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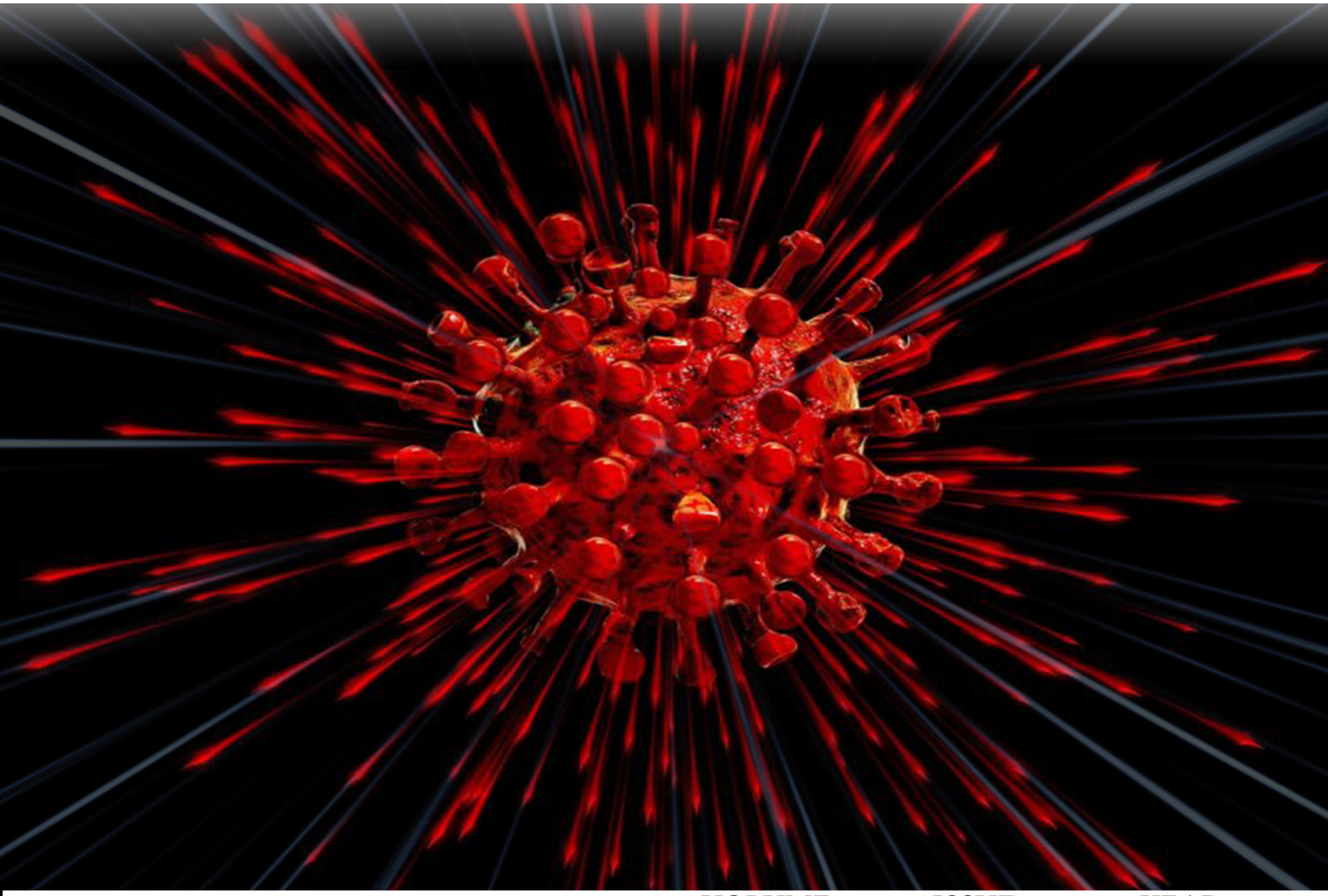

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We are also pleased to announce that the ACMJ has applied for indexing in PubMed and Web of Science. This means that, if our application is successful, our journal will be included in these two major databases, which will make it more accessible to researchers around the world.We are committed to advancing the frontiers of medical knowledge, and we believe that this issue of the ACMJ makes a significant contribution to this goal. We hope that you will join us in our mission to improve the health of people everywhere.

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Lung immune prognostic index as a prognostic predictor in patients with advanced small cell lung cancer

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ABSTRACT

Aims: Identifying prognostic markers in advanced small-cell lung cancer (A-SCLC) patients is important. Therefore, our study aimed to evaluate the prognostic value of pretreatment lung immune prognostic index (LIPI) in A-SCLC.

Methods: This was a retrospective and observational study of A-SCLC patients treated with platinum plus etoposide chemotherapy as first-line treatment. The association of LIPI with progression-free survival (PFS) and overall survival (OS) was analysed.

Results: One hundred eighteen patients were included in this study and divided into three groups LIPI 0 (n=27, 22.9%), LIPI 1 (n=57, 48.3%) and LIPI 2 (n=34, 28.8%). The median PFS of LIPI groups (0/1/2) was 8.9 (95% CI 3.83-13.96), 8 (95% CI 6.41-9.58), and 5.6 (95% CI 4.60-6.60) months, respectively (p=0.1) The median OS of LIPI groups (0/1/2) was 12 (95% CI 9.11-14.88), 10.1 (95% CI 9.16-11.03), and 7.7 (95% CI 6.55-8.84) months, respectively (p=0.02). Cox regression analysis revealed that LIPI 2 score was an independent risk factor for both PFS (HR 1.839, 95% CI: 1.075-3.144, p=0.02) and OS (HR 1.757, 95% CI: 1.006-3.071, p=0.04).

Conclusion: LIPI score can be used as a simple and easily accessible marker to predict prognosis for A-SCLC patients.

Keywords: Lung immune prognostic index (LIPI), prognostic marker, small-cell lung cancer (SCLC), systemic inflammatory indexes

INTRODUCTION

Small cell lung carcinoma (SCLC), a high-grade neuroendocrine carcinoma of the lungs, is characterised by poor histological differentiation, high aggressiveness and poor prognosis.[1-3] SCLC accounts for approximately 15% of all lung cancers and is one of the leading causes of cancer deaths worldwide, with a 5-year relative survival rate of 7% for all SEER stages combined.[4] There are promising developments in oncological procedures for the treatment of SCLC, but the prognosis remains very poor with a modest improvement in overall survival (OS), especially in patients with advanced-stage SCLC (A-SCLC).[3,5] Therefore, identifying prognostic factors to predict treatment response or survival is particularly important for selecting SCLC patients who are considered at risk for poor outcomes. Many factors may be associated with poor prognosis in SCLC patients, including performance status, age, smoking status and stage.[5,6] Moreover, systemic inflammatory indexes have received much attention recently, as the interplay between systemic inflammation and local immune response plays an important role in tumour development and progression.[7,8]

Several indexes such as neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and lung immune prognostic index (LIPI) has been studied and some of them have been associated with poor outcomes in various cancers. However, there are currently no validated biomarkers for SCLC patients.[5] Therefore, our study aimed to evaluate the prognostic value of systemic inflammatory indexes in A-SCLC.

METHODS

The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital, Clinical Researches Ethics Committee (Date: 28.12.2022 Decision No:2012-KAEK-15/2617). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Patients

In this retrospective and observational study, we enrolled 118 SCLC patients who were diagnosed from October 1, 2018, to October 31, 2020, and followed up at our hospital. The inclusion criteria were as follows: patients with pathologically diagnosed SCLC; with advanced (A-SCLC) based on the 8th edition TNM staging system proposed by the International Association for the Study of Lung Cancer (IASLC);[5,9] who treated with platinum plus etoposide chemotherapy as first-line treatment according to the guidelines;[10] with a complete record of pretreatment blood test results; who were over the age of 18 years. The exclusion criteria were as follows: patients with a history of other malignant tumours; who underwent surgery due to SCLC; with recent clinical evidence of acute infection or inflammation; whose clinical information could not be reached.

Data Collection

All clinical data were obtained from our hospital's electronic medical record system or patients' files. The demographic data (age, gender, smoking history, comorbidity), cancer data (date of diagnosis, IASLC stage, tumour size, lymph node involvement, metastasis status and location of metastasis, radiological findings, treatment history, whether cancer has progressed and if so, the date, whether the patient is alive or not, and if he died, the date) and laboratory parameters within 1 week of the initiation of anti-cancer treatment were recorded. The primary survival outcomes were determined as progression-free survival (PFS) and overall survival (OS). Progression-free survival (PFS) was considered as time (months) from the first treatment until disease progression or death due to any cause, whichever occurred first.[6] OS was considered as time (months) from the date of diagnosis of SCLC until the date of death from any cause or the last date of follow-up. Patients who were still alive and still did not show progression were censored at the final follow-up. The cut-off date for follow-up was November 1, 2022.

The systemic inflammatory indexes were calculated for each patient as follows: LIPI=the combination of baseline-derived neutrophil to lymphocyte ratio [dNLR=neutrophil count/(white blood cell count − neutrophil count)] and lactate dehydrogenase (LDH). Our hospital's upper limit of normal (ULN) LDH is 247 U/L. [Good (LIPI 0)=dNLR less than 3 and LDH lower than ULN, Intermediate (LIPI 1)=dNLR greater than 3 and LDH lower than ULN or dNLR less than 3 and LDH higher than ULN, Poor (LIPI 2)=dNLR greater than 3 and LDH higher than ULN], SII=platelet × neutrophil/lymphocyte and SIRI=neutrophil count X monocyte/lymphocyte count, PLR=platelet count/lymphocyte count.

Statistical Analysis

Categorical data were expressed as a number of cases (%) and compared using the Chi-square test or Fisher exact test. The normality of the distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Continuous data were given as mean±standard deviation (SD) for normal distributions and were compared using Student's t-test for two independent groups and the ANOVA with TUKEY's correction for multiple independent groups. Continuous data were presented as medians and interquartile ranges (IQR) for skewed distributions and were compared using Mann-Whitney test for two independent groups, and the Kruskal-Wallis test with Bonferroni correction for multiple independent groups. The median follow-up duration was calculated by the reverse Kaplan-Meier method. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression model analysis was performed to identify risk factors independently associated with OS and PFS, and presented with the hazard ratios (HRs) and 95% confidence interval (95% CI). All significant variables which were identified by the univariate Cox regression analysis ($p<0.05$), were included in the multivariate Cox regression analysis. The optimal cut-off values for inflammatory indexes were determined by receiver operating characteristic (ROC) curves analysis using the highest Youden index, defined as sensitivity + specificity-1, to predict PFS and OS. A p-value of <0.05 was considered statistically significant. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. was used for statistical analyses.

RESULTS

Patient Characteristics

One hundred eighteen [15 (12.7%) females, 103 (87.3%) males, mean age 64.3±7.9] A-SCLC patients were included in the study. Most of the patients (90.7%) had a history of smoking and 74 (62.7%) patients had at least one comorbidity. The most common T category was T4 (n=69, 58.5%). All of the patients were N (+) and 98 (83.1%) patients had multiple metastases (≥2 sides). The most metastasis side was bone (73.7%). The baseline characteristics and laboratory parameters of the study population were given in **Table 1**.

ROC analysis was used to assess the ability of the systemic inflammatory indexes (SIRI, SII, PLR, dNLR) to predict PFS and OS. None of them reached significant predictive value for PFS or OS (**Figure 1a** and **Figure 1b**, respectively).

