic lupus erythematosus	36 (20.7)
Vasculitides	27 (15.5)
Malignancy	13 (7.5)
Infection	13 (7.5)
Familial Mediterranean fever	10 (5.7)
Multiple myeloma	8 (4.6)
Diabetes mellitus	8 (4.6)
Hypertension	7 (4.0)
Rheumatoid arthritis	7 (4.0)
Obesity	5 (2.9)
Monoclonal gammopathy of renal significance	5 (2.9)
Bronchiectasis	4 (2.3)
Thrombotic thrombocytopenic purpura	4 (2.3)
Lymphoproliferative disorders	4 (2.3)
Myeloproliferative disorders	2 (1.1)
Ankylosing spondylitis	4 (2.3)
Psoriasis	3 (1.7)
Mixed connective tissue disease	1 (0.6)
Behcet's disease	1 (0.6)
Obstructive uropathy	1 (0.6)
Inflammatory bowel disease	1 (0.6)
Fabry disease	1 (0.6)
Unknown*	9 (5.1)

*Histopathological diagnoses of patients whose etiological cause could not be found were AA amyloidosis, membranous glomerulonephritis and membranoproliferative glomerulonephritis.

Table 3. Comparison of clinical and laboratory parameters of primary and secondary glomerulonephritides.

Parameters	Primary GN	Secondary GN	*P* - value
Age (years)	42.3 (17.0:84.0)	45.2 (14.0:78.7)	0.057
Gender (male)	162 (62.8%)	84 (48.3%)	0.003
Serum urea (mg/dL)	39.5 (11.0:277.0)	54.0 (10.0:268.0)	< 0.001
Serum creatinine (mg/dL)	1.1 (0.2:13.6)	1.4 (0.4:13.0)	< 0.001
Serum total protein (g/dL)	5.6 (2.8:8.3)	5.9 (2.9:8.7)	0.048
Serum albumin (g/dL)	3.0 (0.3:4.9)	3.0 (0.7:4.9)	0.792
Total cholesterol (mg/dL)	255.0 (80.0:892.0)	200.5 (73.0:642.0)	< 0.001
Haemoglobin (g/dL)	12.9 ± 2.0	11.1 ± 2.2	< 0.001
24-h urine protein (g/day)	4.9 (0.0:49.8)	3.9 (0.0:29.1)	0.066
SPE-albumin (%)	51.2 (6.6:79.0)	47.3 (6.2:64.9)	< 0.001
SPE-alpha-1 (%)	5.6 (1.4:15.5)	6.2 (1.3:14.2)	0.005
SPE-alpha-2 (%)	15.8 (2.9:39.7)	14.0 (1.5:46.2)	0.087
SPE-beta (%)	12.7 (5.9:28.0)	12.2 (5.5:31.4)	0.210
SPE-gamma (%)	13.1 (3.8:27.6)	16.1 (3.2:42.7)	< 0.001
ESR (mm/hour)	26.5 (2.0:120.0)	41.0 (2.0:133.0)	< 0.001
CRP (mg/dL)	0.35 (0.02:18.0)	0.8 (0.03:26.8)	< 0.001
C3 (mg/dL)	126.0 (13.0:223.0)	114.0 (13.0:260.0)	< 0.001
C4 (mg/dL)	29.4 (6.5:138.0)	25.5 (1.7:59.8)	0.008
IgG (mg/dL)	742.0 (143.0:2320.0)	988 (190.0:3380.0)	< 0.001
IgM (mg/dL)	98.3 (16.0:434.0)	95.7 (16.0:1070.0)	0.883

GN: glomerulonephritis, SPE: serum protein electrophoresis, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, C3: complement 3, C4: complement 4, Ig: immunoglobulin.
The values were expressed as median (minimum:maximum), n (%) or mean ± standard deviation.

0.020), and (α1*Ɣ)/albumin ratio (OR, 4.235; 95% CI, 1.739–10.310; $p < 0.001$) were independent predictors for SGn. Other variables lost statistical significance in multivariate analysis.

DISCUSSION

To our knowledge, this is the first study assessing the predictive value of SPEP in classifying glomerular diseases as PGn and SGn. We found that α1, Ɣ, and albumin fractions in SPEP differ significantly between PGn and SGn, and the (α1*Ɣ)/albumin ratio produced from the percentages of SPEP fractions was higher in the SGn group than in the PGn group. Furthermore, serum total protein level was an independent predictor for SGn.

SPEP separates the serum proteins into albumin

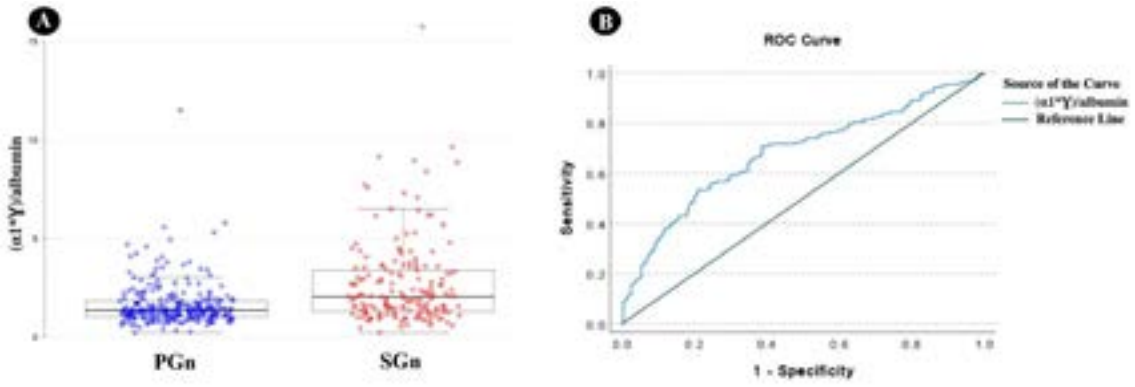

Figure 2. A: Boxplot scheme of (α1*Ɣ)/albumin ratio in primary (PGn) and secondary (SGn) glomerulonephritis groups. The median was indicated as the black line, and circles expressed all individual data. B: The ROC curve (α1*Ɣ)/albumin ratio.

Table 4. Univariate and multivariate logistic regression analysis for the predictors of secondary glomerulonephritides.

Factor	Univariate analysis				Multivariate analysis			
	OR	95% CI		*p* - value	OR	95% CI		*p* - value
		Lower	Upper			Lower	Upper	
Age (years)	1.011	0.998	1.024	0.086	1.016	0.991	1.042	0.222
Gender (male [RC] vs female)	1.818	1.224	2.671	0.003	0.478	0.202	1.127	0.092
Serum urea (mg/dL)	1.011	1.006	1.015	< 0.001	0.991	0.978	1.042	0.228
Serum creatinine (mg/dL)	1.280	1.150	1.424	< 0.001	1.384	0.975	1.964	0.069
Serum total protein (g/dL)	1.184	1.006	1.392	0.042	1.768	1.093	2.861	0.020
Serum albumin (g/dL)	0.981	0.796	1.208	0.854				
Total cholesterol (mg/dL)	0.995	0.992	0.997	< 0.001	1.001	0.996	1.006	0.732
Haemoglobin (g/dL)	0.657	0.589	0.732	< 0.001	0.856	0.665	1.102	0.228
24-h urine protein (g/day)	0.959	0.925	0.994	0.024	0.996	0.909	1.092	0.936
ESR (mm/hour)	1.019	1.011	1.027	< 0.001	1.011	0.994	1.028	0.223
CRP (mg/dL)	1.219	1.109	1.340	< 0.001	1.063	0.900	1.257	0.472
C3 (mg/dL)	0.990	0.984	0.996	< 0.001	0.988	0.974	1.001	0.074
C4 (mg/dL)	0.971	0.953	0.989	0.002	0.981	0.949	1.014	0.260
IgG (mg/dL)	1.001	1.001	1.002	< 0.001	0.999	0.998	1.001	0.304
IgM (mg/dL)	1.001	0.999	1.004	0.279				
(α1*Ɣ)/albumin ratio (low [RC] vs high)	3.811	2.525	5.750	< 0.001	4.235	1.739	10.310	< 0.001

OR: odds ratio, CI: confidential interval, RC: reference category, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

and globulin fractions based on charge-by-mass ratio under an electrical field. Albumin constitutes the most prominent fraction of SPEP. The liver produces albumin, the primary determinant of plasma oncotic pressure. Also, it functions as a transporter of various substances in the blood.16 Numerous clinical conditions accompany hypoalbuminemia in which either decreased production or increased loss results. Due to its low molecular weight and glomerular loss, hypoalbuminemia is frequently encountered in nephrotic syndrome and acute glomerulonephritis.6,17 In addition, clinical conditions driven by inflammation are among the most noteworthy disorders causing hypoalbuminemia. In the case of inflammation, several mechanisms result in hypoalbuminemia: (1) the inhibition of the hepatic secretion of albumin mediated by the proinflammatory cytokine-IL6 and (2) the increase in interstitial volume secondary to the increased capillary permeability by proinflammatory cytokines such as vascular endothelial growth factor and (3) the decrease in circulatory half-life of albumin.18,19 Duration and severity of inflammation have been associated with the severity of hypoalbuminemia.18 Rheumatological diseases, malignancies, and infections, which constitute nearly 3/4 of SGn in our study, are accompanied by severe inflammation at the whole-body level.18 In this context, we attributed the low albumin fraction in SPEP in SGn to the more prolonged and severe inflammation due to the underlying disease.

The α1 fraction of SPEP consists of alpha-1 antitrypsin (A1T), alpha-1-chymotrypsin, transcortin, and thyroid-binding globulin.[5,20] A1T is a plasma serine protease inhibitor and a significant component of the α1 band. It increases after initiating inflammation and is vital in limiting tissue injury mediated by proteases during inflammation.[21] In inflammatory conditions such as infection and tissue damage, A1T may increase up to six times above steady-state levels.[22] Furthermore, it has been reported that A1T can be used as a biomarker for evaluating the efficacy of chronic infections such as tuberculosis since it regresses after treatment.[22,23] Malignancy can also increase the α1 protein band in SPEP.20 The gamma fraction includes mainly serum immunoglobulins. Clonal proliferation of plasma cells, as occurred in multiple myeloma and plasmacytoma, results in monoclonal gammopathy. Overproducing more than one class of immunoglobulins by plasma cells prompts polyclonal gammopathy, associated with liver disease, malignancies, chron-

ic inflammation, and autoimmune disorders such as rheumatological diseases.[24] All these data support the finding in our study that α1 and γ bands are more prominent in SGn.

Although the absolute serum albumin levels in the two groups in our study were similar, significantly lower albumin fractions in SPEP in the SGn group can be explained by the global evaluation of all serum proteins in SPEP because it has been reported that total protein increases in chronic inflammation and malignancies, consistent with our results.[4] With this regard, evaluation of total protein increase using fractional distribution, as in SPEP, maybe more valuable in the differential diagnosis of glomerular diseases.

Glomerulonephritis is a heterogeneous group of diseases causing around 20% of ESRDs, although uncommon.[25] To control the disease in SGn, it is necessary to eliminate the underlying condition in addition to the anti-inflammatory and immunosuppressive therapy used in PGn. Therefore, it is crucial to differentiate between PGn and SGn to direct the most appropriate treatment.[11] However, classifying glomerulonephritis according to aetiology is sometimes challenging because histopathological findings can only sometimes identify secondary causes. Although some recent biomarkers can help the clinician in this distinction, especially in certain types of histopathological glomerulonephritis, new biomarkers are still needed.[12,13] In this context, we proclaim that the (α1*γ)/albumin ratio generated from SPEP, an easy, inexpensive, and easily accessible test, may help differentiate PGn and SGn. By confirming our results with studies investigating the (α1*γ)/albumin ratio in patients with certain glomerulonephritis types and more extensive prospectively designed analyses, this ratio may meet the urgent need for biomarkers.