Table 1. The baseline characteristics and laboratory parameters of the study population

	All Population n, (%)
Age (year±SD)	64.3±7.9
Age, n (%) < 65/≥65	62 (52.5)/56 (47.5)
Sex, n (%) Female/Male	15 (12.7)/103 (87.3)
Smoking (+), n (%)	107 (90.7)
Comorbidity (+), n (%)	74 (62.7)
T status, n (%) T1/T2/T3/T4	1 (0.8)/18 (15.3)/30 (25.4)/69 (58.5)
N status, n (%) N0/N1/N2/N3	-/ 4 (3.4)/27 (22.9)/87 (73.7)
M status, n (%) M0/M1a/M1b/M1c	-/9 (7.6)/12 (10.2)/97 (82.2)
Metastasis Count (< 2/ ≥2)	20 (16.9)/98 (83.1)
Bone Metastasis, n (%)	87 (73.7)
Liver Metastasis, n (%)	40 (33.9)
Adrenal Metastasis, n (%)	26 (22)
Cranial Metastasis, n (%)	18 (15.3)
Laboratory parameters	
White Blood Cell (mean±SD)	9729±2931
Neutrophils (mean±SD)	6852±2735
Lymphocytes (median, IQR)	1630 (1038)
Monocytes (mean±SD)	640±247
Platelets $\times 10^3$ (median, IQR)	282.5 (149)
Haemoglobin (mean±SD)	13.65±1.76
NLR (median, IQR)	3.90 (2.86)
dNLR (median, IQR)	2.54 (1.86)
PLR (median, IQR)	164 (150)
SII (median, IQR)	1053.5 (1169)
SIRI (median, IQR)	2426.5 (2388)
LDH (median, IQR)	301.5 (300)

Association of LIPI with Clinical Characteristics and OS/PFS

Patients were divided into three groups LIPI 0 (n=27, 22.9%), LIPI 1 (n=57, 48.3%), and LIPI 2 (n=34, 28.8%) (**Table 2**). The presence of bone metastasis was significantly lower in the LIPI 0 group. The LIPI 2 group had significantly higher levels of neutrophil-NLR-dNLR-PLR-SII-SIRI-LDH and lower levels of lymphocytes than those in the LIPI 0 and LIPI 1 groups. As none of the indexes reached a significant predictive value for PFS or OS, patients were not divided into groups with high or low levels according to the optimal cut-off values.

Overall, 113 (95.8%) patients had progressed and 106 (89.8%) patients had died during the median follow-up period of 34.9 (95% CI 30.91-38.88) months. The median PFS was 7.4 (95% CI 5.80 -8.99) months and the 1-year PFS was 21.2% in the entire population. The median PFS of LIPI groups (0/1/2) was 8.9 (95% CI 3.83-13.96), 8 (95% CI 6.41-9.58), and 5.6 (95% CI 4.60-6.60) months, respectively (p=0.1, **Figure 2a**) [(LIPI 0 vs LIPI 1, p=0.29), (LIPI 0 vs LIPI 2, p=0.07), (LIPI 1 vs LIPI 2, p=0.12)]. The 1-year PFS of LIPI groups (0/1/2) were 37%, 19.3% and 11.8%, respectively (p=0.05).

The median OS is 9.4 (95% CI 8.48-10.31) months and the 1-year OS was 33.9% in the entire population. The median OS of LIPI groups (0/1/2) was 12 (95% CI 9.11-14.88), 10.1 (95% CI 9.16-11.03), and 7.7 (95% CI 6.55-8.84) months, respectively (p=0.02, **Figure 2b**) [(LIPI 0 vs LIPI 1, p=0.41), (LIPI 0 vs LIPI 2, p=0.01), (LIPI 1 vs LIPI 2, p=0.02)]. The 1-year OS was 51.9%, 36.8% and 14.7%, respectively, and there was a significant difference in OS among LIPI groups (p=0.008).

Univariate and Multivariate Cox Regression Analysis for PFS and OS

A history of smoking, ≥2 metastases and LIPI 2 were associated with PFS on univariate cox regression analyses (p=0.04, 0.04 and 0.04, respectively). On multivariate analysis, a history of smoking (HR 2.417, 95% CI: 1.233-4.737, p=0.01), ≥2 metastases (HR 1.772, 95% CI: 1.042-3.014, p=0.03) and LIPI 2 (HR 1.839, 95% CI: 1.075-3.144, p=0.02) were independent prognostic factors for PFS (**Table 3**). On univariate cox regression analyses, ≥2 metastases, presence of bone metastasis, presence of liver metastasis and LIPI 2 were associated with OS (p=0.004, 0.03 and 0.01, respectively). Therefore, they were included in the multivariate analyses which revealed that ≥2 metastases (HR 2.365, 95% CI: 1.120-4.994, p=0.02) and LIPI 2 (HR 1.757, 95% CI: 1.006-3.071, p=0.04) were found to be the independent prognostic indicators of OS (**Table 4**).

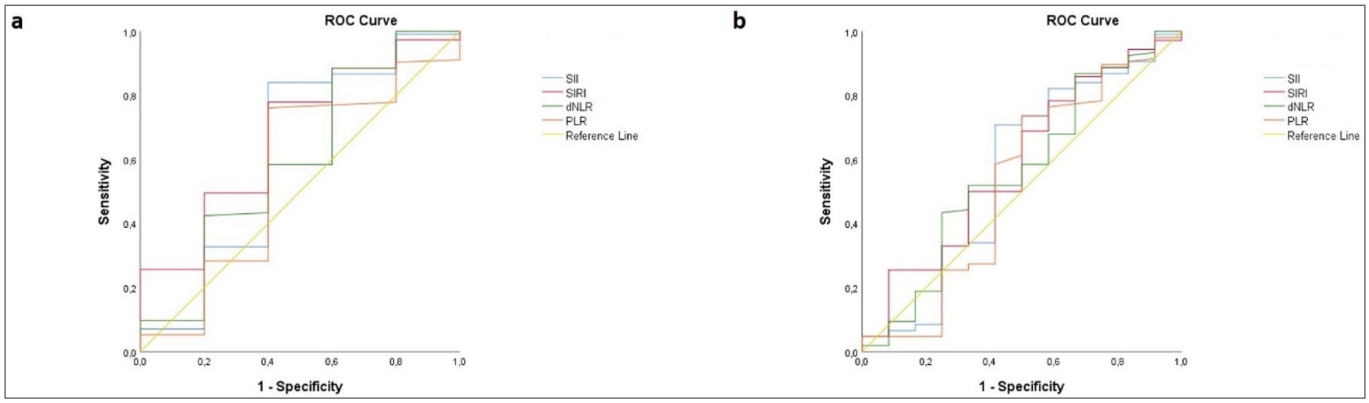

Figure 1. Receiver operating characteristic (ROC) curve of the systemic inflammatory indexes for progression-free survival (a) and overall survival (b)

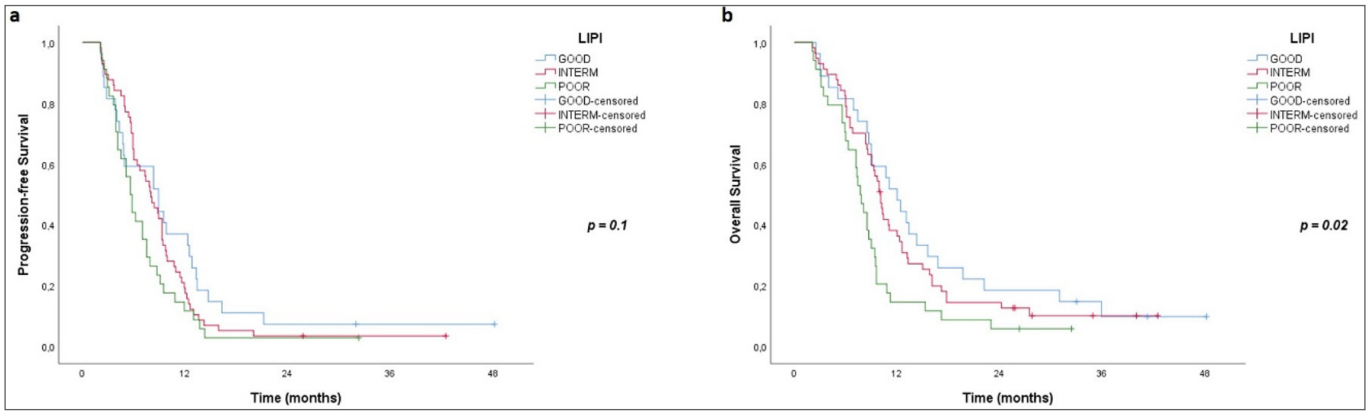

Figure 2. Kaplan-Meier plots of progression-free survival (a) and overall survival (b) according to the lung immune prognostic index (LIPI)

Table 2. The association of LIPI with clinical characteristics and laboratory parameters

	lıpı 0 group (n=27)	lıpı 1 group (n=57)	lıpı 2 group (n=34)	p value
Age (year±SD)	63.7±8.8	63.8±8.2	65.5±6.6	0.59
Age, n (%) <65/≥65	15 (55.6)/12 (44.4)	31 (54.4)/26 (45.6)	16 (47.1)/18 (52.9)	0.74
Sex, n (%) Female/Male	6 (22.2)/21 (77.8)	4 (7)/53 (93)	5 (14.7)/29 (85.3)	0.13
Smoking (+), n (%)	24 (88.9)	54 (94.7)	29 (85.3)	0.3
Comorbidity (+), n (%)	16 (59.3)	33 (57.9)	25 (73.5)	0.3
T status, n (%) T1/T2/T3/T4	- /6 (22.2)/8 (29.6)/13 (48.1)	1 (1.8)/7 (12.3) /13 (22.8)/36 (63.2)	-/5 (14.7) /9 (26.5)/20 (58.8)	0.76
N status, n (%) N0/N1/N2/N3	-/1 (3.7) / 8 (29.6)/18 (66.7)	-/2 (3.5) / 14 (24.6)/41 (71.9)	-/1 (2.9) / 5 (14.7)/28 (82.4)	0.7
M status, n (%) M1a/M1b/M1c	4 (14.8)/3 (11.1)/20 (74.1)	4 (7)/5 (8.8)/48 (84.2)	1 (2.9)/4 (11.8)/29 (85.3)	0.5
Metastasis Count (<2/≥2)	8 (29.6)/19 (70.4)	9 (15.8)/48 (84.2)	3 (8.8)/31 (91.2)	0.09
Bone Metastasis, n (%)	14 (51.9)	45 (78.9)	28 (82.4)	0.01
Liver Metastasis, n (%)	8 (29.6)	22 (38.6)	10 (29.4)	0.58
Adrenal Metastasis, n (%)	7 (25.9)	14 (24.6)	5 (14.7)	0.46
Cranial Metastasis, n (%)	5 (18.5)	7 (12.3)	6 (17.6)	0.68
Laboratory parameters				
WBC (mean±SD)	9256.7±2575.1	9426.7±2989.3	10613.2±2989.5	0.11
Neutrophils (mean±SD)	5734±2015	6254.9±2527	8741.5±2678.6	<0.001
Lymphocytes (median,IQR)	2150 (950)	1740 (1125)	1220 (705)	<0.001
Monocytes (mean±SD)	684±247	637±223	612±286	0.52
Platelets $\times 10^3$ (median,IQR)	320 (172)	271 (143.5)	282.5 (156.2)	0.58
Haemoglobin (mean±SD)	13.5±1.8	13.7±1.7	13.5±1.7	0.74
NLR (median, IQR)	2.65 (1.51)	3.27 (2.12)	6.84 (5.83)	<0.001
dNLR (median, IQR)	1.80 (0.97)	2.16 (1.07)	4.31 (2.82)	<0.001
PLR (median, IQR)	147 (84)	151 (107)	275 (180)	<0.001
SII (median, IQR)	827 (657)	839 (879)	2116 (1587)	<0.001
SIRI (median, IQR)	1721 (1609)	2020 (1923)	3927 (4036)	<0.001
LDH (median, IQR)	205 (42)	326 (244)	476 (689)	<0.001

Table 3. The univariate and multivariate analyses of factors associated with progression-free survival

Variables	Progression-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% Cl	p	HR	95% Cl	p
Age						
< 65 (Ref)	1					
≥65	1.195	0.824-1.732	0.34			
Gender						
Female (Ref)	1					
Male	0.91	0.530-1.573	0.74			
Smoking						
No (Ref)	1			1		
Yes	1.94	1.011-3.731	0.04	2.417	1.233-4.737	0.01
Comorbidities						
No (Ref)	1					
Yes	0.891	0.606-1.308	0.55			
Number of metastasis						
< 2 (Ref)	1			1		
≥2	1.700	1.012-2.857	0.04	1.772	1.042-3.014	0.03
Bone metastasis						
No (Ref)	1					
Yes	1.359	0.884-2.090	0.16			
Liver metastasis						
No (Ref)	1					
Yes	1.071	0.726-1.580	0.73			
Adrenal metastasis						
No (Ref)	1					
Yes	1.073	0.690-1.670	0.75			
Cranial metastasis						
No (Ref)	1					
Yes	1.149	0.683-1.933	0.6			
LIPI						
0 (Ref)	1			1		
1	1.260	0.781-2.033	0.34	1.123	0.694-1.818	0.63
2	1.731	1.022-2.933	0.04	1.839	1.075-3.144	0.02

Table 4. The univariate and multivariate analyses of factors associated with overall survival

Variables	Overall Survival					
	Univariate analysis			Multivariate analysis		
	HR	95% Cl	p	HR	95% Cl	p
Age						
< 65 (Ref)	1					
≥65	1.331	0.906-1.955	0.14			
Gender						
Female (Ref)	1					
Male	0.800	0.447-1.433	0.45			
Smoking						
No (Ref)	1					
Yes	1.807	0.877-3.722	0.1			
Comorbidities						
No (Ref)	1					
Yes	1.040	0.699-1.546	0.84			
Number of metastasis						
< 2 (Ref)	1			1		
≥2	2.289	1.296-4.041	0.004	2.365	1.120-4.994	0.02
Bone metastasis						
No (Ref)	1			1		
Yes	1.633	1.037-2.572	0.03	0.889	0.483-1.635	0.7
Liver metastasis						
No (Ref)	1					
Yes	1.211	0.811-1.810	0.34			
Adrenal metastasis						
No (Ref)	1					
Yes	0.841	0.529-1.338	0.46			
Cranial metastasis						
No (Ref)	1					
Yes	0.943	0.536-1.658	0.83			
LIPI						
0 (Ref)	1			1		
1	1.197	0.734-1.953	0.47	1.097	0.665-1.810	0.71
2	1.960	1.144-3.358	0.01	1.757	1.006-3.071	0.04

DISCUSSION

The present study investigated the association between pretreatment systemic inflammatory indexes and survival characteristics in patients with A-SCLC. Our results suggest that LIPI can serve as a reliable prognostic factor of PFS and OS, while the remaining systemic inflammatory indexes are not useful as prognostic factors associated with PFS and OS.

The development of biomarkers as an important component of oncology is ongoing. Recent studies have shown that systemic inflammation is one of the main mechanisms of cancer pathogenesis and plays a critical role in tumour development, growth and metastasis, as well as in response to treatment agents.[8,11,12] Therefore, systemic inflammatory indexes reflect the degree of systemic inflammation can be used as promising markers for predicting patient prognosis. Moreover, these indexes are attracting widespread interest because they are easy and cost-effective to obtain and reflect the level of inflammation in the host immune system.[12] However, few studies have been published on SCLC.

The LIPI score can be used to classify patients into poor (LIPI 0), intermediate (LIPI 1) and good (LIPI 2) prognostic groups based on the combination of dNLR and LDH levels.[13,14] High LDH levels and high dNLR levels are unfavourable prognostic factors in various tumours.[11,15] It can be assumed that the LIPI score proved to be a promising marker for predicting prognosis as it represents a combination of these values. In line with our study, Li et al.[16] and Qi et al.[17] reported that the LIPI score was an independent prognostic factor for OS in A-SCLC patients. Sun et al.[6] also demonstrated that LIPI stratification was a significant factor against OS or PFS of limited disease (LD)-SCLC patients. Sonehere et al.[13] showed that the LIPI score was an independent favourable prognostic factor for OS in patients with extensive disease (ED)-SCLC, but not in patients with LD-SCLC, and suggested that LD-SCLC had a lower systemic inflammatory response than ED-SCLC and was difficult to be reflected on NLR. On the other hand, the LIPI score had no prognostic relevance for LD-SCLC in Schnöller et al.'s[14] study and for ED-SCLC in Qi et al.'s[7] study. Even though there were some different results, our study supports the use of LIPI score as a prognostic marker in A-SCLC patients.

Although the underlying mechanisms are not yet fully elucidated, some theories can be put forward about the factors contributing to the prognostic value of the LIPI score. This score, based on LDH and circulating neutrophils and lymphocytes, indicates the interaction between the tumour microenvironment and the immune response.[18] Neutrophils play an important role in carcinogenesis, tumour cell proliferation, tumour progression and metastasis by releasing angiogenic factors such as growth factors, interleukins (IL-1, IL-6 and IL-8) and reactive oxygen species.[12,19] Lymphocytes significantly impact antitumour immunity by inducing cytotoxic cell death and inhibiting tumour cell proliferation and migration. Therefore, a reduced number of lymphocytes results in a poorer lymphocyte-mediated immune response to malignancy.[18,20] Furthermore, LDH, a key enzyme in tumour metabolism, regulates anaerobic glycolysis which is closely related to tumour cell proliferation. This enzyme can also promote tumour survival by inhibiting apoptosis and preventing necrosis in an anoxic environment.[11,17,21] Elevated levels of LDH reflect the tumour burden.[21] Taken together, a systemic inflammatory index dependent on increased neutrophils and LDH levels and decreased lymphocyte count may be a suitable predictive biomarker for assessing the survival status of A-SCLC patients.

Our study has some limitations. First, this was a retrospective study at a single centre with a small number of patients. Nevertheless, our results are promising and should be validated by prospective studies with a larger sample size. Second, all patients in the present study had an acceptably good performance status to receive cancer therapy, so the study population may not represent the entire SCLC population. However, our study was designed to provide a homogeneous group.

CONCLUSION

Our results show that the LIPI score can be used as a simple and easily accessible marker to predict prognosis for A-SCLC patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital, Clinical Researches Ethics Committee (Date: 28.12.2022 Decision No:2012-KAEK-15/2617).

Informed Consent: Because the study was designed retrospectively, no written informed consent was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Efficacy of magnetic resonance imaging among pregnant patients diagnosed with acute abdomen in the emergency department

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ABSTRACT

Aims: Diagnostic procedures are very important for fetal safety during pregnancy. Magnetic resonance imaging (MRI) is characterized by a higher accuracy rate compared to medical follow-up and post-surgical diagnoses. However, it is very important to use it at the right time in order to maintain cost-effectiveness of the technique. In this study, we aimed to determine the efficacy of MRI in pregnant patients admitted to the emergency department with acute abdominal pain when the etiology has not been defined by other techniques.

Methods: The data of pregnant patients who admitted to the emergency department due to acute abdominal pain between January 2013 and February 2018 were retrospectively analyzed. All these patients evaluated with pelvic magnetic resonance screening, as they could not be diagnosed by physical examination findings, laboratory tests, or ultrasonography. Diagnostic performance of MRI, sensitivity, specificity, and negative and positive predictive values were assessed.

Results: The etiology of the pain was detected in 29 of 57 patients who applied to the emergency department with acute abdominal pain and evaluated with pelvic MRI. The most common cause of acute abdominal pain was acute appendicitis which all of them histopathologically confirmed (n=14). Pelvic abscess, severe hydronephrosis, giant ovarian cyst, pyelonephritis, ovarian torsion, and uterine fibroid torsion were among other causes.

Conclusion: MRI is a highly effective imaging method for diagnosing both acute appendicitis and other pelvic emergencies. Therefore, it would be beneficial for the diagnosis in pregnant patients with acute abdominal pain.

Keywords: Acute abdominal pain, appendicitis, pregnant, magnetic resonance imaging

INTRODUCTION

There are many causes of acute abdomen during pregnancy. The incidence of acute abdominal pain range from 1 in 500 to 1 in 635 pregnant women. Acute abdominal pain may be categorized as obstetric, non-obstetric, or gynecological. In order to make a differential diagnosis, a detailed patient history needs to be gathered, and patients should be evaluated in conjunction with the findings obtained from physical examinations and laboratory tests.

Diagnostic procedures are very important for fetal safety during pregnancy. Ultrasonography (US) should be preferred due to its non-invasive nature for patients presenting with acute abdominal pain.[1] However, the compressive effect of a growing uterus and the resulting displacement of intra-abdominal organs may cause US to be an inadequate diagnostic technique.[2] Therefore, a normal US does not necessarily exclude acute abdomen among pregnant patients.

The inability to use techniques such as radiography and computed tomography (CT) routinely during pregnancy due to the risk of radiation exposure makes it difficult to achieve an accurate differential diagnosis.[2] When these techniques are used in such cases, the patient should be made aware of the cost-benefit analysis, and the amount of radiation to be administered should be carefully considered.[3]

In pregnancy, magnetic resonance imaging (MRI) is characterized by a higher accuracy rate compared to medical follow-up and post-surgical diagnoses.[4] MRI provides a detailed information of biological structures,

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and, like US, is a non-invasive imaging technique[4] MRI has also been shown to be useful in reducing rates of negative laparotomy and perforated appendicitis in pregnant patients with acute abdomen.[5]

In this study, we aimed to determine the efficacy of MRI in pregnant patients admitted to the emergency department (ED) with acute abdominal pain when the etiology has not been defined by other techniques.

METHODS

The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 07/11/2018, Decision No:2018.11.1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

MR images and data of pregnant patients who admitted to the ED with acute abdominal pain between January 2013 and October 2018 were retrospectively analyzed. Pregnant patients with acute abdominal pain who could not be diagnosed by physical examination, laboratory tests and US and therefore additionally pelvic MRI performed were included in this study. Patients with incomplete medical records and follow-up data and who did not undergo an MRI scan for diagnosis were excluded from the study. All patients' physical examination carried out by a general surgeon and an obstetrician. MRI images were evaluated by a radiologist with eight years of experience in that field.

Imaging Technique

All patients evaluated by a 1.5 Tesla MRI device (Philips MRI Systems, Achieva Release 3.2 Level 2013-10-21, Philips Medical Systems Nederland B.V.) with a standardized protocol for pregnant patients. According to the protocol, sagittal, coronal, and axial turbo spin echo (TSE) T2, axial TSE T1, axial and coronal balanced fast field echo (BFFE), axial T1 and T2 SPIR, and axial diffusion-weighted imaging (DWI, b500-b1000) sequences were obtained.

The upper level of field of view (FOV) was set to the upper poles of the kidneys to include both kidneys. No oral contrast agent was administered during the examination. Intravenous contrast agent administered if the radiologist thought that it is going to significantly improve the diagnostic performance and also improve maternal and fetal outcome.