The strengths of our study were that all patients were followed for at least five years after diagnosis due to the possibility of underlying systemic reasons for the PGn group and a relatively high number of participants. Nevertheless, our study had limitations: a retrospective design and an inability to test the predictive value of SPEP by performing particular analyses for each etiological reason of SGn. Additionally, accompanying conditions that may change SPEP findings, such as acute infection, A1T deficiency, and iron deficiency anaemia, may have impacted our findings. Therefore, prospective studies that exclude patients with such confounding conditions must confirm our results.

CONCLUSIONS

We conclude that the (α1*γ)/albumin ratio generated from fractions of SPEP may differentiate glomerular diseases between PGn and SGn. This ratio may help clinicians in this regard after confirmation of our results in more extensive prospective studies.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Uludag University, Bursa, Turkey. (Decision number: 2017-14/30, date: 03.10.2017).

Authors' Contribution

Study Conception: MG, ABS; Study Design: MG, ABS, AM; Supervision: MG, AM, AE, AO; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ABS, SB, SEGB; Statistical Analysis and/or Data Interpretation: GO, ABS, AM; Literature Review: ABS, AO, AE, SB, SEBG; Manuscript Preparation: ABS, AO, SEGB, SB; and Critical Review: MG, AE, AM, AO, GO.

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Cardiovascular Medicine and Haematology

Retrospective evaluation of patients who underwent allogeneic stem cell transplantation for bone marrow failure

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A B S T R A C T

Background Bone marrow failure is a disease that develops due to different etiologies. Aplastic anaemia (AA) and hypocellular myelodysplastic syndrome (HMDS) are the most common bone marrow failure disorders. Treatment options include supportive therapy, immunosuppressive therapy, and allogeneic hematopoietic stem cell transplantation (allo-HCT). Allo-HCT is the only curative treatment option. This study aimed to retrospectively evaluate the demographic characteristics, treatment, and transplantation results of patients who underwent Allo-HCT for bone marrow failure.

Methods This single-centre retrospective study enrolled 11 patients (9 with severe AA and 2 with HMDS) who underwent allo-HCT for bone marrow failure. The patients' records until 17.08.2023 were analysed. Age, gender, diagnosis, donor age and gender, type of transplantation, pre-transplant ferritin levels, time to transplantation, volume of infused product, number of CD34+ cells in the infused product, post-transplant engraftment times, discharge time, transplant-related complications, post-transplant follow-up and overall survival times were obtained.

Results Eleven patients underwent 12 allo-HCTs for bone marrow failure. Seven patients were male, and four were female. The median age was 40, and seven patients were ≥ 40 years old at the time of transplantation. Eleven transplants were performed from HLA fully matched siblings and one from a 9/10 matched sibling donor. Bone marrow was used as a stem cell source in 8 transplants and peripheral blood in 4 transplants. The conditioning regimen was fludarabine/cyclophosphamide/anti-thymocyte globulin in all patients. The median time from diagnosis to transplantation was five months. The median time for neutrophil engraftment was 23 days. The median platelet > 20.000/mm^3 engraftment time was 16 days. A statistically significant positive correlation was found between ferritin levels and platelet > 20.000/mm^3 engraftment (days) (r = 0.653, p = 0.040) and platelet > 50.000/mm^3 engraftment (days) (r = 0.720, p = 0.029). There was a statistically significant negative correlation between the number of infused CD34 positive cells (10^6/kg) and platelet > 50.000/mm^3 engraftment (days) (r = -0.670, p = 0.024). Patients were discharged in a median of 23 days. Acute graft versus host disease (GvHD) was observed in one patient, while chronic GvHD was not observed in any patient. The median overall survival time was 48 months, and the median post-transplant follow-up was 37 months. Secondary malignancy and MDS were not detected in any patient during the follow-up period. All 11 patients who underwent Allo-HCT from a matched sibling donor are alive and continue to have a complete haematological response. There was no increase in mortality and morbidity in patients aged 40 years and older.

Conclusions In patients with severe AA and high-risk HMDS without comorbidities between the ages of 40 and 50, allo-HCT should be considered as first-line treatment in the presence of an HLA-matched sibling donor.

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INTRODUCTION

Bone marrow failure is a group of disorders that develop due to different etiologies. The leading causes of acquired bone marrow failure include aplastic anaemia (AA) and hypocellular myelodysplastic syndrome (HMDS). AA is defined as pancytopenia with hypocellular bone marrow without infiltration or fibrosis. Supportive therapy, immunosuppressive therapy (IST), and allogeneic stem cell transplantation (allo-HCT) are among the treatment options. Supportive therapy includes erythrocyte and platelet transfusion, prevention and treatment of infections, thrombopoietin mimetic eltrombopag, and iron chelation. Standard first-line IST combines horse-derived anti-thymocyte globulin (ATG) and cyclosporine-A (CsA).[1] HLA typing should be performed at the time of diagnosis for all newly diagnosed AA patients who may be potential transplant candidates. Allo-HCT is the only curative treatment option. However, it may only be a suitable option for some patients. Although the approach is still being determined because of the rarity of the diseases, bone marrow transplantation should be the first-line treatment in patients with severe AA, especially in patients aged < 40 years if there is an HLA-compatible sibling donor.[2] The appropriate age limit for transplantation is gradually increasing. Transplant-related morbidity and mortality is gradually improving with advances in treatment. A limit between 35 and 50 years of age has been proposed depending on the patient's comorbidities in selected patients who are medically fit for patients between 41 and 60.[3] IST is applied in patients unsuitable for allo-HCT.[4]

Myelodysplastic syndrome (MDS) is a clonal bone marrow neoplasm characterised by morphological dysplasia findings in hematopoietic cells, peripheral cytopenia(s), ineffective hematopoiesis, recurrent genetic abnormalities, and increased risk of transformation to acute myeloid leukaemia.[5] The role of allo-HCT in treating low-risk MDS has yet to be fully established. It has been shown that progression-free and overall survival rates of patients with multiple molecular abnormalities are significantly reduced compared with patients who do not carry mutations. It may be recommended that these patients and patients with TP53 mutation be closely monitored, the HLA typing should be studied, and they should be directed to HCT.1 HMDS is an MDS subgroup comprising 10-15% of MDS patients characterised by bone marrow hypocellularity. IST is an essential component of the clinical approach in patients with HMDS; early allo-HCT should also be considered in some patients.[6]

In this study, we retrospectively evaluated the allo-HCT results of patients diagnosed with acquired severe AA and HMDS. It was aimed to determine the clinical characteristics and transplantation results of patients who underwent allo-HCT for bone marrow failure.

MATERIAL AND METHODS

Patient selection

The study included patients over 18 who underwent allo-HCT and were diagnosed with acquired severe AA and HMDS in our haematology department between January 2016 and April 2023. The conditioning regimen: fludarabine (30 mg/m^2/day; days -8, -7, -6, -5) + cyclophosphamide (300 mg/m^2/day; days -8, -7, -6, -5) + ATG (rabbit sourced; 3.75 mg/kg/day; days -4, -3, -2, -1) in all patients. Graft versus host disease (GvHD) prophylaxis: methotrexate 10 mg/m^2 IV on day +1 and CsA 3 mg/kg/day on day -1 were administered to all patients. After transplantation, all patients received prophylactic acyclovir, trimethoprim-sulfamethoxazole, triflucan, and ciprofloxacin.

Response assessment

Neutrophil and platelet engraftment was defined as absolute neutrophil count > 500/mm^3 and platelet count > 20000/mm^3 on three consecutive days without transfusion support, respectively. Primary graft failure (GF) was defined as failure to achieve engraftment 28 days after HCT. Secondary GF was described as a neutrophil count < 500/mm^3 after initial engraftment. Post-treatment blood counts were classified as complete response (CR), partial response (PR), and no response.1 Standard criteria were used for stage 2-4 acute GvHD and chronic GvHD.7,8 Chimerism determination was routinely performed in the 1st post-transplant month. Post-transplant cytomegalovirus (CMV) follow-up by PCR was performed twice a week in peripheral blood for the first 100 days.

Statistical analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". The data were analysed for normality, and Shapiro-Wilk values were determined as $p < 0.05$. Therefore, the Spearman correlation test was used to determine the relationship between continuous variables. $p < 0.05$ was considered statistically significant.

RESULTS

Twelve allo-HCTs were performed in 11 patients with bone marrow failure (9 severe AA and 2 HMDS). The median age was 40, and seven patients were ≥ 40 years old at the time of transplantation. Allo-HCT was administered as first-line treatment in 9 patients and second-line therapy in 2 patients. The median time from initial diagnosis to transplantation was five months. Patient and transplant characteristics were summarised in Table 1.

The median time to neutrophil > 500/mm^3 engraftment was 23 days, and the median time to platelet 20000/mm^3 engraftment was 16 days.

Table 1. Patient (n: 11) and transplant (n: 12) characteristics.

Number of transplants	12
Transplant for the second time	1
Recipient Gender (female/male)	4/7
Recipient transplant age (years)	40 (21:55)
Diagnosis	
Severe aplastic anaemia	9 (81.8)
Hypocellular MDS	2 (18.1)
Donor	
Sibling	12 (100)
Age (years) median, (min-max)	39.5 (25:63)
Diagnosis-transplant time (months)	5 (2:35)
Number of transfusions (U)	
Erythrocyte suspension	11.5 (5:55)
Platelet suspension	12.5 (2:69)
Pre-transplant ferritin level (µg/L)	1291 (284:3970)
Conditioning regime	
Flu/Cy/ATG	12 (100)
HLA matching	
9/10	1 (8.3)
10/10	11 (91.6)
Stem cell source	
Bone marrow	8 (66.6)
Peripheral blood	4 (33.3)
Infused product volume (cc)	
Bone marrow	1250 (320:1500)
Peripheral blood	520 (105:720)
Number of infused CD34+ cells (10^6/kg)	
Bone marrow	0.98 (1:5.4)
Peripheral blood	5.67 (2:6.65)
Infused product CD34+ cell count (µL)	
Bone marrow	76 (52:812)
Peripheral blood	1149 (192:4991)

MDS: myelodysplastic syndrome, CsA: cyclosporine A, ATG: antithymocyte globulin.
The values were expressed as n (%) or median (minimum: maximum).

Table 2. Results of transplantation.

Engraftment time (days)	
Neutrophils >500/mm^3	23 (13:31)
Platelets >20.000/mm^3	16 (11:24)
Platelets >50.000/mm^3	22 (14-33)
Engraftment failure	1 (8.3)
Discharge duration (days)	23 (20:39)
Chimerism 30 days after transplantation	6 (60)
100	4 (40)
85-100	
Complication after transplantation	
FEN	5 (41.6)
Grade 1-2 mucositis	4 (33.3)
Grade 1-2 nausea and vomiting	9 (75)
GvHD	
Acute	1 (8.3)
Chronic	0
CMV infection after transplant	
Yes	6 (54.5)
One time	6 (54.5)
Two times	3 (27.2)
No	5 (45.4)
Hematological Response	
Complete remission	11 (91.6)
No response	1 (8.3)
Last status	
Alive	11 (100)
Exitus	0
Post-transplant follow-up time (months)	37.48 (4.30:92.63
Overall survival (months)	48.20 (9.30:95.17

The values were expressed as n (%) or median (minimum maximum).

Post-transplant patients were complicated with febrile neutropenia (FEN), grade 1-2 mucositis, and grade 1-2 nausea-vomiting. No focus of infection was found in 3 of 5 patients complicated with FEN, and the response was obtained with piperacillin-tazobactam. *E.coli* was also grown in blood culture in 2 patients, and a response was received with meropenem. Patients were discharged on the median 23rd day (20-39 days). CMV infection was observed in six patients. All of these were in the first 100 days of transplantation. Three patients experienced CMV reactivation for the second time after the 100th day of transplantation. CMV-DNA negativity was achieved in all patients with oral valganciclovir treatment. The chimerism of 6 patients who could be chimerised in the first month was 100%, and four patients had an

Table 3. The relationship between engraftment times and various variables.