Image Analysis

In MR images, an appendix calibration greater than 7 mm and the presence of T2 hyperintense fluid inside the appendix lumen were considered signs of acute appendicitis. A thicker appendix wall - compared to those of other intestinal segments - and the presence of hyperintensities suggesting inflammation in both the appendix wall and adjacent mesentery, especially in the T2-weighted series were used as supporting criteria.

Increased ovarian volume with stromal inflammation was considered a sign of ovarian torsion.[6]

Hydronephrosis usually occurs as a result of the compression of ureter between the uterine and psoas muscle at the level of the sacral promontorium in pregnant. Ureteral stones were distinguished from hydronephrosis by observing the filling defects inside the ureter in the images obtained with the BFFE sequence.

Disorders like inflammatory bowel disease, diverticulitis, or obstruction recognized by observing hyperintensity in the bowel wall with a thickening in the fat-suppression T2-weighted series. Moreover, fistulae and abscesses as a result of complication of inflammation diagnosed by MRI.[7]

Statistical Analysis

Descriptive statistic methods used for calculate positive and negative predictive values, categorical variables, and frequency calculations. The SPSS 20 (SPS Inc., Chicago, IL) software package was used for statistics of the study.

RESULTS

Among the 65 pregnant patients who underwent pelvic MRI to define acute abdominal pain etiology, eight were excluded due to insufficient follow-up duration. The remaining 57 patients had a mean age of 24.5±5.2 (range 18-37) years. All patients evaluated with US before performing pelvic MRI. US revealed pericecal fat tissue edema in five patients and intra-abdominal free fluid in seven patients. The appendix could not be visualized by US in any patient.

In 29 patients, MRI determined the cause of acute abdominal pain. Among these, the most common cause of acute abdominal pain was acute appendicitis (n=14) which all of them histopathologically confirmed (**Figure 1**). Two of the patients with acute appendicitis had perforated appendix and periappendicular abscess was observed in one of them. Three patients operated with the diagnosis of ovarian torsion, myoma torsion and retroperitoneal cyst (**Figure 2**). The remaining twelve patients whose abdominal pain etiology was determined by MRI, laboratory and physical examination had only medical treatment. Of these patients, 4 have giant ovarian cysts, 3 have marked hydronephrosis, 3 have PID and 2 have pyelonephritis (**Figure 3**).

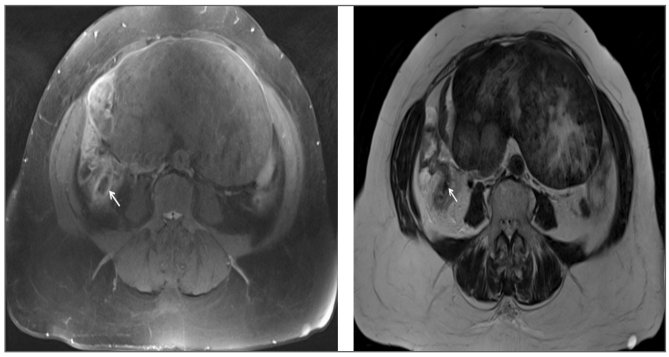

Figure 1. Acute appendicitis. Axial, fat-suppressed contrast enhanced T1-weighted MR image shows an enlarged appendix with thickened and enhancing wall (A) (white arrow). Axial T2-weighted MR image shows a T2-hyperintense, enlarged appendix with an intraluminal T2 hypointense dot represents appendicolith (B) (white arrow).

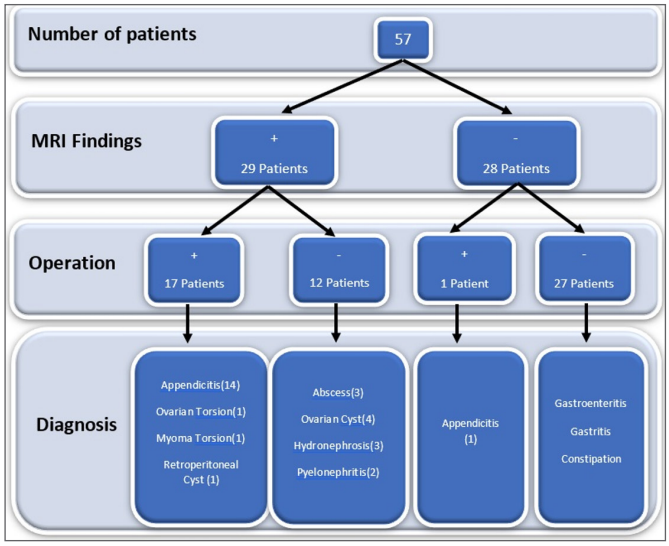

Figure 2. The flow chart shows the distribution of patients according to their MRI findings, operation, and diagnosis.

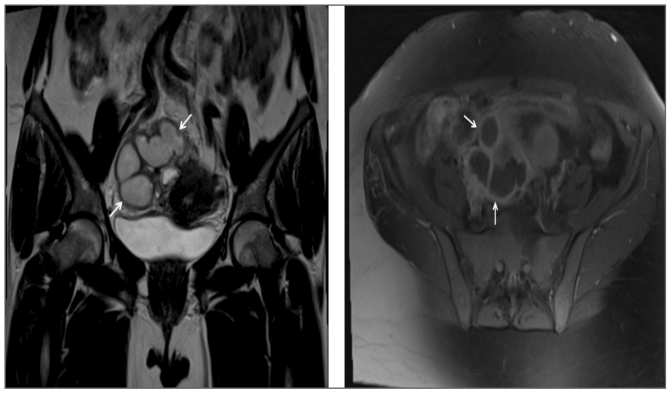

Figure 3. Hydrosalpinx and tubo-ovarian abscess. Coronal T2-weighted MR image of the pelvis demonstrates a dilated, tortuous, right fallopian tube filled with T2 hyperintense content, representing hydrosalpinx (A) (white arrows). Axial coronal contrast-enhanced, fat-suppressed T1-weighted MR image of pelvis shows a peripheral rim enhancement after contrast administration (B) (white arrows).

In 28 patients, the cause of abdominal pain could not be determined by MRI. 27 patients were discharged after regression of clinical findings. One patient who remained undiagnosed by radiological studies and whose clinical findings did not improve underwent a diagnostic laparotomy. Laparoscopic appendectomy procedure was performed to the patient and the diagnosis of appendicitis was confirmed histopathologically.

Mean appendix diameter measured on MRI sections was measured as 9.7±2.9 mm (range 7-15 mm) in patients with acute appendicitis, and 5±0.3 mm (range 5-6) in rest of the patients. In 64% of acute appendicitis cases, the patients were in the second trimester of pregnancy. Appendix diameters and trimester information measured on MR images of patients operated for acute abdomen are summarized in **Table 1**.

Table 1. Diagnoses, appendix diameters, and trimesters of operated patients

Patients	Diagnoses	Appendix diameter (mm)	Trimester
1	Appendicitis	15	3
2	Appendicitis	12	2
3	Appendicitis	13	2
4	Appendicitis	8	2
5	Appendicitis	9	2
6	Appendicitis	10	2
7	Appendicitis	7	2
8	Appendicitis	9	1
9	Appendicitis	15	2
10	Appendicitis	7	1
11	Appendicitis	7.5	1
12	Appendicitis	8	2
13	Appendicitis	8	2
14	Appendicitis	8	3
15	Ovarian torsion	5	2
16	Myoma torsion	Not visualized	2
17	Retroperitoneal cyst	Not visualized	2

The negative predictive value of MRI for detecting acute appendicitis was 75% (95% CI 21-98) and positive predictive value was 100% (95% CI 73-100). Sensitivity and specificity were 93% (95% CI 66-99) and 100% (95% CI 30-100.0), respectively. The negative predictive value of MRI for detecting pelvic pathologies was 96% (95% CI 79-99) and positive predictive value was 100% (95% CI 85-100). Sensitivity and specificity were 96% (95% CI 80-99) and 100% (95% CI 84-100), respectively.

No complications, including allergic reactions, were observed in patients given contrast agent.

DISCUSSION

Gray scale US is the most commonly used imaging tool for pregnant admitted to the ED with abdominal pain.[8] Being non-invasive, safe, and easy to use make the US technique superior to other imaging methods. However, operator dependency and poor image quality due to obesity and abdominal gas are major limitations.[1] MRI allows cross-sectional imaging without exposing patients to the radiation, as well as diagnosing fetal and maternal disorders in pregnant patients.[9]

Acute appendicitis is the most common non-obstetric condition requiring surgery in pregnancy.[8] The effectiveness of the ultrasonography method in showing the appendix for the diagnosis of acute appendicitis has a wide range. In a study by Lim et al.[10] of 45 pregnant subjects with suspected appendicitis, US was 100% sensitive and 96% specific, with only three patients (7%) remaining undiagnosed by US. Zhang et al.[11] in a series of 65 cases, reported that US was able to make a diagnosis of appendicitis in 26 patients (40%). MRI is a good alternative to US when the latter is non-diagnostic in pregnant patients. It may not be easy to separate normal appendix from other intestinal segments. But the inflammation of appendix makes it more visible on MRI section which is very sensitive method to detect the hydrogen molecules. Pedrosa et al.[12] reported the rate of evaluation of the appendix separately from other intestinal segments on an MRI was 10%, while we reported as 42.1% in this study. Our study revealed a high specificity, sensitivity, and positive predictive value for appendicitis (100%, 93%, and 100%, respectively).

Acute appendicitis may occur in every trimester. Some studies have reported a higher prevalence in the third trimester.[11,13] Our study also demonstrated that it was most common in the second trimester, followed by the third and first trimesters.

The difficulty of diagnosing acute appendicitis results from a higher negative laparotomy rate in pregnant women than non-pregnant women. There is no difference between negative laparotomy and an appendectomy procedure performed early in pregnancy, with respect to the risk of preterm labor, and both impose minimal risk on the mother and the fetus. Therefore, a diagnosis must be made as quickly as possible.[13] In our study, no patient underwent a negative laparotomy procedure.

It is well understood that appendix perforation is more common in pregnant women than the normal population.[14] This may be due to the delayed hospital admission of pregnant women, attribution of their symptoms to pregnancy, and the absence of specific signs and symptoms associated with acute appendicitis. A delay of surgery for 24 hours increases the risk of perforation from 0% to 66%. While maternal mortality is 0.1% in unperforated cases, it rises to 4% when perforation occurs.[13] Perforation and abscess formation significantly increase the fetal mortality. The rate of fetal loss is 3-5% in acute appendicitis, and 26-30% in cases with complications.[13] In our study, two patients had perforation, one of whom also had an abscess. Maternal or fetal mortality did not occur in those patients.

MRI allows us to make a variety of diagnoses apart from appendicitis in patients with acute abdominal pain. Some patients may have rare causes of acute abdomen.[15] In a study, the rate of making a clinical diagnosis of appendicitis or other causes of acute abdominal pain in pregnant patients with MRI was reported to be 43%.[16-18] In our study, apart from the 14 patients diagnosed with appendicitis, three patients had an abscess, four had severe hydronephrosis, four had a giant ovarian cyst, two had pyelonephritis, and two had torsion. Ovarian torsion is present in 2-3% of all gynecological emergencies.[19,20] Therefore, it is a great advantage that pathologies other than appendicitis which cause pelvic pain in pregnant patients with pre-diagnosis of acute appendicitis can be detected with MRI technique.

The retrospective design and limited number of patients were the main limitations of the study. There is a need for prospectively designed study with larger patient population.