		Neutrophil >500/mm^3 engraftment (day)	Platelet >20.000/mm^3 engraftment (day)	Platelet >50.000/mm^3 engraftment (day)
Recipient transplant age	r	0.361	0.018	–0.067
	p	0.249	0.956	0.846
Donor age	r	0.445	0.198	0.169
	p	0.147	0.538	0.620
Pre-transplant ferritin (µg/L)	r	0.445	0.653*	0.720*
	p	0.197	0.040	0.029
Infused product volume (cc)	r	0.549	0.250	0.483
	p	0.065	0.433	0.133
Number of CD34+ infused cells (10^6/kg)	r	–0.507	–0.531	–0.670*
	p	0.092	0.076	0.024
Number of infused product CD34+ cells (µL)	r	–0.532	–0.346	–0.579
	p	0.075	0.270	0.062

A correlation was significant at 0.05 level (Spearman correlation test).

85-100% donor profile. Acute GvHD was observed in one patient, while chronic GvHD was not observed in any patient. After transplantation, one transplant was considered non-responsive, and the others were complete responders. Although chimerism was 100% in the unresponsive patient, a second allo-HCT was performed 15 months after the first transplant due to secondary graft failure from another fully matched sibling (patient number 8 in Table 4). The results of transplantation were summarised in Table 2.

There was a statistically significant positive correlation between ferritin levels and platelet > 20.000/mm^3 engraftment (day) (r = 0.653, p = 0.040) and platelet > 50.000/mm^3 engraftment (day) (r = 0.720, p = 0.029). A statistically significant negative correlation was found between the number of infused CD34 positive cells (10^6/kg) and platelet > 50.000/mm^3 engraftment (days) (r = –0.670, p = 0.024) (Table 3).

No statistically significant difference was found between CMV infection and age groups (< 40 and ≥ 40 years) (p = 0.558) and between neutrophil and platelet engraftment times and age groups (< 40 and ≥ 40 years) (p = 0.104 and p = 0.682, respectively). One patient was complicated by BK virus (during her second transplant) (transplant number 11 in Table 5). Pregnancy was detected in one patient in the 5th month of transplantation (patient number 6 in Table 4). No complications or disease recurrence were observed during pregnancy. Delivery was performed uneventfully by standard vaginal delivery at 39 weeks.

The median follow-up period was 48 months, and the median post-transplant follow-up period was 37 months. All patients were still in our follow-up after transplantation; complete haematological responses

Table 4. Data of the study patients at the time of diagnosis.

Patient no	Gender	Diagnosis	Neutrophil (/mm^3)	Haemoglobin (g/dL)	Platelets (/mm^3)	Corrected reticulocyte (%)	Transfusion dependence
1	Male	SAA	50	7.6	13000	0.2	Yes
2	Male	HMDS	780	9.5	13700	0.9	Yes
3	Male	SAA	480	8.1	26000	0.6	Yes
4	Male	SAA	640	8.1	9600	0.5	Yes
5	Male	SAA	990	7.5	18000	2.4	Yes
6	Female	SAA	330	5.7	21000	0.7	Yes
7	Male	AA	1100	13	54000	1.3	No
8	Female	SAA	1600	3.9	8000	0.4	Yes
9	Male	SAA	600	4.9	3900	0.4	Yes
10	Female	SAA	480	9.1	4400	0.3	Yes
11	Female	HMDS	1500	6.1	19000	1.1	Yes

SAA: severe aplastic anaemia, HMDS: hypocellular myelodysplastic syndrome.

Table 5. Transplantation data of the patients

HCT no	Age	Diagnosis	Year	Time until HCT (month)	HLA compatibility	Stem cell source	Number of infused CD34+ cells (10^6/kg)	Neutrophil ET (day)	Platelet >20000 /mm^3 ET (day)	GF	Acute GvHD	Chronic GvHD	OS (month)	Last status
1	46	SAA	2016	3	10/10	BM	2.04	26	18	No	No	No	95	Alive
2	47	HMDS	2017	7	10/10	PBSC	6.63	14	12	No	No	No	85	Alive
3	40	SAA	2018	4	10/10	BM	1.37	31	19	No	No	No	61	Alive
4	36	SAA	2018	6	9/10	BM	1.26	21	21	No	No	No	62	Alive
5	21	SAA	2019	2	10/10	BM	1	25	21	No	No	No	49	Alive
6	25	SAA	2020	3	10/10	BM	5.4	15	13	No	No	No	47	Alive
7	40	SAA	2021	35	10/10	BM	2	25	11	No	No	No	66	Alive
8*	54	SAA	2022	9	10/10	PBSC	2	30	24	Yes	No	No	29	Alive
9	36	SAA	2022	3	10/10	PBSC	4.72	13	14	No	No	No	21	Alive
10	27	SAA	2023	3	10/10	BM	1.25	20	13	No	No	No	9	Alive
11*	55	SAA	2023	22	10/10	BM	1.6	27	18	No	No	No	29	Alive
12	46	HMDS	2023	30	10/10	PBSC	6.65	18	13	No	Yes	No	34	Alive

HCT no: hematopoietic stem cell transplantation number, ET: engraftment time, GF: graft failure, GvHD: graft versus host disease, OS: overall survival, SAA: severe aplastic anaemia, HMDS: hypocellular myelodysplastic syndrome, BM: bone marrow, PBSC: Peripheral blood stem cells.

* Numbers 8 and 11 were data from two different transplants of the same patient.

continued. Secondary malignancy and MDS were not detected in any patient during the follow-up period. Patient data were given in Tables 4 and 5.

DISCUSSION

Severe AA is a life-threatening disease with a high mortality rate due to bleeding and infections, and therefore, effective treatment is essential.[9] In severe AA, allo-HCT with an HLA-compatible sibling donor is recommended in patients under 40.[2] In young patients with poor risk characteristics in HMDS, HLA typing should be analysed. Allo-HCT should be considered in appropriate patients. Forty years is the cut-off age for first-line HCT from a fully matched sibling donor in most centres. Today, improved treatment conditions and decreasing transplant-related morbidity and mortality have raised the recommended age for transplantation. Although the cut-off age for HCT is shifting towards 50 years, a consensus has yet to emerge.

In our study, the median age at recipient transplantation was 40 years, and seven patients were 40 or older. The oldest patient was 55 years old. There was no correlation between the patient's age and engraftment duration. Only the patient with secondary engraftment failure was the oldest, and successful engraftment was achieved in the second allo-HCT. No statistically significant difference between patients under and over 40 regarding engraftment times was found. Therefore, the upper age limit of HCT from a fully matched sibling donor can be raised above 40 years for appropriate patients. For patients over 40 years of age with a fully HLA-matched sibling donor, patients with severe AA or high-risk HMDS with a low probability of response to IST can be transplanted in experienced transplantation centres if they do not have comorbidities and are willing for transplantation.

The risk of chronic GvHD increases with using Peripheral blood stem cells (PBSC) as a stem cell source. Therefore, bone marrow as a stem cell source is recommended for all patients with AA. PBSC are an alternative stem cell source when bone marrow cell collection is contraindicated, or the donor is unwilling to donate bone marrow. Despite early engraftment with the use of PBSC, it has been shown that inferior results are obtained, especially in young patients.[10] A study confirmed the survival advantage of bone marrow grafting in all age groups.[11] Our study's major stem cell source was bone marrow. Acute GvHD developed in 8.3% of the patients. The stem cell source was peripheral blood in this patient with acute GvHD. No patient developed chronic GvHD. Therefore, we reported relatively low GvHD rates compared to the literature.[9-13] Although acute GvHD can be controlled in almost all cases and is associated with a very low risk of death, chronic GvHD remains a problem. Cumulative incidences ranging from 0% to 44% have been reported when the marrow is used as a graft source.[8,14-17] The incidence of chronic GvHD was 16% in patients in whom bone marrow grafts were limited to $\leq 2.5 \times 10^8$/kg nucleated cells.10 It was thought that the low rate of chronic GvHD in our study might be related to the low number of cells in the infused product.

Our cohort's median time to neutrophil and platelet engraftment was within the range reported in the literature.[12-14] The amount of CD34 positive cells in the infused product (10^6/kg) did not correlate with neutrophil and platelet > 20.000/mm^3 engraftment time (days). However, there was a statistically significant negative correlation between the number of CD34 positive cells in the infused product (10^6/kg) and platelet > 50.000/mm^3 engraftments (days) ($r = -0.670$, $p = 0.024$). In agreement with our results, a study conducted in allo-HCT patients suggests that low CD34+ cell counts in allografts may be associated with delayed platelet engraftment.[18]

Most of our study patients were red cell transfusion-dependent before transplantation and had high ferritin levels. A significant positive correlation was found between ferritin elevation and platelet engraftment times. Some studies have reported lower OS among patients with high pre-transplant ferritin levels.[19,20] This was not observed in our study cohort due to the small sample size.

A low stem cell dose is known to increase the risk of GF, and a bone marrow stem cell dose of at least 2×10^6 CD34+ cells/kg is recommended.[21] Fatal GF is frequently seen in 3-5% of patients with severe AA. The aetiology of GF includes previous immunosuppressive therapy, excessive transfusion, advanced age, viral infection, and drug effects. GF is a life-threatening complication of HCT. Therapeutic strategies for GF include cytokine therapy, immunosuppressive therapy, donor leukocyte infusion (DLI), allogeneic PBSC, and second HCT.15 The median number of in-

fused CD34+ cells in our study was 0.98 × 10^6/kg in bone marrow-derived products and 5.67 × 10^6/kg in PBCS. While primary GF was not observed in any of the patients, secondary GF was observed in one transplant whose stem cell source was PBCS. Similarly, there were cases in the literature that were successfully treated for GF.[13]

In our study, no fatal infection was observed in the post-transplant period. FEN developed in 41.6% of patients after transplantation. The median duration of FEN was +11th day of transplantation. There was no growth in the cultures of 3 of these patients, while gram-negative bacteria growth was observed in 2 patients. The incidence of CMV infection was 50%. This rate was within the range reported in the literature.11,14 We also observed that CMV infection was significantly higher in patients transplanted after the COVID-19 pandemic (33% before and 67% after COVID-19).

The limitations of our study included the fact that it was a single-centre retrospective study and the number of patients was relatively small.

CONCLUSIONS

We concluded that allo-HCT should be considered first-line treatment in patients aged 40-50 with SAA who have HLA-matched sibling donors without comorbidities. Patients aged 40-50 years with a diagnosis of HMDS and high-risk characteristics should be evaluated for sibling HLA antigen compatibility, and transplant-eligible patients with fully matched sibling donors should be considered for Allo-HCT as first-line treatment.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Bursa Uludag university, Bursa, Turkey. (Decision number: 2023-17/12, date: 19.10.2023).

Authors' Contribution

Study Conception: TE, VÖ; Study Design: TE, VÖ; Literature Review: TE, VÖ; Critical Review: TE, VÖ; Data Collection and/or Processing: TE, VÖ,; Analysis and/or Data Interpretation: TE, VÖ; Manuscript preparing: TE, VÖ.

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Intensive Care

Contrast-induced acute kidney injury in patients followed at the intensive care unit after aneurysmal subarachnoid hemorrhage (Fisher grade IV) surgery: A Retrospective study

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ABSTRACT

Background Contrast-enhanced imaging studies are widely used to diagnose and follow up acute cerebrovascular diseases. Exposure to contrast media may lead to nephropathy. This study investigated the incidence of contrast-induced acute kidney injury during intensive care follow-up of patients who underwent aneurysmal subarachnoid haemorrhage surgery and the impact of this condition on patient outcomes.

Material and Methods Patients >18 years of age with no known renal injury and admitted to the intensive care unit after Fisher Grade IV aneurysmal subarachnoid haemorrhage and surgery between January 2017 and June 2022 were retrospectively analysed. Renal injury was defined as a renal injury occurring within 48 hours of exposure to contrast media in line with the Kidney Disease Improving Global Outcomes criteria.

Results Among the 85 patients with subarachnoid haemorrhage who received at least one contrast medium, the mean age was 55, and 40% were female. 11.8% of the patients were found to have early acute kidney injury and were non-oliguric. At 48 hours, six, three, and one patients had Stage 1, 2, and 3 injuries, respectively. None of the patients required renal replacement therapy. Patients received a mean of 2 mL/kg/h saline infusion after contrast media administration and had a mean arterial pressure of 93.6 mmHg. There was no association between acute kidney injury and comorbidities, Glasgow coma scale, or APACHE II scores.

Conclusions The study found that the incidence of contrast-induced acute kidney injury was low and transient in patients followed at the ICU after aneurysmal subarachnoid haemorrhage (Fisher Grade IV) surgery. Adequate hydration and hemodynamic stability were found to be effective in reducing acute kidney injury in these patients.

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INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH) is a devastating condition with high mortality and morbidity.[1] Acute brain injury causes changes in hemodynamic functions due to catecholamine fluctuations and other neurohumoral changes. It increases the risk of acute kidney injury (AKI).[2] The risk of renal dysfunction may be higher for patients with hypertension, diabetes mellitus, and those on nephrotoxic drugs. AKI occurring after aSAH contributes to increased mortality and morbidity.[3]

Computed tomography (CT) is an important imaging modality to diagnose and follow up various diseases. In some cases, intravenous contrast media (IVCM) administration may be required to improve image quality.[4] Contrast agents used in imaging studies to diagnose and follow up intracranial aneurysms are thought to cause an increased risk of renal injury.[5]

IVCM administration has been reported to be the third most common cause of hospital-acquired AKI.[6,7] Increasing contrast media (CM) use has led to growing interest in contrast-induced nephropathy in recent years.6 Contrast-induced AKI (CI-AKI) is an acute decline in renal function after intravascular administration of contrast medium without an alternative cause.[8] The pathophysiological basis of CI-AKI has yet to be fully understood. Still, it is thought to be related to an interaction of hemodynamic changes, an increase in free oxygen radicals, and direct toxic effects on renal tubular cells.[9] IVCM used in imaging is thought to increase the risk of AKI, especially in the high-risk population admitted to the intensive care unit (ICU) after aSAH.[10] This study sought to determine the incidence of AKI according to Kidney Disease Improving Global Outcomes (KDIGO) criteria and its effects on outcomes among patients who had undergone IVCM-enhanced imaging during postoperative care at the ICU after aSAH.

MATERIAL AND METHODS

After obtaining approval from the ethics committee (2011-KAEK-25 2022/06-06), the authors scanned hospital records to identify adult patients aged ≥ 18 years who had received at least one contrast-enhanced cranial radiologic imaging during follow-up at the ICU after surgery for aSAH by the same surgical team between January 2017 and June 2022. Patients were excluded if they had a history of chronic kidney disease, AKI, need for dialysis at the time of hospitalisation, repeated hospitalisations (referral from different department, readmission to intensive care within one month), and missing medical records (incomplete creatinine data in the first 48 hours after IV contrast agents [specimen rejection]). The study was conducted in accordance with the Declaration of Helsinki. This study used the AKI definition published in 2012 by the KDIGO working group (Table 1).11 This definition was based on 24 and 48-hour levels after contrast exposure.

Clinical data were retrospectively analysed using the hospital information system database and patient medical records. The authors recorded demographic variables (age and sex), comorbidities, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Glasgow Coma Score (GCS), IV fluid therapy, urine output, haemoglobin and serum creatinine levels before contrast-enhanced CT (CECT), serum creatinine levels at 24 and 48 hours after CECT, additional risk factors for AKI after ICU admission including sepsis, hemodynamic fluctuations (mean arterial pressure below 60 mmHg and/or need for high vasoactive drugs [> 0.1 microgram/kg/min]), presence of potential nephrotoxic drugs (aminoglycosides, glycopeptides, trimethoprim-sulfamethoxazole, loop diuretics, etc.), n-acetylcysteine (NAC) therapy, contrast agent used and its quantity, the requirement for renal replacement therapy (RRT) within 48 hours of CECT, length of ICU stay, need for permanent renal support at discharge from ICU and ICU discharge status.

Statistical analysis

Patient data collected for the study were analysed using the IBM Statistical Package for the Social Sciences version 23.0 for Windows (IBM Corp., Armonk, NY). Descriptive values were expressed in frequency and percentage for categorical data and median, minimum, and maximum for continuous data. Intergroup comparisons were performed using the Mann-Whitney U test, and categorical variables were compared using the Chi-squared or Fisher's exact test. Statistical significance was set at $p < 0.05$.

RESULTS

The study included 85 patients who were followed at the general ICU after aSAH surgery between January 2017 and June 2022 and met the inclusion crite-

Table 1. KDIGO AKI definition.[11]

AKI stage	Serum creatinin	Urine output
I	1.5-1.9 times baseline or ≥ 0.3 mg/dL increase	< 0.5 mL/kg/h for 6-12 hours
II	2.0-2.9 times baseline	< 0.5mL/kg/h for ≥ 12 hours
III	3.0 times baseline or increase in SCr to ≥ 4.0 mg/dL or initiation of RRT or in patients < 18 years, decrease in eGFR to < 35 mL/min/1.73 m^2	< 0.3 mL/kg/h for ≥ 12 hours or anuria for ≥ 12 hours

KDIGO: Kidney Disease Improving Global Outcomes, AKI: acute kidney injury, SCr: serum creatinine, RRT: renal replacement therapy, eGFR: estimated glomerular filtration rate.

ria (Figure 1). One patient who developed meningitis after aSAH surgery, one who was shocked at the imaging time, and one with only one kidney were excluded. Patients who underwent CECT imaging at our institution during the study's time frame received iohexol (omnipaque, GE Healthcare, USA) and iopromide (ultravist, Bayer Healthcare, Germany) at 0.5-0.75 mL/kg.

According to the Fisher classification system, all patients in the study were diagnosed with Grade IV aSAH.[12] The anterior cerebellar aneurysm was present in 76 patients (89.4%), and the posterior cerebellar aneurysm was present in 9 (10.6%). Seventy-two patients (84.7%) had external ventricular drainage systems in the postoperative period.

Thirty-four patients (40%) were female, and 51 (60%) were male. The median age was 55 years and ranged 21-86 years. Seven patients (8.2%) were smokers, and 48 (56.5%) had at least one comorbid condition. Hypertension was the most common comorbidity in patients with comorbidities, with 51.8% (n: 44). The patients had a median APACHE II score of 26 (5-67.2) and 8 (3-15) median GCS. The mean haemoglobin level was 11.8 g/dL (8.3-16).

Table 2 showed stages of AKI that developed within the first and second day, as well as clinical and laboratory parameters. At 48 hours, six, three, and one patient had Stage 1, Stage 2, and Stage 3 injuries, respectively. None of the patients required RRT. The length of stay at the ICU ranged from 1 to 180 days, with a median length of stay of 5 days. 57.6% (n: 49) of the patients were transferred from the ICU to the ward, and 42.4% (n: 36) died in the ICU. The distribution of demographic and clinical characteristics of the patients by occurrence of AKI within the first and second day was given in Tables 3 and 4. There was no statistical difference between patients with and without AKI regarding comorbidities, amount of

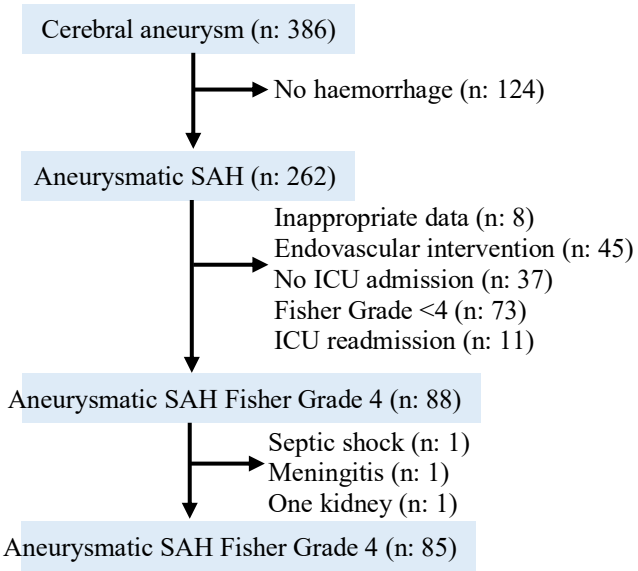

Figure 1. Flow chart of the study. SAH: subarachnoid haemorrhage, ICU: intensive care unit.

Table 2. Distribution of acute kidney injury and clinical characteristics of patients (n: 85).

Age (year)	55 (21:86)
Gender (female/male)	34 (40)/51 (60)
Smoking	7 (8.2)
Comorbidities	48 (56.5)
Hypertension	44 (51.8)
Diabetes mellitus	7 (8.2)
Heart disease	4 (4.7)
Lung disease	3 (3.5)
Other	3 (3.6)
Glasgow coma scale (GCS)	8 (3:15)
APACHE II	26 (5:67.2)
Before CECT	
Haemoglobin	11.8 (8.3:16)
Hematocrit	35.1 (25.3:48.7)
Creatinine	0.8 (0.4:1.8)
BUN	15.8 (4.7:35)
eGFR	96.4 (37.2:164.4)
After CECT first day	
Creatinine	0.8 (0.5:2.1)
BUN	16.9 (5.6:41.0)
eGFR	91.2 (11.3:158.7)
1. day acute kidney injury	
non-AKI patients	75 (88.2)
Stage I	7 (8.2)
Stage II	2 (2.4)
Stage III	1 (1.2)
After CECT second day	
Creatinine	0.8 (0.4:4.4)
BUN	18.3 (7.0:61.2)
eGFR	95.9 (9.8:158.5)
2. day acute kidney injury	
non-AKI patients	75 (88.2)
Stage I	6 (7.1)
Stage II	3 (3.5)
Stage III	1 (1.2)
Sepsis	0
Nephrotoxic drug after CECT (48 hours)	26 (30.6)
Intravenous saline (cc/h; 48 hours)	141.9 (71.4:287.5)
Blood/blood product (48 hours)	6 (7.1)
N-acetylcysteine	12 (14.1)
Vasoactive drug use (48 hours)	17 (20)
RRT (within 48 hours)	0
Length of stay in ICU (day)	5 (1:180)
RRT after discharge	0
ICU discharge	
Exitus	36 (42.4)
Ward	49 (57.6)

APACHE II: acute physiology and chronic health evaluation, CECT: contrast-enhanced computer tomography, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, RRT: renal replacement therapy, ICU: intensive care unit.
The values were expressed as n (%) or median (minimum: maximum).

hydration, hemodynamic parameters, and use of nephrotoxic drugs.

DISCUSSION

This study analysed the KDIGO-defined incidence of AKI within the first 48 hours of contrast-enhanced imaging during ICU stay after aSAH surgery. This study also examined potential risk factors and effects on patient outcomes. Results indicate that 11.76% of the patients had AKI after exposure to CM. These patients did not require RRT during their stay at the ICU. RRT was neither required for seven patients with AKI who were discharged to the ward. The incidence of AKI after exposure to CM is unclear and was reported in one meta-analysis, which ranged from 1% to 20%.[13] These differences have been attributed to differences in the definition of AKI, patient populations and procedures, timing of patient follow-up, and possible changes in patient hydration status.[14] The incidence of CI-AKI reported in the literature varies markedly depending on the definition. A systematic review published by the National Institute for Health and Care Excellence reported a need for full agreement on the definitions for detecting AKI and predicting its outcomes.[15] A prospective study by Jabara[16] used four different definitions to determine CI-AKI and reported that the incidence could vary between 3.3% and 10.5% depending on the definition used.

This study aimed to determine the incidence of CI-AKI according to the criteria adopted by the KDIGO in 2012, which was used in the publications of Laforcade *et al*.[17] in 2021 and included in the latest guidelines of the French Societies of Nephrology and Radiology.[18] Therefore, the incidence reported in our series may not be comparable with studies using different definitions. McDonald *et al*.[19] reported an AKI rate of 9.9% in the group that received IVCM. However, since their study included patients undergoing abdominal, pelvic, and thoracic CT angiography and diagnostic or interventional cardiac catheterisation, they reported that heterogeneity between procedures and patient groups may affect the results. Clec'h *et al*.[20] reported a CI-AKI rate of 16.78% in patients admitted to the medical-surgical ICU. They noted that RRT was required in 29.16% of patients, increased risk of death in the ICU, and prolonged length of ICU stay. They also stated that the populations included in the study had multiple risk factors for the develop-

Table 3. Distribution of demographic and clinical characteristics by occurrence of acute kidney injury (day 1).