CONCLUSION

MRI is a valuable examination tool for making a diagnosis in pregnant patients presenting with acute abdomen. It is highly effective for diagnosing both acute appendicitis and non-appendicitis pelvic emergencies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 07/11/2018, Decision No: 2018.11.1).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Impact of long-term glycemic variability on interdialytic weight gain in diabetic hemodialysis patients

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ABSTRACT

Aims: Interdialytic weight gain (IDWG) was shown to be associated with mortality and correlated with long-term glycemic indices in diabetic hemodialysis (DHD) patients. The aim of this study was to investigate the association between glycemic variability (GV) and IDWG in DHD patients.

Methods: 82 DHD patients were studied for 6 months. Six measurements of monthly predialysis glucose were used to calculate glycemic indices. The weight gain over the dry weight of the last 10 consequent hemodialysis sessions was measured for each patient to calculate IDWG.

Results: IDWG was positively correlated with GV, HbA1c (p=0.025, r=0.247 and p=0.006, r=0.304, respectively) and inversely correlated with age (p=0.01, r=-0.283). GV was positively correlated with HbA1c (p<0.001, r=0.638), mean predialysis glucose (p<0.001, r=0.737) and negatively correlated with serum sodium (p=0.014, r=-271). HbA1c and age were found to be independently related to IDWG after linear regression analysis.

Conclusion: GV should be taken into account to improve IDWG in DHD patients.

Keywords: Hemodialysis, interdialytic weight gain, diabetes mellitus, glycemic variability, HbA1c

INTRODUCTION

Diabetes mellitus is the leading cause of end-stage renal disease and glycemic control is associated with mortality in diabetic hemodialysis (DHD) patients.[1,2] Glycemic control has been based on long-term glycemic indicators. Recently, not only long-term control, but also glycemic variability (GV) is found to have important clinical outcomes in diabetic patients.[3] GV has been put forth as an alternative glycemic indicator in the past decade and the number of studies about the impact of GV in literature is still increasing. GV is defined as the fluctuations of glucose or long-term glycemic indices over a certain time. GV can be calculated either as short-term (ie by continuous glucose monitoring devices within hours or a few days) or as long-term (ie by visit to visit glucose measurements within weeks or months). GV is found to be related to coroner artery disease, cerebrovascular disease, diabetic neuropathy, retinopathy, nephropathy, and even mortality in diabetic population.[3,4] Even before the onset of diabetes, GV was found to be related to the occurrence of diabetes, macrovascular complications and mortality.[5,6] GV was also studied in end-stage renal disease patients. It was found to be associated with severe hypoglycemia in DHD patients, and also with mortality in both DHD and peritoneal dialysis patients.[7-9]

Interdialytic weight gain (IDWG) is described as the weight gain over the dry weight to express excess water between two dialysis sessions in hemodialysis (HD) patients. It has been recommended that IDWG should be less than 4%-4.5% of dry weight.[10] IDWG was related to intradialytic hypotension, higher blood pressure, increased hospital admissions, extra HD sessions and thereby increased costs in previous studies.[11-13] Moreover, IDWG is shown to be related to poor survival in DHD patients.[14,15] Concordantly, decreased IDWG was associated with less intradialytic cardiac damage.[16] IDWG is found to be higher in DHD patients than non-diabetics and also to be correlated with HbA1c levels.[12,17,18] However, the impact of GV on IDWG has not been studied yet. The aim of our study is to search the association between GV and IDWG in diabetic HD patients.

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METHODS

The study was carried out with the permission of the KTO Karatay University Medical Faculty Clinical Researches Ethics Committee (Date: 21.09.2022, Decision No: E-41901325-200-43559-024) and carried out in compliance with Helsinki declaration. This study was performed in two HD centers between January and July 2022. 82 DHD patients aged over 18 years who were at least 3 months on HD were enrolled in this study. Patients who were under 18 years, who had blood transfusion in the past 3 months, who had hemoglobinopathies, who had residual diuresis more than 100 ml/day and whose data were missing more than 1 measurement were not included in the study. They were all on a 4 hours, thrice-weekly HD schedule, using low flux membranes. Dialysate fluid glucose concentration was 100 mg/dl and sodium concentration was 138 mEq/L. Dialysis adequacy was calculated as Kt/V. Patient characteristics like gender, age, weight and height were noted. Body mass index (BMI) was calculated for each patient as kilograms/squared meters. Serum creatinine, blood urea nitrogen, sodium, potassium, calcium, phosphorus, albumin, parathormone and complete blood count samples were acquired just before the beginning of the HD session.

Glycemic Indices

Serum glucose samples were obtained predialysis once monthly for six months as spot glucose and were irrelevant of previous meal. Glucose tests were done by Roche COBAS 8000 c 702 module. Mean predialysis glucose (MPG) was calculated by dividing the sum of predialysis glucose (PG) by 6 for each patient. GV was calculated -as visit to visit PG- by the sum of absolute differences of 6 PG dividing by 5. HbA1c was obtained from the fourth month's predialysis samples. HbA1c measurements were tested by Arkray ADAMS HA-8180V system.

Interdialytic Weight Gain

Each patient's predialysis weight was acquired from last month's last 10 consecutive HD sessions. The difference of every measurement from the patients' dry weight was calculated. The sum of 10 absolute weight gain was divided by 10 to find the mean absolute weight gain for each patient. Finally, to find IDWG, mean absolute weight gain was divided by each patient's dry weight and then multiplied by 100.

Statistical Analysis

Statistics were done by SPSS version 22. According to Kolmogorow-Smirnov normality test, normally distributed measure correlations were done by using Pearson correlation. Non-normally distributed measure correlations done by Spearman correlation. After grouping GV according to mean GV, two groups were tested by Mann-Whitney U test. Then, a linear regression using backward elimination was done with IDWG related parameters. A p value of <0.05 was accepted as statistically significant.

RESULTS

82 DHD patients were included in this study, 48 (58.5%) of whom were female. Mean age was 63.23±10.85 years. The mean IDWG was 3.19±1.34%. Some characteristics of patients are shown in **Table 1**. IDWG was statistically significantly and positively correlated with GV (**Figure 1**), HbA1c and negatively correlated with age (**Table 2**). After grouping GV according to mean GV (49.37 mg/dl/month), high GV group had higher IDWG (3.56±1.43% vs 2.95±1.23%, p=0.032). GV was positively correlated with HbA1c (p<0.001, r=0.638), MPG (p<0.001, r=0.737) and inversely correlated with predialysis serum sodium (PSNa) (p=0.014, r=-271). HbA1c was positively correlated with MPG (p<0.001, r=0.706), hemoglobin (p=0.044, r=0.223) and conversely correlated with age (p<0.001, r=-0.401) and PSNa (p=0.024, r=-0.249). MPG was negatively correlated with age (p=0.022, r=-0.252) and PSNa (p<0.001, r=-0.385). Gender did not reveal any statistically significant difference in terms of HbA1c, mean glucose, GV and IDWG. After linear regression analysis, HbA1c was found to be a positive and age was found to be a negative independent predictors of IDWG (p=0.049 each) (**Table 3**).

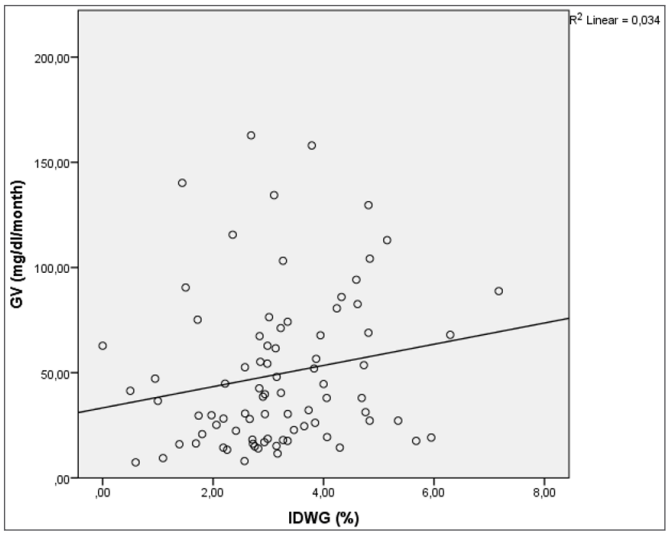

Figure 1. Scatter plot of correlation between GV and IDWG (p=0.025, r=0.247).

Table 1. Demographic and laboratory parameters of patients

Parameters	% or mean values
Female gender	48 (58.54%)
Age (years)	63.23±10.85
BMI (kg/m)	27.6±5.6
HbA1c (%)	6.67±1.73
MPG (mg/dl)	184.63±72.92
GV (mg/dl/month)	49.37±36.56
IDWG (%)	3.19±1.34
PSNa (mEq/l)	139.9±4.3
Hemoglobin (g/dl)	11.18±1.23
Kt/V	1.48±0.21

Table 2. The correlation of IDWG with GV, HbA1c and age by Spearman's rho test

Parameter	IDWG
GV	p= 0.025, R= 0.247
HbA1c	p= 0.006, R= 0.304
Age	p= 0.01, R= -0.283

Table 3. Regression analysis according to IDWG

Parameters	Backwards stepwise Model 1(R2=0.178)		Backwards stepwise Model 2 (R2=0.177)	
	Standardized β (CI%95)	p	Standardized β (CI%95)	p
(constant)		0.010		0.007
Age	-0.238 (-0.059-0.001)	0.055	-0.241 (-0.059-0.000)	0.049
HbA1c	0.252 (-0.034-0.425)	0.094	0.241 (0.001-0.372)	0.049
GV	-0.017 (-0.010-0.009)	0.896		

DISCUSSION

IDWG was found to be correlated with GV in the present study. To our knowledge it was the first study to investigate and find a relationship between GV and IDWG. Hyperglycemia leads to increasing osmolarity, which further leads to thirst via central mechanisms. Thus, chronic hyperglycemia detected by HbA1c in DHD patients leads to higher IDWG. As one end of GV is hyperglycemia, the same scenario may also be valid for GV. On the other hand, when it comes to how hypoglycemic end of GV affects IDWG, it may be more complicated. First, an over eating reaction as a consequence of hypoglycemia may lead to secondary hyperglycemia, which will further causes thirst. Secondly, it may be due to sugar-containing drinks. Especially younger patients, who were found to be associated with IDWG in our study, may be more proned to consume glucose-containing drinks due to their social environment. Drinking sugar-containing fluids resolve hypoglycemia quickly, while it causes an increase in blood glucose as a consequence. Besides, drinking fluids also enhances IDWG. In this study IDWG was also found to be correlated with HbA1c. Ifudu et al.[17] showed for the first time that IDWG was correlated with HbA1c in DHD patients, while it was a small group of 33 patients. Davenport,[19] on 175 DHD patients, revealed a correlation of IDWG with HbA1c. Similarly, Creme et al.[18] found a significant correlation between HbA1c and IDWG in a study including 412 DHD patients. All these studies are consistent with our results.

In this study, GV was found to be correlated well with both HbA1c and MPG. Fang et al.[20] revealed that GV was associated with HbA1c in a study including 291 diabetic patients. In a study on 93 DHD patients, Khan et al.[21] found that GV was associated with HbA1c levels, which was consistent with our study. This finding shows that decreasing GV may also improve HbA1c. Also, a well correlation of HbA1c and MPG was shown in this study, likewise put forth previously.[2]

Age was negatively correlated with IDWG, HbA1c and MPG in this study. Ipema et al.[23] revealed that younger HD patients have higher IDWG. In a study with 300 HD patients, Jalalzadeh et al.[24] showed that younger HD patients were significantly proned to higher IDWG. They concluded that higher fluid intake was a consequence of increased social and physical activity. This conclusion may be also true for poor glycemic control in young patients. On 649 diabetic patients, Shamshirgaran et al.[25] found that glycemic control was better in the elderly group, which is consistent with the current study.