Variables	Acute kidney injury (day 1)		*P*-value
	Absent	Present	
Age (year)	56 (30:86)	52 (21:70)	0.336
Gender (female/male)	30 (40)/45 (60)	4 (40)/6 (60)	1.000
Comorbidities	43 (57.3)	5 (50)	0.741
Hypertension	41 (54.7)	3 (30)	0.186
Diabetes mellitus	7 (9.3)	0 (0)	0.592
Glasgow coma scale	8 (3:15)	9 (3:14)	0.626
APACHE II	26 (5:63.9)	32.2 (11.3:67.2)	0.214
Pre-CECT			
Haemoglobin	11.7 (8.6:16)	12.1 (8.3:13.7)	0.364
Hematocrit	35.1 (25.8:48.7)	36.2 (25.3:40.1)	0.433
Creatinine	0.8 (0.4:1.7)	0.9 (0.5:1.8)	0.093
BUN	15.8 (4.7:35)	14.5 (6.9:28.5)	0.854
eGFR	97.6 (37.2:164.4)	87.1 (42.4:154.7)	0.481
Day 1 after CRT			
Creatinine	0.8 (0.5:1.6)	1.5 (1.0:2.1)	< 0.001
BUN	16.4 (5.6:41)	21.7 (8.9:39.3)	0.035
GFR	96.7 (11.3:158.7)	59.1 (28.9:98.3)	< 0.001
Mean arterial pressure (first 24 h)	92.5 (66.6:121.8)	87.5 (70.3:118.9)	0.364
Urine output (hours cc/h)	130.2 (48.8:307)	134.8 (45:200)	0.978
N-acetylcysteine	12 (16)	0 (0)	0.344
Length of stay at the ICU (day)	5 (1:180)	8 (2:105)	0.228
Exit from the ICU			0.737
Ward	44 (58.7)	5 (50)	
Exitus	31 (41.3)	5 (50)	

APACHE II: acute physiology and chronic health evaluation, CECT: contrast-enhanced computer tomography.
The values were expressed as n (%) or median (minimum: maximum).

ment of AKI. The present study was conducted with a patient group (Fisher Grade IV aSAH), which we thought would have fewer confounding factors. We tried to determine the direct effect of CM on the kidney by minimising potential clinical confounders and found that CM had a minimal and transient impact on renal function.

The American College of Radiology reported that AKI after exposure to CM may be associated with the patient's underlying comorbidities rather than with CM.[4] Patients diagnosed with aSAH are usually relatively healthy young individuals. These patients have a low prevalence of comorbidities such as diabetes mellitus, hypertension, and heart failure.[21] Although the patient group in this study was relatively young (a mean age of 55), 48 (56.5%) had at least one comorbid condition that could affect the kidney. In addition, six patients who developed AKI had at least one comorbidity. A history of premorbid hypertension is a known risk factor for aSAH.[22] Although hypertension was present in 51.8% of the patients in this study, it had no significant association with AKI. However, the definition and duration of premorbid hypertension are unknown.

The incidence of CI-AKI in patients with mild-to-moderate renal impairment and diabetes mellitus has been reported to range from 9% to 50%.23 Unlike McCullough's series[24], which included 24.8% diabetic patients and reported that AKI might be associated with diabetes mellitus, the series in the present study had a lower incidence of diabetes (8.2%). While none of the patients who developed AKI on day 1 had diabetes mellitus, 10% of those who developed AKI had diabetes mellitus. Although one study reported that CM injection may increase susceptibility to AKI in patients with diabetes mellitus [25], the present study found that the presence of diabetes mellitus did not increase the risk of AKI. This difference may be due to

Table 4. Distribution of demographic and clinical characteristics by occurrence of acute kidney injury (day 2).

Variables	Acute kidney injury (day 2)		*P*-value
	Absent	Present	
Age (year)	55 (23:86)	57 (21:72)	0.978
Gender (female/male)	29 (38.7)	5 (50)	0.512
	46 (61.3)	5 (50)	
Smoking	7 (9.3)	0 (0)	0.592
Comorbidities	42 (56)	6 (60)	1.000
Hypertension	39 (52)	5 (50)	1.000
Diabetes mellitus	6 (8)	1 (10)	1.000
Glasgow coma scale (GCS)	8 (3:15)	13 (3:15)	0.422
APACHE II	26.2 (5:58)	21 (8.7:67.2)	0.881
Pre-CECT			
Haemoglobin	11.8 (8.6:16)	11.8 (8.3:13.4)	0.662
Hematocrit	35.1 (25.8:48.7)	35.6 (25.3:39.4)	0.521
Creatinine	0.8 (0.4:1.8)	0.8 (0.6:1.3)	0.854
BUN	15.8 (4.7:35)	14.8 (11.0:34.1)	0.989
eGFR	96.4 (37.2:154.7)	92.4 (42.4:164.4)	0.761
CECT 48 hours			
Creatinine	0.8 (0.4:2.0)	1.4 (0.9:4.4)	<0.001
BUN	17.8 (7:43)	26.5 (16.8:61.2)	0.001
eGFR	100.5 (36.9:158.5)	47 (9.8:101.6)	<0.001
Mean arterial pressure (first 48 hours)	93.6 (64.8:174.6)	95.2 (73.2:107.1)	0.956
Nephrotoxic drug after CECT	23 (30.7)	3 (30)	1.000
Hourly IV fluid (48 hours)	141.9 (71.4:287.5)	136.3 (92.5:265)	0.723
Urine (cc/h)	132.7 (48.8:307)	115.4 (45:238.2)	0.544
Blood/blood product (48 hours)	6 (8)	0	1.000
N-acetylcysteine	12 (16)	0	0.344
Vasoactive drug use	14 (18.7)	3 (30)	0.411
Length of stay at the ICU (day)	5 (1:115)	7 (2:180)	0.317
Exit from ICU			1.000
Ward	43 (57.3)	6 (60)	
Exitus	32 (42.7)	4 (40)	

APACHE II: acute physiology and chronic health evaluation, CECT: contrast-enhanced computer tomography, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, IV: intravenous, ICU: intensive care unit.

The values were expressed as n (%) or median (minimum: maximum).

the relatively younger age of the patients or the shorter disease duration, which may influence the development of micro- and macrovascular complications of diabetes mellitus. Kellum *et al*.[26] reported that even small increases in serum creatinine may affect survival in critically ill patients. Zhang *et al*.[27] reported that the development of AKI after intracranial aneurysm clipping surgery was associated with poor prognosis. Retrospective studies by McDonald *et al*.[28] and Davenport *et al*.[29] compared clinically similar patients who underwent CT scanning with or without contrast enhancement. Both studies achieved results similar to the present study; exposure to CM did not affect clinical outcomes related to AKI in patients with normal baseline renal functions.

Serum creatinine levels and glomerular filtration rate are important parameters that provide information about renal function.[30] This study minimised confounding factors by recruiting patients with normal baseline glomerular filtration rate and creatinine levels. Furthermore, good baseline renal functions may reduce the risk of AKI after IVCM exposure in aSAH patients who are relatively young and have few comorbidities. A single-centre retrospective study by Clec'h *et al*.[20] reported a CI-AKI incidence of 16.8% in adult patients who underwent CECT imaging for emergency diagnosis. However, they noted that they were unable to investigate how the incidence of AKI

was affected by the presence of coexisting risk factors for kidney injury, such as sepsis, nephrotoxic drugs, and hemodynamic impairment, or how it was affected by CM volume and implementation of prophylactic measures. Hydration, a prophylactic measure against CI-AKI, is important in preventing ischemic conditions.[31] A prudent approach for all patients receiving CM is to ensure adequate hydration before and after imaging.[32] Urine viscosity increases in proportion to the volume of CM injected. Adequate hydration has been shown to decrease urine viscosity.[33] To better characterise patients regarding hydration status, this study analysed intravenous fluid administered to the patients. The guidelines published by the European Society of Cardiology in 201434, which contains important preventive strategies against CM-associated AKI, recommend peri-procedural hydration with intravenous saline at a rate of 1-1.5 mL/kg/h 3-12 hours before CM administration and 1-1.5 mL/kg/h 12-24 h after the procedure. The patient population in the present study received a mean saline infusion of 2 mL/kg/h within the first 48 hours of CM administration. This fluid regimen may have played a role in the transience of AKI. The same guideline recommends using iso-osmolar or low-osmolar CM in addition to hydration.[34] The contrast agents administered to the patients in this study were nonionic iso-osmolar iohexol (omnipaque, GE Healthcare, USA) and iopromide (ultravist, Bayer Healthcare, Germany). Some authors doubt whether modern iodinated (iso-osmolar) contrast is nephrotoxic.[35] Several studies have evaluated the renal safety of nonionic contrast agents in patients with impaired renal function after intra-arterial contrast injection only during percutaneous coronary angiography (PCA).[35] However, few publications have evaluated the incidence of CI-AKI after intravenous injection of iso-osmolar CM and found a low risk.[36,37] Although CI-AKI found in this study was higher than in previous studies, it was transient and did not lead to permanent kidney damage or need for renal support. The amount of iso-osmolar CM used for patients in this study was similar, approximately 0.5-0.75 mL/kg and may be relatively low compared to doses used in interventional intra-arterial applications such as PCA.

N-acetylcysteine (NAC) is most commonly used as a mucolytic in ICUs to facilitate ciliary activity.[38] It is also used for the treatment of paracetamol toxicity[39] and hepatic failure[40], acute lung injury,[41] sepsis, renal failure, and carbon monoxide poisoning.[42] Tepel *et al*.[43] reported that IV or oral administration of NAC was nephroprotective in preventing CI-AKI by eliminating free radicals. On the other hand, Suva *et al*.[44] emphasised that the use of NAC to prevent CI-AKI ended with inconsistent and uncertain results. There is no routine protocol used to avoid CM damage in our unit. However, NAC has been reported to be a potential prophylactic treatment against CI-AKI.[45] In the present study, NAC was used to increase mucolytic activity in 14.1% of the patients in the ICU. Analysis of the prophylactic role of NAC against CI-AKI in this study did not yield a statistical difference. However, none of our patients who developed AKI had received NAC therapy, suggesting it might be clinically important. This effect can be determined in future studies with a larger sample size.

Many studies suggested that most cases of AKI following contrast administration may be related to incidental nephrotoxic exposures (e.g., hypovolemia, cardiac dysfunction, and infection) that were present at the time of CM exposure.[46,47] CI-AKI prevention requires discontinuing nephrotoxic drugs and adjusting hemodynamic parameters.[48] In the present study, 30.6% of the patients were on nephrotoxic medications, and there was no significant difference between patients with and without AKI. The short hospital stays among the patients in this study may have played a role in preventing the occurrence of AKI caused by nephrotoxic drugs.

Zhang *et al*.[28] reported that preoperative aneurysm rupture was a risk factor for AKI. The existence of a link mediated by cytokines in this process is yet to be investigated.[49,50] All of the patients in this study were patients with ruptured aSAH. Patients with above-normal creatinine levels during postoperative follow-up at the ICU were excluded from the study to try to rule out the possibility of an early contribution of the procedure to the development of AKI. However, cytokine release may also have an effect on AKI during the later period. Although the combination of induced hypertension, hypervolemia and hemodilution (triple-H therapy) is often utilised to prevent and treat cerebral vasospasm after aSAH, its efficacy and precise role in managing the acute phase remains unclear.[51] In this study, triple-H therapy is hypothesised

to impact CI-AKI outcomes. Hemodynamically, this hypothesis seems supported by mean arterial pressures as high as 93.6 (64.8-174.6) mmHg.

GCS is widely used to assess patients with head trauma or other types of acute brain injury to guide early treatment. Lee *et al*.[5] investigated the incidence and clinical effect of CI-AKI after coil embolisation in patients with aSAH. They found that 50% of the patients in the CI-AKI group had a GCS below [8], compared to 19.7% in the group without CI-AKI. They reported that a low baseline GCS score may be associated with CI-AKI. Patients followed during postoperative ICU in the present study had a mean baseline GCS score of [8]. There was no significant correlation between GCS and AKI observed at 24 and 48 hours after CM exposure. Compared with other types of AKI (such as ischemic AKI), contrast-induced AKI is usually characterised by a relatively rapid recovery of renal functions. Serum creatinine levels that increase in CI-AKI return to baseline within 3-7 days.[52] Since AKI is typically mild, most patients (except those with moderate-to-severe chronic kidney disease) are non-oliguric.[53] This suggests that treatments to maintain hemodynamic stability and adequate hydration are effective.

In the present study, the mortality rate was 36%, and transient AKI that developed early during hospital stay was not associated with mortality. Ehrlich *et al*.[54] reported that renal functions were not affected after contrast-enhanced CT in patients presenting with acute stroke, and CT angiography offered additional clinical value. This result is in line with the present study, which showed that renal injury was transient and reversible in patients with normal renal function during diagnosis and treatment.

Limitations

The major limitation of this retrospective study was that patients with aSAH who received CECT were not compared with those who did not. Thus, the isolated effect of aSAH on renal function could not be investigated. However, this can be overlooked since the primary aim of this study was not to determine the absolute toxicity of IVCM but to determine the incidence of CI-AKI and to identify potentially dangerous conditions that should be considered before exposing patients to IVCM. Also, the small number of patients with CI-AKI may increase the possibility of error. Therefore, a larger-scale study may improve the statistical reliability of the associated findings. Finally, this study excluded patients with AKI and thus did not investigate the adverse effect of CM on renal function in patients with aSAH and AKI or CI-AKI.

CONCLUSIONS

This study found that young patients with mild comorbidities and without aggravating factors such as severe anaemia, hypovolemia, and hypotension might have reversible fluctuations in renal function that did not affect clinical outcomes. This means that clinically required imaging studies should not be avoided due to fear of CI-AKI.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Healt of Sience University, Bursa Training and Research Hospital, Bursa, Turkey. (Decision number: 2011/KAEK-25, date: 06.06.2022).

Authors' Contribution

Study Conception: HAK, IC; Study Design: HAK, IC; Literature Review: RA; Critical Review: IC; Data Collection and/or Processing: HAK,; Analysis and/or Data Interpretation: IC; Manuscript preparing: HAK, RA, IC.

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Pathology

Adrenal cystic lymphangioma with radiological, clinical and histopathological findings: Case report

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ABSTRACT

Cystic lymphangiomas are benign lesions originating from lymphatic endothelial cells. It occurs due to developmental anomalies of lymphatic vessels. They are usually localized in the head and neck region. Cystic lymphangiomas of adrenal origin are very rare. This presentation aims to report a case of left-sided adrenal cystic lymphangioma detected incidentally on radiological examination due to abdominal pain, with clinical, radiological and pathological findings. A 65-year-old female patient was admitted to our clinic with abdominal pain. In the abdominal examination, the pain was detected in the epigastric region and left the upper quadrant with palpation. No pathology was observed in the complete blood count and biochemical parameters, except for a CRP elevation of 10.2 mg/dL. In examination with ultrasonography (US), in the left upper quadrant of the abdomen, in the localisation of the adrenal gland, a multilocular cystic lesion with partially dense contents, which is not vascularised by Doppler US, containing thin echogenic septa was detected. Enhanced contrast multidetector computed tomography was performed to determine the nature and characterisation of the mass. A 60x57 mm cystic lesion with multi-lobulated contour and fluid density was defined in the left adrenal gland. The patient was diagnosed with cystic lymphangioma radiologically and was operated upon due to symptoms and size. Pathological diagnosis was reported as cystic lymphangioma. Preoperative clinical and radiological correct diagnosis is critical because the treatment approach and prognosis may differ from other adrenal tumours or cysts.

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INTRODUCTION

Cystic lesions of adrenal origin are rare, and their incidence has been reported as 0.06% in the literature. Cystic lymphangiomas of adrenal origin, also known as adrenal lymphangiomas, are extremely rare tumours. Due to their rarity, specific incidence rates for adrenal lymphangiomas are not well-established in the medical literature.[1] Cystic adrenal gland lesions are classified into four main histopathological groups: endothelial cysts, pseudocysts, epithelial cysts and parasitic cysts. Endothelial-derived cysts are further subdivided into lymphatic and angiomatous cysts based on the histological origin of the endothelium. Lymphatic cysts are also called adrenal lymphangiomas and adrenal cyst of lymphangiomatous origin (ACLO) according to their single or multi-local status.1 Cystic lymphangiomas originate from lymphatic endothelial cells. It occurs due to the developmental abnormality of the lymphatic channels. They are usually localised in the head and neck but can develop in different body parts, including the adrenal glands. Although they may occur at any age, it has been reported that they are more common in decades 3-6, in females and on the right side.[2]

Adrenal gland cystic lymphangiomas are typically discovered incidentally during imaging studies such as ultrasonography (US), computed tomography scans, or magnetic resonance imaging performed for unrelated reasons or intra-abdominal operations.[3-5] An adrenal gland cystic lymphangioma is characterised by forming cystic spaces filled with lymphatic fluid. They are usually asymptomatic. In some cases, however, larger cystic lymphangiomas can cause symptoms such as abdominal pain, a palpable mass, or hormonal imbalances if they interfere with the normal functioning of the adrenal gland. There is limited information available about their specific characteristics and management. Treatment is surgical if necessary. When deciding on surgery for adrenal masses, their size, hormonal activity, imaging findings suggestive of malignancy, and growth rates on follow-up examinations should be considered.[6] This presentation aims to report a case of cystic lymphangioma of adrenal origin, which was detected incidentally in the radiological examination due to abdominal pain, with clinical, radiological and pathological findings.

CASE REPORT

A 65-year-old female patient was admitted to our clinic with a complaint of abdominal pain for three weeks. The abdominal examination detected pain in the epigastric region and the left upper quadrant with palpation. No pathology was observed in complete blood count and biochemical parameters, except for a 10.2 mg/dL increase in CRP. In the US examination of the entire abdomen, In the left upper quadrant of the abdomen, in the localisation of the adrenal gland, a multilocular cystic lesion with partially dense contents, which is not vascularised by Doppler US, containing thin echogenic septa was detected (Figures 1 and 2).

In intravenous contrast-enhanced multidetector computed tomography (MDCT) performed for the nature and characterisation of the mass, a 60 × 57 mm cystic lesion with multi-lobulated contour and fluid density was defined in the left adrenal gland (Figures 3 and 4). The patient was diagnosed with cystic lymphangioma radiologically and was operated upon due to its symptoms and size. A cystic lesion on the cross-sectional surface measuring 6 × 5 × 2 cm was observed in the macroscopic evaluation. Histopatho-

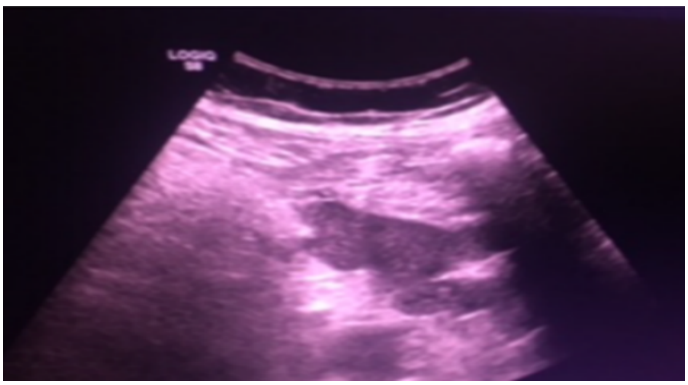

Figure 1. Multilobular, dense, cystic lesion with thin echogenic septa on abdominal ultrasonography examination.

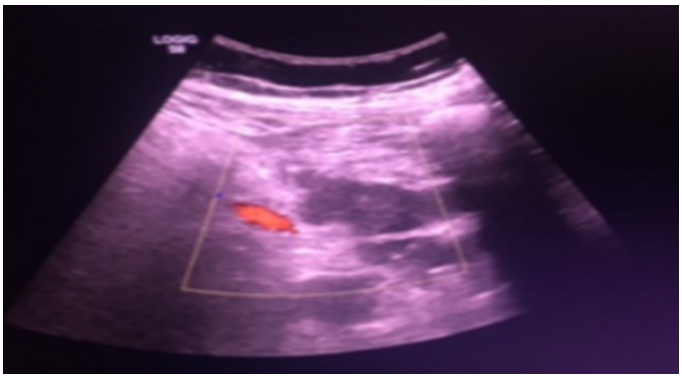

Figure 2. Non-vascularized, slightly dense, multiloculated cystic lesion on Doppler ultrasonography examination.

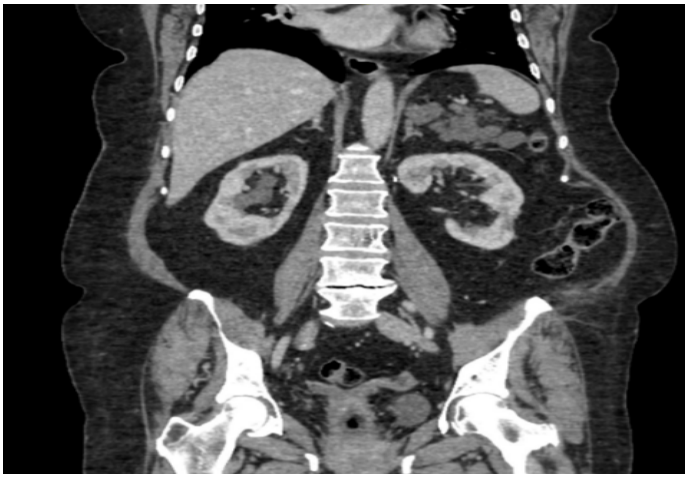

Figure 3. Coronal computed tomography sections: non-enhancing multilobulated cystic lesion in the left adrenal gland.

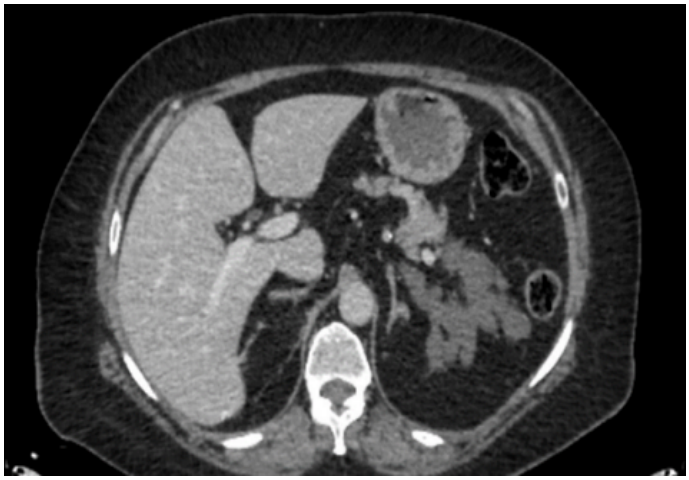

Figure 4. Axial computed tomography sections: multilobulated, non-enhancing cystic lesion in the left adrenal gland.

logical examination revealed that the lesion consisted of cystic structures lined with endothelium, and the case was reported as cystic lymphangioma (Figure 5).

Radiological imaging was performed with (GE brand Logic S7 Expert model) ultrasound and 64-section MDCT (Optima CT 660, General Electric Medical Systems, Milwaukee, Wisconsin, USA) devices. Water-soluble nonionic intravenous contrast agent (350 mgI/mL) was administered with an automatic double-injector system at a dose of 1 mL/kg at a rate of 4-5 mL/s through an 18-gauge cannula inserted into the antecubital vein. Intravenous contrast agent timing was performed with a bolus monitoring technique.