GV, MPG and HbA1c were found to be negatively correlated with PSNa levels. Hyperglycemia is known to reduce serum sodium levels by increasing the osmolality, thus causing translocational hyponatremia. Furthermore, hyperglycemia leads to excessive water consumption, which further causes a dilutional decrease in sodium levels, especially in anuric HD patients. In the study of Davenport[19] on 175 DHD patients, a negative correlation of HbA1c and PSNa was found. On 1549 HD patients, Waikar et al.[26] showed that serum sodium levels were lower in DHD patients and were negatively correlated with HbA1c. Similarly, in a study including 697 HD patients, Sahin et al.[27] also found that PSNa were lower in DHD patients and were negatively correlated with HbA1c in DHD patients. These results too, are concordant with our study.

Our study has a few limitations. Despite it was a two-center study, our case number was relatively low. Increased patient numbers may reveal a stronger and independent correlation. Even so, high GV group was found to have increased IDWG. Besides, the number of patients below 40 years of age was only 3. Increased number of young patients could show a better relation of age with IDWG and glycemic indices. Finally, we had only one measurement of serum sodium. However, serum sodium tends to be stable over time in HD patients, so this may be overlooked as a real limitation.[28] Indeed, to our knowledge, this study was the first to investigate and show the correlation of GV with IDWG in DHD patients.

CONCLUSION

GV, HbA1c and age are associated with IDWG in DHD patients. Therefore, not only long-term markers of glycemic control, but also the variability of glucose should be taken into account to improve IDWG in HD units.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the KTO Karatay University Medical Faculty Clinical Researches Ethics Committee (Date: 21.09.2022, Decision No: E-41901325-200-43559-024).

Informed Consent: Written informed consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Borderline ovarian tumors: twenty years of experience at a tertiary center

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ABSTRACT

Aims: To investigate whether there is a difference between serum tumor markers panel (CA 125, CA 19-9, CA 15-3, and carcinoembryonic antigen (CEA)) and tumor size and histopathology in well-staged patients with borderline ovarian tumors (BOTs).

Methods: Over the past 20 years (January 2001 to January 2021), the results of four tumor markers (CA 125, CA 19-9, CA 15-3, and carcinoembryonic antigen (CEA)) have been clinically analyzed for for this retrospective cohort study of 156 patients who underwent surgery and were diagnosed with histopathology consistent with a borderline ovarian tumor.

Results: The average age of patients with borderline ovarian tumors was determined to be 51.67 (4.726) years. Before the first surgery, high CA 125 levels (>35 U/l) were found in 53 patients (34%), high CEA levels (>4 ng/ml) were found in 24 patients (15.4%), high CA 19-9 levels (>37 U/ml) were found in 29 patients (18.6%), and high CA 15-3 (>30 ng/ml) levels were found in 12 patients (7.7%). The average CA 125 levels in tumors with serous histopathology [372.8 (1805.2)] were higher than those in tumors with mucinous histopathology (p=0.006). There was no statistically significant difference in tumor markers between tumors smaller than 8 cm and larger than 8 cm [(CA 125 p=0,257), (CEA p=0.9), (CA 19-9 p=0.295), (CA 15-3 p=0.404)].

Conclusion: Our primary outcome of the study is an increase in CA 125 levels, which indicates serous histopathology. Our secondary outcome is the higher levels of tumor markers, but it does not suggest larger tumors.

Keywords: Borderline epithelial ovarian tumors, tumor markers, CA 125

INTRODUCTION

Borderline epithelial ovarian tumors (BOTs) make up 10-20% of all epithelial ovarian tumors and are primarily derived from ovarian epithelial lesions. They are considered a type of carcinoma with low-grade malignant potential.[1] The histologic diagnosis of BOT is determined by the presence of epithelial cellular proliferation features such as stratification of the epithelial lining of the papillae, multi-layering of the epithelium, mitotic activity, and nuclear atypia, in the absence of stromal invasion. The lack of obvious stromal invasion is the primary diagnostic criterion for BOT.[2] A significant portion of BOTs have serous and mucinous histological types. In addition, a small percentage of BOTs can be of clear cell, endometrioid, mixed, transitional, or Brenner type. Approximately 30% of serous borderline tumors are bilateral and frequently have peritoneal implants as a form of extraovarian invasion. Most peritoneal implants are non-invasive, with invasive peritoneal implants seen in approximately 30-35% of cases. Surgical resection is typically considered sufficient. In contrast, bilaterality and extraovarian spread is less frequently observed in mucinous borderline tumors.[3]

It is known that these tumors, which are more commonly seen in young women, have a better prognosis compared to malignant ovarian tumors.[4] Most patients present with asymptomatic adnexal mass. The main goal of treatment for these tumors in young women is to surgically remove the tumor completely. Unilateral oophorectomy is sometimes used as a conservative treatment for Stage I tumors that are limited to only one ovary in young women. For women who have completed their childbearing, the best treatment option is a combination of total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, multiple peritoneal biopsies, and examination of fluid collected during the surgery for any abnormal cells. In cases of mucinous tumors, it is also recommended to perform an

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appendectomy. While lymph node removal is not typically recommended as part of the surgical treatment for BOTs, studies have shown that even when there is involvement of the lymph nodes, the survival and recurrence rates remain similar.[5] Currently, there is a lack of research showing the benefits of adjuvant treatments like chemotherapy or radiotherapy for patients with advanced stage BOT or invasive peritoneal implants. It is known that patients with advanced stage BOT respond well to cisplatin-based adjuvant chemotherapy regimens, however, it does not significantly improve on long-term survival.[6]

With this information in mind, we aimed to investigate the relationship between tumor markers, tumor size, and histopathology in patients diagnosed with BOT who underwent surgery in our clinic over the past 20 years.

METHODS

The study was carried out with the permission of Okmeydanı City Hospital Clinical Researches Ethics Committee (Date: 26.12.2022, Decision No: 364). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Over the past 20 years (January 2001 to January 2021), 156 patients who underwent surgery and were diagnosed with histopathology consistent with a borderline ovarian tumor have been clinically analyzed for retrospective cohort study. All patients were evaluated for tumor size, FIGO stage, histopathology, and other clinicopathologic characteristics. They were staged according to surgical findings and the FIGO criteria (2014), and their histological types were determined using the WHO system (2003). Pathological specimens were evaluated by experienced gynecologic pathologists, and patients were divided into 3 histological types: serous, mucinous, and endometrioid. Serous borderline tumors with complex micropapillary structures and a filigree pattern were diagnosed as micropapillary lesions. Microinvasion was defined as a stromal invasion limited to an area of no more than 10 mm^2. The aim of this study is to determine the levels of serum tumor markers including CA 125, CA 15-3, CA 19-9 and CEA, in patients with borderline ovarian tumors and investigate whether there is a difference in the frequency of histopathology types according to tumor size.

The serum levels of CA 125, CA 19-9, CA 15-3 and CEA were analyzed using an automatic microparticle enzyme immunoassay (MEIA). The cutoff limits for normal tumor marker values were taken as 35 U/ml for CA 125, 37 U/ml for CA 19-9, 30 U/ml for CA 15-3 and 4 ng/ml for CEA. Preoperative CA 125, CA 19-9, CA 15-3 and CEA levels were available for all patients.

All patients with high preoperative serum CA 15-3 levels underwent either mammography or breast ultrasound to rule out any related breast conditions. Patients with high CA 19-9 and CEA levels were also evaluated for possible gastrointestinal origin through upper and lower endoscopies. Currently, there is a standardized procedure for measuring ovarian tumors during surgery. The largest diameter of the ovarian tumor is measured at the time of the initial operation and recorded.

Statistical Analysis

Statistical analysis was conducted using SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to check if the data followed a normal distribution. The Student's t-test was applied for normally distributed data and mean (standard deviation (SD)) were used as a descriptive statistical method. For data that did not follow a normal distribution, the Mann-Whitney U test was applied, and the median (as well as the 25th and 75th percentiles) were used as descriptive statistics. The Chi square test was used for categorical data and n(%) was used as descriptive statistics. A p-value of <0.05 was considered statistically significant.

RESULTS

The average age of patients diagnosed with borderline ovarian tumors at the time of diagnosis was 51.67 (4.726). 47.4% of the cases were postmenopausal. 21.1% of the patients were nulliparous, 78.9% were multiparous.

Histopathologically, there were 76 cases of serous (48.7%), 77 cases of mucinous (49.4%), and 3 cases of endometrioid type BOT. 115 cases were stage 1a (73.7%), 10 cases were stage 1b (6.4%), 22 cases were stage 1c (14.1%), 2 cases were stage 2a (1.3%), 4 cases were stage 3a (2.6%), and 3 cases were stage 3c (1.9). The distribution of surgical stage and histological subtype of BOTs are given in **Table 1**.

Table 1. The distribution of surgical stage and histological subtype of BOTs

Stage		Serous (n:76) (49.3%)	Mucinous (n:77) (48.7%)	Endometrioid (n:3) (2%)	Total
1a	Count	48	64	3	115
	%	41.7%	55.7%	2.6%	100.0%
1b	Count	5	5	0	10
	%	50.0%	50.0%	0.0%	100.0%
1c	Count	15	7	0	22
	%	68.2%	31.8%	0.0%	100.0%
2a	Count	2	0	0	2
	%	100.0%	0.0%	0.0%	100.0%
3a	Count	4	0	0	4
	%	100.0%	0.0%	0.0%	100.0%
3c	Count	2	1	0	3
	%	66.7%	33.3%	0.0%	100.0%
Total	Count	76	77	3	156
	%	48.7%	49.4%	1.9%	100.0%

At the time of the initial surgery, 53 patients (34%) had high CA 125 levels (>35 U/l), 24 patients (15.4%) had high CEA levels (>4 ng/ml), 29 patients (18.6%) had high CA 19-9 (>37 U/ml) and 12 patients (7.7%) had high CA 15-3 (>30 ng/ml) levels.

The mean of CA 125 in tumors with serous histopathology [372.8 (1805.2)] was significantly higher than the mean of patients with mucinous BOT [44.75 (56.11)] (p=0.006). No statistical difference was observed between histopathological subtypes in terms of other tumor markers.

When looking at the FIGO stage, 27.8% of patients with Stage 1 BOTs had high CA 125 levels. When dividing the patients into two groups, early-stage (Stage 1) and advanced stage (Stage 2 and above), the percentages of patients with CA 125 levels <35 and >35 were found to be statistically significant between the groups (p=0.033). No statistically significant difference was found when evaluating the other tumor markers.

When the tumor size is divided into two groups, smaller than 8 cm and 8 cm or larger, there was no statistically significant relationship between the tumor markers and the tumor volume [(CA 125, p=0.257), (CEA, p=0.9), (CA 19-9, p=0.295), (CA 15-3, p=0.404)].

In nulliparous women, the average level of CA 125 was found to be significantly higher than in multiparous women (p=0.022).

In multiparous women, the average level of CEA was found to be higher than in nulliparous women (p=0.03). There was no significant difference found between nulliparous and multiparous women in terms of CA 19-9 (p=0.077) and CA 15-3 (p=0.39).

When looked at in terms of parity, there was no significant difference in stages between nulliparous and multiparous patients (p=0.865).

In patients with borderline ovarian tumors, 41.1% of unilateral tumors were of the serous histopathology, 56.6% were of the mucinous histopathology, and 2.3% were of the endometrioid histopathology. 85.2% of bilateral tumors were of the serous histopathology and 14.8% were of the mucinous histopathology. Unilateral tumors were more often of the serous histopathology, while bilateral tumors were more often of the mucinous histopathology (p<0.001). The results are summarized in **Table 2**.

Table 2. Unilateral and bilateral frequency in serous, mucinous and endometriod tumors

		Serous	Mucinous	Endometrioid	Total
Unilateral	Count	53	73	3	129
	%	41.1%	56.6%	2.3%	100.0%
Bilateral	Count	23	4	0	27
	%	85.2%	14.8%	0.0%	100.0%
Total	Count	76	77	3	156
	%	48.7%	49.4%	1.9%	100.0%
Chi-square p<0.001					

Positive peritoneal cytology was detected in 27 (17.3%) patients with BOTs. Peritoneal washing cytology results were positive in 45.3% of patients with high preoperative CA 125 tumor marker levels (p<0.001). The difference between high preoperative tumor markers and positive peritoneal cytology was not statistically significant. It was observed that 48.1% of the BOT patients with positive peritoneal cytology were of the serous histopathological type and 48.1% were of the mucinous histopathological type. There was no statistically significant difference in histopathological type rates between cytology positive and negative groups (p=0.759).

Patients with advanced-stage disease or who are finished childbearing are treated with radical surgery consisting of peritoneal washings, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, complete peritoneal resection of macroscopic lesions, or multiple peritoneal biopsies; in case of mucinous BOTs, patients also are treated with an appendectomy. Fertility-sparing surgery including unilateral salpingo-oophorectomy or cystectomy, was performed in 40 patients who desired to preserve early-stage fertility.

DISCUSSION

The Carbohydrate Antigen 125 (CA125) was first identified in the early 1980s.[7] CA 125, also known as Cancer Antigen 125 or Tumor Antigen 125, is a mucin-type glycoprotein produced by the MUC16 gene and found on the surface of cells. In laboratory tests, a variety of tumor markers (including CA125, CA19-9, CA15-3, CEA, AFP, LDH, hCG, VEGF, OVX1, immunosuppressive acidic protein, inhibin, sFas, human kallikrein, hK10 and macrophage-colony stimulating factor etc.) have been examined to determine their ability to identify ovarian carcinoma in women.[8]

In studies, CA 125 levels were found to be higher in patients with serous borderline ovarian tumors.[9] There are numerous publications in the literature that support this statement.[10] In our study, CA 125 levels were higher in serous BOT tumors than in mucinous tumors (p=0.006). The difference in terms of CA 125 tumor markers in early and advanced BOTs was statistically significant (p=0.033). There are publications supporting this data in the literature.[11,12] In terms of parity, high CA125 levels were found in nulliparous women,[13] and the mean of CA 125 was found to be higher in nulliparous women in the current study (p=0.022). On the other hand, there are publications that correlate CA 125 levels with peritoneal cytology and peritoneal implants.[10,13] In our study, on the contrary, there was no difference in cytology positivity between patients with high and normal tumor markers.

CA19-9 is a monosialoganglioside that is commonly found in various types of mucinous tumors in the gastrointestinal tract such as the pancreas and biliary tract.[14] Measurement of serum CA19-9 is important in identifying and determining the progression of colorectal, pancreatic, and biliary tract cancers. Elevated levels of serum CA19-9 may indicate the presence of mucinous BOTs.[15] In similar studies, high CA 19-9 levels in serous and mucinous BOTs were found to be 51.5% and 44.7%, respectively,[12] and in another study, they were found to be 44.24% and 36.4%, respectively.[16] In our study, on the contrary, there was no difference in CA 19-9 between mucinous and serous BOTs. Studies have associated high levels of CA 19-9 with larger tumor size.[13] In our study, no relationship was found between tumor sizes and CA 19-9 tumor markers.

CEA, a naturally occurring high molecular weight glycoprotein found in fetal tissues, is often used as a marker for gastrointestinal malignancies. Published studies have shown that high CEA levels are associated with advanced stage and tumor size, with specific nuances.[12,13] On the contrary, there are also publications that do not associate high CEA levels with the stage of FIGO.[17] No association between CEA levels and the stage of FIGO was found in the current study. The CA 15-3 test is used to measure the presence of the MUC-1-encoded glycoprotein, which is commonly known as polymorphic epithelial mucin. This protein is expressed at the surface of most glandular epithelial cells. It is widely used as a marker for breast cancer, but it can also be present at high levels in patients with ovarian cancer.[18] In a similar study, CA 15-3 levels were found to be normal in patients with BOT.[19] In our study, no difference was observed between serous and mucinous BOTs in terms of CA 15-3.

Although in current applications, tumor markers are used to evaluate treatment response and recurrence, they can be helpful in the diagnosis and management of BOTs. We acknowledge the limitations of this study, in particular the small number of women, and not examining the possible inflammatory and proliferative markers on high tumor markers levels. Future prospective studies with large sample size in well-staged patients with BOTs examining the tumor markers levels are needed.

CONCLUSION

Our primary outcome of the study is an increase in CA 125 levels, which indicates serous histopathology. Our secondary outcome is the higher levels of tumor markers, but it does not suggest larger tumors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Okmeydanı City Hospital Clinical Researches Ethics Committee (Date:26.12.2022, Decision No:364).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The role of saline infusion sonohysterography in the evaluation of infertility

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ABSTRACT

Aims: The study aimed to evaluate possible intrauterine pathologies that may not be visible in basal transvaginal ultrasonography in infertile patients using saline infusion sonohysterography.

Methods: Between January 2019 and January 2020, 110 patients who presented to the Ankara University Faculty of Medicine, Obstetrics and Gynecology Infertility Polyclinic were enrolled in the study. Saline infusion sonohysterography was performed on primary and secondary infertile patients who were not diagnosed with endometrial pathology via ultrasonography.

Results: Pathological findings were detected in 11 out of 110 patients (10.6%) during saline infusion sonohysterography, including polyps, myomas, and adhesions. These patients were referred to hysteroscopy by their practitioner. After the procedure, pathological findings were detected in 54.5% of cases by hysteroscopy. According to these data, the sensitivity of saline infusion sonohysterography in detecting intracavitary pathologies was 60%, specificity was 80.7%, positive predictive value was 54.5%, negative predictive value was 84%, and reliability was 75%.

Conclusion: Saline infusion sonohysterography can detect endometrial pathologies not identified by TV USG, suggesting its cost-effective addition to routine evaluations for infertile patients and potential endometrial pathologies.

Keywords: Saline infusion sonohysterography, infertility, endometrium, ultrasonography

INTRODUCTION

Infertility is generally defined as the inability to achieve pregnancy after one year of regular, unprotected sexual intercourse.[1] The global prevalence of infertility is between 8-12%.[2] This means that approximately 15% of couples are affected by infertility. However, the prevalence of infertility may vary across countries and age groups.[3]

Currently, the tests performed at the first consultation of infertile couples include semen analysis, evaluation for infectious diseases and cervical evaluation, ovarian reserve tests and evaluation of ovulation, and assessment of uterine cavity and tubal patency.[4] Among these tests, transvaginal ultrasound (TV USG) and hysterosalpingography (HSG) are commonly used for the evaluation of the endometrial cavity.[5] Hysteroscopy, which was frequently used in the past for initial evaluation, is no longer used for this purpose as it is an invasive procedure that requires anesthesia and cannot provide information about the myometrium and adnexa.[6] Saline infusion sonohysterography (SIS) is a method that is cheap, well-tolerated, and applied without exposure to radiation for the evaluation of the endometrial cavity.[7] In addition, SIS has been shown to have no significant adverse effects and is a cost-effective method.[8]

Previously, other methods such as TV USG, HSG, and office hysteroscopy have been compared for the evaluation of the endometrial cavity in infertile patients.[9-11] In this study, the aim was to evaluate potential intrauterine pathologies that were not detected in basal TV USG with SIS in infertile patients.

METHODS

The study was carried out with the permission of Ankara University Clinical Researches Ethics Committee (Date: 26.11.2018 Decision No: 19-1301-18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Study Design and Data Collection

Between January 2019 and January 2020, patients who applied to the Infertility Clinic of the Department of Obstetrics and Gynecology, Ankara University Faculty of Medicine, were evaluated. Among the 1208 patients who met the criteria and accepted the procedure, those who were between the ages of 20-35 and had normal TV USG findings were included in the study as primary or secondary infertility patients. Patients with a history of systemic endocrinological disease or previous uterine surgery were excluded from the study. Detailed medical history was obtained from each patient, and routine investigations including TV USG for endometrial thickness and adnexal pathology, hormonal profile on day 3, HSG, and semen analysis for male infertility evaluation were performed. Eligible patients were provided with detailed information about the study. As can be seen in the details in **Figure**, 110 patients who agreed to participate and signed the informed consent form were included in the study.

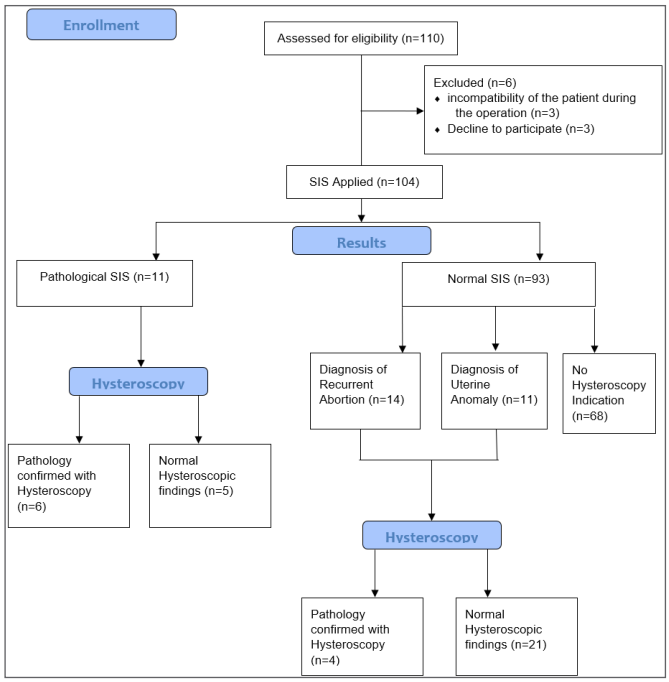

Figure. CONSORT 2010 Flow diagram

SIS Procedure

Patients included in the study were subjected to SIS on the 5th-6th day of their menstrual cycle. All procedures were performed by the same operator. The cervix was visualized with a speculum in the lithotomy position on the gynecological table. Povidone iodine solution was applied to the cervix, and then it was grasped with a tenaculum at the upper end. We utilize the tenaculum to facilitate the accurate insertion of the catheter into the uterine cavity, as well as to prevent any potential oversight of pathologies resulting from uterine malpositioning and to ensure standardization among patients. The cervical ostium was reached with a HSG catheter, and the balloon was inflated. The speculum was removed, and the TV ultrasound probe was inserted into the vagina. Approximately 5-10 cc of saline was injected through the catheter, and the uterine cavity was observed.

Statistical Analysis

Software program SPSS 28.0.1 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The distribution of the parameters was evaluated using the Kolmogorov-Smirnov test. The mean and standard deviation were used to describe the data. The G Power 3.1.9.7 software was used to determine the sample size based on the referenced article. According to these calculations, it was concluded that at least 98 patients should be included in the study.

RESULTS

The average age of patients included in the study was calculated as 28.8±5.8 years. Their mean BMI was calculated as 25.75±4.7 kg/m². The TV USG showed that the ovaries of 19 patients had a multifollicular appearance. The AMH value of 12 patients was below 1 ng/ml (**Table 1**).