DISCUSSION

Adrenal lymphangioma typically presents as painless masses and may grow slowly over time. Symptoms, if present, can vary depending on the size and location of the cystic lymphangioma. They may include abdominal pain or discomfort, palpable mass in the abdomen, hormonal disturbances if the tumour affects the production of adrenal hormones, or compressive symptoms if it presses on nearby structures. Mostly, adrenal gland lymphangiomas may be discovered incidentally during imaging studies.[7] Extensive lesions may produce symptoms related to rupture or be detected incidentally.6 Our case was admitted to

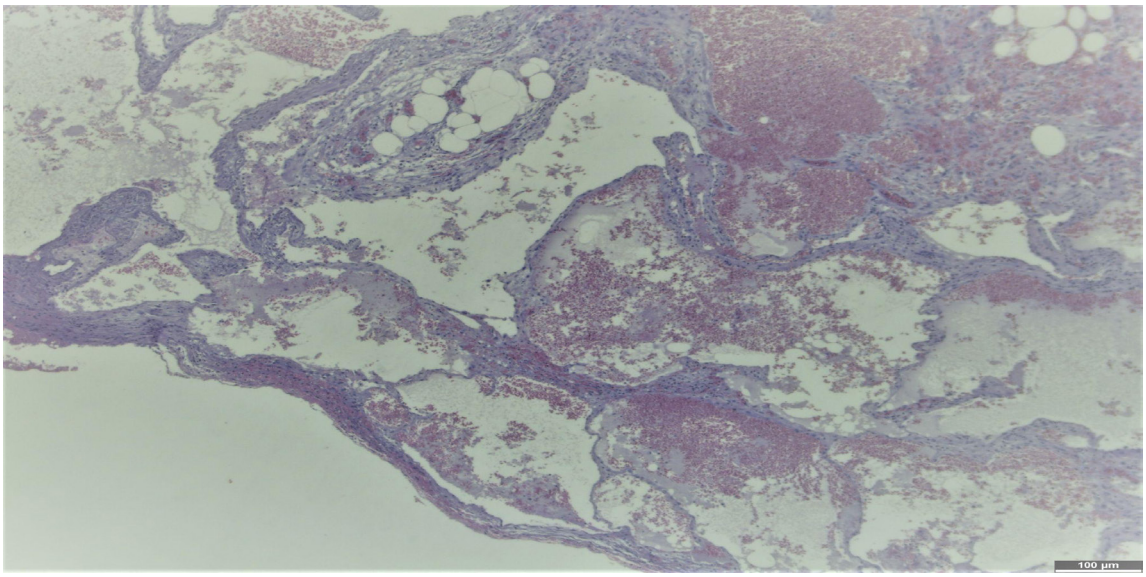

Figure 5. Cystic structures lined with endothelium (hematoxylin and eosin x40).

our clinic with abdominal pain for three weeks.

An adrenal gland cystic lymphangioma is usually diagnosed through imaging studies. These imaging techniques can help visualise the tumour and its characteristics, such as size, location, and cystic nature.[3-5] The technical developments in radiology and the availability of devices such as US, computed tomography, and magnetic resonance examination in many centres have increased the rate of diagnosing adrenal cystic lymphangioma cases. Radiologically, they appear as multilocular cystic lesions, which are approximately 3-6 cm in size, thin-walled, may contain septa, rarely show contrast enhancement in the walls and septa, and may contain millimetric calcifications at a low rate.[2,8] Although rare, it can grow rapidly and reach gigantic sizes.[9] During the abdominal examination performed with the US in our case, Doppler US revealed a multilocular cystic lesion with no vascularity, partially dense content, and thin echogenic septa in places.

Treatment options for adrenal gland lymphangiomas may include surgical removal of the tumour if it is causing symptoms or if there is a concern for malignancy. In some cases, a partial or complete removal of the affected adrenal gland may be necessary. However, a laparoscopic minimally invasive method can also be applied.1 There is no consensus on the surgical indication's mass size. Some authors recommended surgery if it is larger than 6 cm and surgery if it is smaller than 6 cm and has a risk of malignancy. Some authors have recommended surgery for masses larger than 3 cm.6,10 However, due to the rarity of these tumours, there is limited consensus on the optimal management approach, and decisions are often made on a case-by-case basis. Our patient was diagnosed with cystic lymphangioma radiologically and was operated upon due to its symptoms and size.

In the radiological differential diagnosis, adrenal cyst, adrenal hemangioma, retroperitoneal teratoma, cystic pheochromocytoma, cystic schwannoma, adrenal hydatid cyst and cystic metastasis can be considered.[11-13] However, the multilobular lesion, containing septa and a dense cystic appearance, suggests cystic lymphangioma. If contrast enhancement occurs in radiological images, it may be confused with adrenal carcinoma.[9] In our case, a 60 × 57 mm cystic lesion with multilobular contour and fluid density was observed in the left adrenal gland on IV contrast-enhanced MDCT.

Although there may be diagnostic difficulties in some cases before the operation, the pathological diagnosis of the surgically removed cyst is not difficult. Some of the radiologically diagnosed cysts are not included in the differential diagnosis because of their histologically distinctive histological features. In case of difficulty in diagnosis, differential diagnosis is made using an antibody panel such as CD31, CD34, pan cytokeratin AE-1/AE-3, D2-40, and factor VII from histopathologically similar cystic lesions.[2] Since there was no difficulty in the differential diagnosis in our case, an immunohistochemical examination was not performed.

CONCLUSIONS

It is important to consult a qualified healthcare professional, such as an endocrinologist or a surgeon specialising in adrenal gland disorders, for an accurate diagnosis and appropriate treatment plan.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: KG; Study Design: KG, ANK; Literature Review: ASA, AM; Critical Review: ANK; Data Collection and/or Processing: ASA, AM,; Analysis and/or Data Interpretation: ANK, AM; Manuscript preparing: ASA, AM, KG.

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An unusual cause of bilateral adrenal incidentaloma: a case report of primary adrenal lymphoma

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ABSTRACT

Primary adrenal lymphoma (PAL) is an extremely rare among the causes of adrenal incidentaloma. Most were diagnosed with adrenal insufficiency and B symptoms (unexplained weight loss, night sweats, fever). This article presented a 57-year-old woman who was investigated for bilateral adrenal masses found incidentally on computed tomography (CT). Physical examination and laboratory tests revealed no evidence of adrenal insufficiency or B symptoms. Only 24-hour urinary metanephrine and normetanephrine excretion were increased. Tumour F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) scan showed the greatest dimension was 14 cm in the left adrenal mass and the maximum standardised uptake value (SUV max) was 26.1 (relative to mean SUV in the normal liver parenchyma, which was 2). An adrenal biopsy was performed after taking adequate precautions against the possibility of a catecholamine crisis. Histopathology revealed high-grade B-cell lymphoma. Bone marrow involvement and brain metastasis were not observed. She received the R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen and intrathecal methotrexate therapy as central nervous system prophylaxis. The patient responded well to treatment, and close clinical follow-up continues. PAL should always be considered when a bilateral adrenal mass is detected.

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INTRODUCTION

An adrenal incidentaloma is incidentally detected adrenal lesions during routine imaging without complaints or physical examination findings originating from the adrenal gland.[1] Nonfunctional adrenocortical adenoma, adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma, metastases, and primary adrenal lymphoma (PAL) are the leading causes of the aetiology. However, PAL is an uncommon cause of adrenal incidentaloma, representing less than 1% of all non-Hodgkin lymphoma (NHL).[2,3] It is an aggressive high-grade lymphoma with a poor prognosis. Both adrenal gland invasion is seen in 70% of the cases.[4] Hepatosplenomegaly, lymphadenopathy, and bone marrow involvement can rarely occur. Patients typically present with adrenal insufficiency and B symptoms (fever, night sweats, and weight loss). Rarely, PAL may be diagnosed incidentally.[5-7] In this report, we present a case of an incidental finding of bilateral PAL.

CASE REPORT

A 57-year-old female with a history of hypertension presented to the emergency department with bilateral flank pain (never before) after a fall. The patient referred to our centre as the contrast-enhanced computed tomography (CT) revealed suspicious lesions in the suprarenal region. She was hemodynamically stable on admission, and her physical examination was unremarkable except for bilateral costovertebral tenderness. She had no palpable lymphadenopathy or splenomegaly. Her initial basic laboratory tests were unremarkable except for anaemia of the chronic disease, mild thrombocytopenia (131 × 103/μL) and hyponatremia (126 mEq/L). ACTH and cortisol tests sent initially for adrenal insufficiency evaluation were within normal range. Hyponatremia was consistent with a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elevated levels of beta-2 microglobulin (3,043 ng/mL) and LDH (512 U/L) were found in laboratory tests. A CT scan with adrenal protocol revealed suprarenal lesions, with the largest measuring 10x4 cm on the left, causing adrenal gland thickening and a prominent soft tissue mass surrounding the glands (Figure 1). A tumour F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrated intensive FDG uptake in the left supraclavicular-mediastinal-abdominal-mesenteric lymph nodes and bilateral adrenal masses (Figure 2). The greatest dimension was 14 cm in the left adrenal mass, and the maximum standardised uptake value (SUVmax) was 26.1 (relative to the mean SUV in the normal liver parenchyma, which was 2). Before the left adrenal gland biopsy, in the 24-hour urine, metanephrine and normetanephrine levels were measured to exclude pheochromocytoma, which was

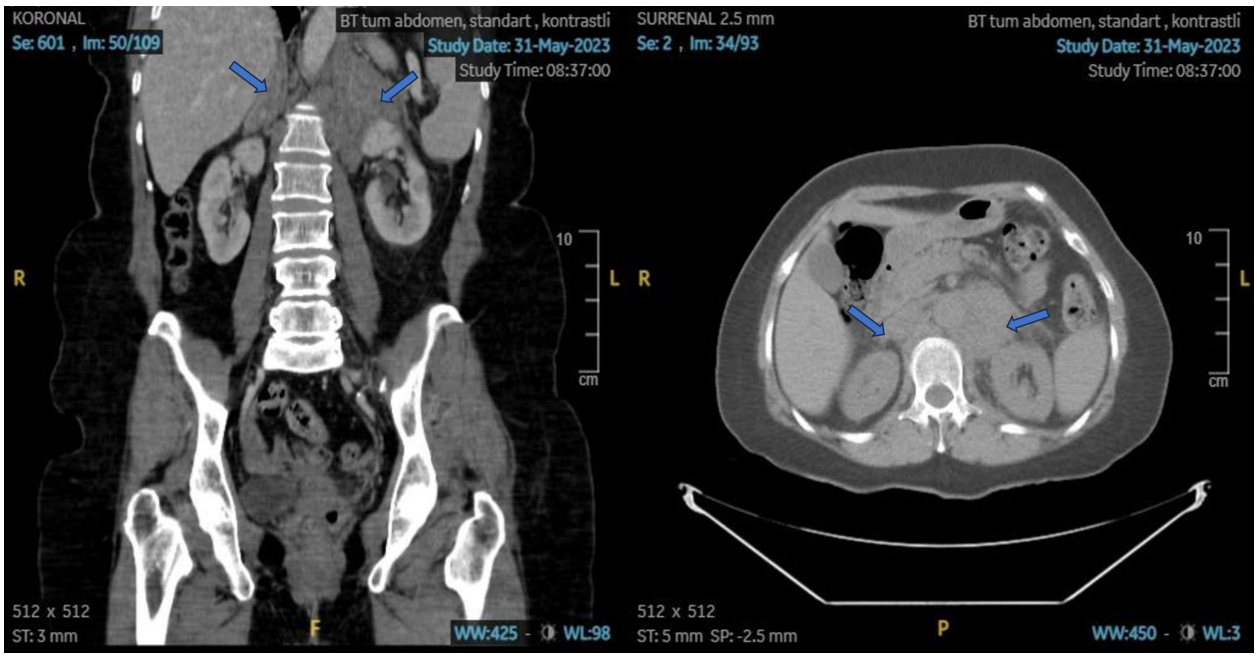

Figure 1. Coronal and axial contrast-enhanced abdominal CT sections showed suprarenal lesions (blue arrow) on the left. The largest was 10x4 cm, causing adrenal gland thickening and a prominent soft tissue lesion surrounding the glands.

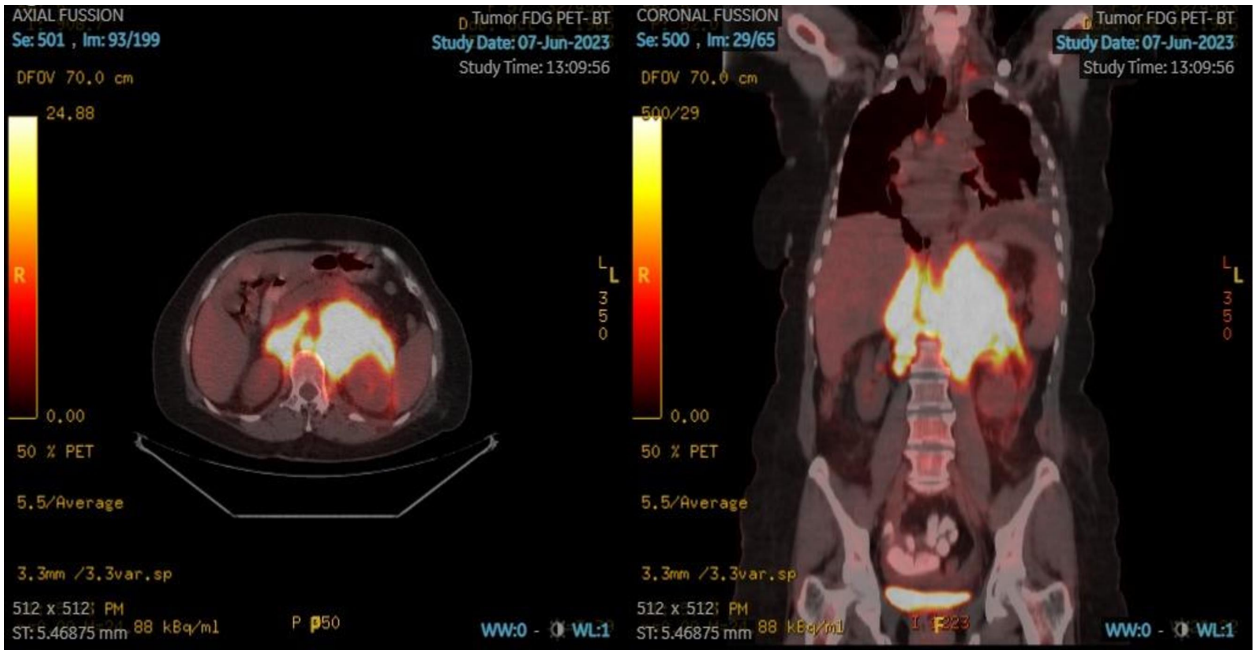

Figure 2. FDG-PET/CT scan showed intense FDG uptake in left supraclavicular-mediastinal-abdominal-mesenteric lymph nodes and bilateral adrenal masses.

found to be significantly increased (metanephrine: 1,432 µg/24-hour, normal range: 164-558 µg/24-hour; normetanephrine 1,426 µg/24-hour, normal range: 128-484 µg/24-hour).

Alpha-blocker therapy (doxazosin 2 mg/day) was initiated for blood pressure control. Biopsy of the left adrenal mass under image guidance revealed a diagnosis of diffuse large B cell lymphoma with non-germinal centre B cell phenotype. Immunohistochemical stains were strongly positive for CD20, Bcl-2 and MUM-1, with faint positivity for Bcl-6, and negative for CD10, CD5, and cyclin D1. Ki67 stain showed a proliferative index of %90. MYC staining was not available in the immunohistochemical examination.

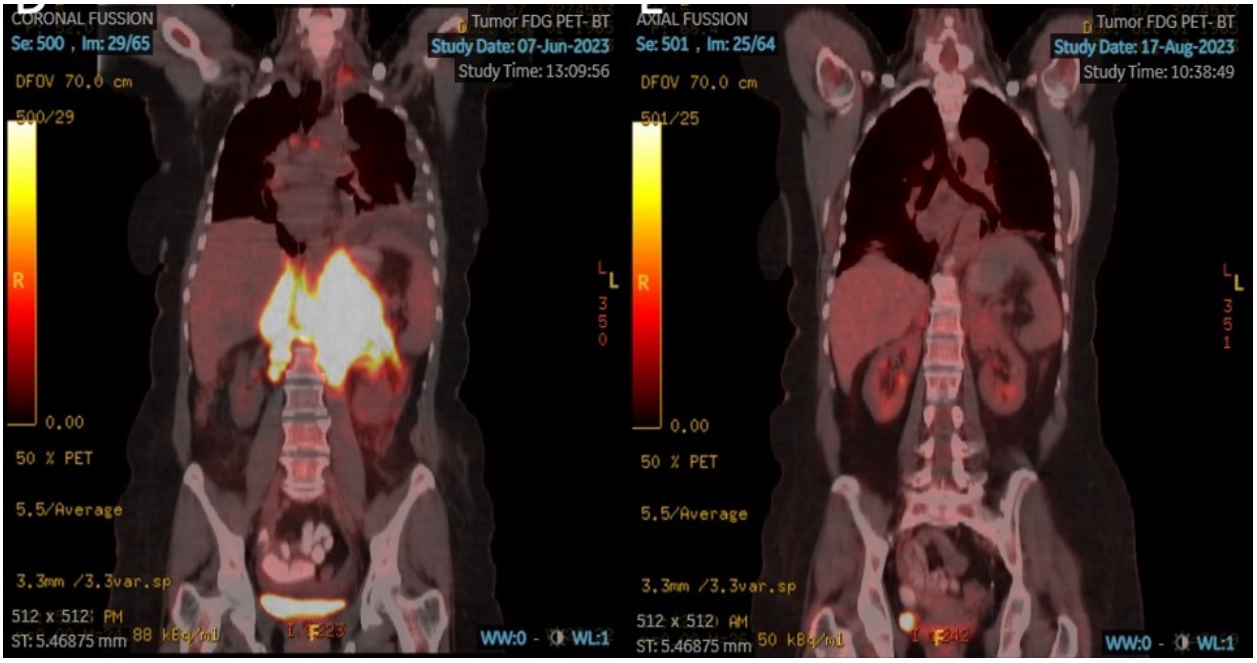

Figure 3. FDG-PET/CT scan in the third month of treatment showed a complete metabolic response.

Bone marrow aspiration and biopsy revealed no bone marrow invasion. No brain metastases were detected on cranial imaging. Her Eastern Cooperative Oncology Group (ECOG) performance status was Grade 2 at diagnosis. She was in the high-risk group by the International Prognostic Index (IPI). According to the Ann Arbor staging system, it was determined as stage 4. The patient received three cycles of R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) regimen, and intrathecal methotrexate therapy was included as central nervous system prophylaxis. PET-CT showed a complete metabolic response at the three months of treatment control (Figure 3). R-CHOP (rituximab, prednisone, vincristine, cyclophosphamide, and doxorubicin) chemotherapy treatment continued, and the patient was under close clinical follow-up.

DISCUSSION

Although there is no consensus, adrenal incidentaloma is described as an adrenal mass greater than 1 cm in diameter detected during imaging for reasons other than suspected adrenal disease. The differential diagnosis for adrenal incidentaloma includes non-secreting adenomas, subclinical cortisolic adenomas, pheochromocytoma, adrenal carcinomas and metastases. Occasionally, PAL may also be an incidental diagnosis on imaging.[5-7] PAL is an exceptionally rare and aggressive form of NHL originating in the adrenal glands. It represents fewer than 1% of all NHL, with approximately 200 cases documented in the literature.[7,8] The exact aetiology of primary adrenal lymphoma remains largely unknown, but it is believed to arise from B-cell lymphocytes within the adrenal glands. Some studies demonstrated that Ebstein-Barr virus (EBV) can be a possible causative agent.[9] Immunocompromised states, such as human immunodeficiency virus (HIV) infection, immunosuppressive therapy, or autoimmune diseases, may increase the risk of developing this malignancy.[10] Genetic defects in p53 and c-kit have also been implicated in the aetiology of the disease.[7]

Primary adrenal lymphoma predominantly affects males with a median age of diagnosis around 60-70 years. Bilateral adrenal gland invasion is seen in the most of the cases.[7] Patients typically present with B symptoms, abdominal pain, back pain, and adrenal insufficiency (AI), while 1% of cases are found incidentally.[5-7] Although 60 to 70% of patients present with AI regardless of the tumour size and involvement,11 our patient did not have any AI-related symptoms and were completely asymptomatic except for flank pain, which was developed after a fall. Some studies suggested that bilateral lesions and older age are factors significantly related to AI in PAL cases. However, the exact cause remains unclear.[7] In addition, regarding differential diagnosis, adrenocortical adenomas and carcinomas are usually unilateral, whereas pheochromocytoma and PAL are usually bilateral. Therefore, the differentiation of pheochromocytoma and PAL is very significant.

An adrenal gland biopsy should be done for definitive diagnosis. Before biopsy, urine catecholamine levels should be measured to rule out pheochromocytoma. If these levels are elevated, alpha-blocker therapy should be initiated to prevent a hypertensive crisis. Diffuse large B-cell lymphoma (DLBCL) is the more prevalent form of PAL, representing over 70% of cases.[7,12] DLBCL can be further classified into two subtypes: germinal centre B cell (GCB) or non-germinal centre B cell (non-GCB). Non-GCB subtype is associated with a worse prognosis.[7,8]

The treatment of primary adrenal lymphoma is challenging, primarily due to its aggressive nature and the lack of standardised therapeutic guidelines. The rarity of the disease limits the availability of large-scale clinical trials, resulting in no universally accepted treatment approach. Treatment options include chemotherapy, radiotherapy, and adrenalectomy. Several studies have demonstrated that adrenalectomy has no benefit to survival.[12-14] Chemotherapy with R-CHOP remains the most used treatment approach for PAL. A retrospective study of 50 primary adrenal lymphoma patients reported that patients treated with the R-CHOP regimen had better overall survival (OS) rates than patients who underwent surgery and received supportive treatment only (84.2% vs 41.7%).10 Another study has shown that patients who received R-CHOP therapy had increased 2-year OS rates compared to patients treated with traditional CHOP regimens (57% vs 38%, $p < 0.001$).[15] Additionally, central nervous system involvement significantly decreases survival in DLBCL cases.[16] Therefore, in our case, methotrexate was administered as intrathecal prophylaxis in addition to standard chemotherapy. However, a recent meta-analysis showed that intravenous or intrathecal CNS prophylaxis did not significantly reduce the recurrence rate in patients at high

risk of CNS.[17]

Primary adrenal lymphoma has a poor prognosis, primarily due to the advanced stage of disease at diagnosis and the aggressive behaviour of the tumour. While earlier studies reported 2-year OS rates of PAL to be 20%, recent studies have demonstrated 2-year OS rates of PAL ranging between 68 and 72.5%.7,10,12 In another study, the estimated 5-year PAL OS rate was less than 20%.18 Our patients were in the high-risk group according to IPI score. Multiple extranodal involvement is a prognostic factor for IPI score. Recent validation studies have also proven this.19 Several factors have been identified as poor prognostic indicators in PAL cases. These include older age, bilateral involvement of the adrenal glands, larger tumour size, high serum lactate dehydrogenase levels, AI, nongerminal centre B-cell-like classification, and a high Ki-67 proliferation index.[2,12,20] All poor prognostic factors were present in our case except AI.

Conflict of Interest

None declared.

Patient consent

Written informed consent for publication of their details was obtained from the patient.

Authors' Contribution

Conception and design: M.T, N.N.G; analysis and interpretation of the data: M.T, N.N.G, M.I.E; drafting of the article: M.T, N.N.G; Critical revision of the article for important intellectual content: U.Y.M, O.A.U; Final approval of the article: M.T, N.N.G, M.I.E, O.A.U.

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