Table 1. Demographic Results

Demography	**Mean±SD**
Age (year)	28.8±5.8
BMI (kg/m²)	25.75±4.7
Infertility period (year)	5.3±4.4
Infertility Status	**N (%)**
Primary	92 (88.5%)
Secondary	12 (11.5%)
Multifollicular ovarian morphology	19 (18.2%)
AMH <1 ng/ml	12 (11.5%)

The average infertility duration of patients who underwent SIS was calculated as 5.37±4.4 years. Twelve patients had secondary infertility (11.5%), 8 had male infertility (7.6%), and the remaining patients were evaluated as having infertility with an unknown cause.

Intracavitary pathology was not detected in the TV USG and HSG evaluations of these patients. Patients who were found to have septum or t-shaped uterus appearance in HSG were evaluated as having uterine shape anomaly and were not considered as endometrial pathology, and included in the study

Three patients who met the criteria were not treated during the procedure due to their incompatibility. The procedure was postponed in 7 patients who had findings compatible with active pelvic infection. Cultures were taken from the patients, appropriate treatments were given, and new appointments were made for the procedure. The procedure was performed on 3 of these 7 patients. Pathological filling defects were detected

in 11 of the 104 patients (10.6%) who underwent SIS. Hysteroscopy was performed on these patients. After hysteroscopy, pathologies such as polyps, myomas, and adhesions were detected in 6 patients (54.5%).

Hysteroscopy was performed on 14 of the 93 patients whose SIS result was normal due to recurrent pregnancy loss diagnosis and on 11 patients due to a diagnosis of uterine shape anomaly. Endometrial polyps were detected in 4 cases and these polyps were 2-5 mm in diameter and located near the tubal ostium. The endometrial cavity was evaluated as normal in 21 cases. No complications were observed in the patients after the procedure.

According to our calculations with these data, the sensitivity of SIS in detecting intracavitary pathologies was calculated as 60%, specificity as 80%, positive predictive value as 54.5%, and negative predictive value as 84% (**Table 2**).

Table 2. Detection status of intracavitary pathologies of SIS

	Hysteroscopy positive	Hysteroscopy negative	
SIS positive	6	5	54.5% (PPV)
SIS negative	4	21	84% (NPV)

DISCUSSION

Fertility problems are a health issue that affects both individuals and society, with biological, social, cultural, and psychological dimensions. In a study, it was found that about 10-15% of couples who want to conceive are unable to do so and seek medical attention.[12] Among infertile couples who begin treatment, abnormal uterine cavity findings are observed in approximately 34-62%.[9,13]

The first option to evaluate the uterine cavity is usually TV USG. This is a non-invasive and relatively simple procedure where a specially designed ultrasound probe is inserted into the vagina to visualize the uterus, endometrium (lining of the uterus), and ovaries.[14] TV USG can help identify structural abnormalities or pathology such as uterine fibroids, polyps, adhesions, or abnormalities of the endometrial lining that may affect fertility or menstrual function. If necessary, further tests such as SIS, HSG or hysteroscopy may be performed to provide more detailed information.[12]

Direct visualization and treatment of the uterine cavity is an advantage of the gold standard method hysteroscopy.[15] However, hysteroscopy is an expensive method that requires operating room conditions and anesthesia.[16] The inSIGHT study, a multicenter randomized study evaluating the routine use of hysteroscopy as a diagnostic method, showed that hysteroscopy did not change the live birth rate and was not recommended to be performed before the first IVF treatment in asymptomatic patients.[17]

In a study by Yu et al.[18] 215 women underwent hysteroscopy before their first IVF cycle, while 284 women only received TV USG. Both groups were similar in terms of demographic and clinical characteristics. There were no significant differences in cycle pregnancy rate (CPR) (43% versus 44%), miscarriage rate (15.2% versus 16%), and live birth rate (LBR) (34% versus 35.6%) between the two groups. It was concluded that hysteroscopy performed before IVF treatment did not change the implantation or live birth rates.

Another study involved 421 patients between 24-40 years old who had undergone multiple failed IVF cycles with good quality embryo transfers. They were randomly divided into two groups: Group I (211 patients) did not undergo an office hysteroscopy evaluation before IVF treatment, while Group II (210 patients) did. Group II was further divided into two subgroups: IIa (154 patients) with normal hysteroscopic findings and IIb (56 patients) with abnormal findings. The study found no significant differences in terms of first-trimester abortions across all groups.[19]

According to a study by Aslam et al.[20] SIS had higher sensitivity and specificity compared to TV USG. Specifically, SIS had 92.9% sensitivity and 89.7% specificity, whereas TV USG had 71.4% sensitivity and 67.7% specificity. Additionally, there was higher agreement between SIS and hysteroscopy compared to TV USG. SIS demonstrated better diagnostic performance for endometrial hyperplasia, polyps, and submucous myoma compared to TV USG, with SIS showing 100% sensitivity and specificity for submucous myoma compared to 61.55% and 97.7%, respectively, for TV USG. In our study, SIS was able to detect 60% of the pathologies that could not be detected by TV USG. We believe that the reason for the sensitivity remaining at around 60% in these patients is due to the small size of the polyps in these cases, which are located near the tubal ostium.

In another study conducted by Brown et al.[9] HSG, SIS, and office hysteroscopy were compared with hysteroscopy. Patients were evaluated with each of the three radiological methods on separate outpatient visits. If pathology was detected, the patient was admitted for operative hysteroscopy under anesthesia. Of the 46 patients in the study, pathology was detected in at least one method in 27 patients, who were then referred for hysteroscopy. It was noted that only 33% of the identified pathologies were detected by all three radiological methods. Similarly, 60% of the pathologies observed in hysteroscopy were correctly classified in HSG, 72% in office hysteroscopy, and 52% in SIS. Additionally, when the 25 patients examined with SIS were compared to hysteroscopy, a correct diagnosis was made in 13 patients

(54%). Similarly, in our study, out of the 11 patients where SIS detected pathology, a correct diagnosis was made in 6 (54.54%), which is consistent with the literature.

Obajimi et al.[21] published a retrospective analysis of data from a clinic that routinely performed SIS before IVF treatment. Of the 760 patients reviewed, pathology was detected in 349. The sensitivity of SIS was calculated as 96% compared to hysteroscopy performed later in these patients. In our study, we calculated a sensitivity of 60%. The difference in rates may be due to the higher number of patients in the study by Obajimi et al.[21] additionally, the small size and proximity to the tubal ostium of polyps that we could not detect with SIS may also contribute to this difference.

Radwan et al.[22] also conducted a study to evaluate the role of SIS in the assessment of endometrial polyps in patients diagnosed with infertility. The study compared SIS and hysteroscopy in 241 infertile patients, and endometrial polyp diagnosis was confirmed by both hysteroscopy and SIS in 72 patients. Seven patients were suspected to have polyps on SIS but were not seen on hysteroscopy, and two patients had no pathology on SIS but were found to have polyps on hysteroscopy. The study did not provide information on whether TV USG findings showed pathology in patients. However, in our study, we included only patients with normal TV USG findings. Although hysteroscopy was performed in every patient in Radwan et al.'s study, recent studies have shown that performing hysteroscopy does not provide additional benefits. Furthermore, it was found that hysteroscopy to identify 72 polyps in 241 patients would not be cost-effective, and SIS was deemed sufficient. Radwan et al.[22] also noted that the polyps that were not detected on SIS were located near the tubal ostium and had dimensions of 2×3 mm. It was concluded that these undetected polyps could not be seen on SIS due to their small size and location near the tubal ostium. Similarly, in our study, the polyps that were not visible on SIS had small dimensions and were located near the tubal ostium.

Despite the advanced technology of TV USG, endometrial pathologies may still go undetected. In this study, we aimed to evaluate potential endometrial pathologies in cases where no pathology was detected by TV USG, using SIS, which allows for more advanced evaluation of the endometrial cavity.

Our study included 104 patients, and SIS detected additional endometrial pathology in 10.6% of cases where no pathology was detected by TV USG. Therefore, considering SIS as a patient-friendly examination, we believe that it should be included in routine infertility evaluations.

Our study had some limitations; although our sample size was adequate, we were unable to compare the cost-effectiveness and patient comfort of SIS to other testing techniques in a single sentence, necessitating further research to potentially establish SIS as a routine procedure. Moreover, we did not perform hysteroscopy on all patients, as it was not recommended as a routine procedure in previous multicenter randomized controlled prospective studies. Consequently, our assessment of the sensitivity and specificity of SIS may have been limited. The inclusion of hysteroscopy could have provided a more comprehensive evaluation of the diagnostic accuracy of SIS. In order to further assess SIS, we could have evaluated patients' pain experiences; however, the use of the tenaculum, which was employed to assess diagnostic boundaries and standardize patients in our study, hindered the evaluation of the pain scale. In future studies, the advantages of performing the SIS procedure without using a tenaculum in terms of patient comfort can be assessed.

CONCLUSION

We aimed to demonstrate that endometrial pathologies could be detected by SIS even when not identified by TV USG. Based on these results, we believe that SIS is a cost-effective application and should be included in the routine evaluation of not only infertile patients but also all potential endometrial pathologies, in addition to TV USG.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara University Non-invasive Clinical Researches Ethics Committee (Date: 26.11.2018, Decision No: 19-1301-18).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The evolution of hemorrhoids publications during 1980-2021: a global and medical view with bibliometric analysis

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ABSTRACT

Aims: Hemorrhoids is a common anorectal disorder and significantly affects quality of life. Although the number of global studies on hemorrhoids has increased in recent years, there is still no bibliometric study in the literature. In this study, it aimed that analyzing the scientific articles published on hemorrhoids holistically.

Methods: The articles published between 1980 and 2021 were analyzed using bibliometric and statistical methods on hemorrhoids. Network visualization maps were used to identify trending topics and international collaborations. Spearman's correlation coefficient was used for correlation studies. The Exponential Triple Smoothing estimator was used to estimate the number of articles expected to be published in the coming years.

Results: A total of 3203 publications were found. 1863 (58.1%) of these publications were articles. The most active author is Gupta PJ. (n=26). The first 2 journals that published the most articles were Diseases of the Colon & Rectum (n=228) and Colorectal Disease (n=82). Singapore General Hospital (n=35) and University of Rome La Sapienza (n=19) were the 2 most active institutions. According to the average number of citations per article, the top 2 most influential journals were British Journal of Surgery and American Journal of Gastroenterology.

Conclusion: In this comprehensive study on hemorrhoids, a statistical analysis of 1863 articles was shared. It was determined that the trend topics in hemorrhoid researches were THD, mucopexy, transanal hemorrhoidal dearterialization, colorectal surgery, embolization, constipation, risk factors, Milligan-Morgan, classification, recurrence and randomized controlled trial. This article can be a useful resource for scientists and clinicians in terms of the global output of hemorrhoids yesterday, today and tomorrow.

Keywords: Hemorrhoids, haemorrhoids, bibliometric analysis, citation analysis, trends

INTRODUCTION

Hemorrhoidal disease is a common anorectal disorder that causes physical and psychological discomfort and significantly affects quality of life.[1,2] The main symptoms of hemorrhoids are bleeding, itching, soiling, pain, prolapse, and mucus discharge.[1-3] Especially a good history and careful physical examination can make an accurate diagnosis. Internal hemorrhoids that do not protrude can only be found during endoscopy.[1,2] Complete endoscopic evaluation of the colon is indicated in patients with rectal bleeding.[4]

Bowel habits and lifestyles can be risk factors for hemorrhoids.[3] A low-fiber diet and constipation are thought to increase the risk of hemorrhoids.[2] Dietary modification (rich in adequate fluid and fiber intake) and behavioral therapies such as defecation habits counselling, medical treatment (e.g. stool softeners, topical nitroglycerin), and warm water sitz baths typically constitute the first-line conservative treatment for patients with symptomatic hemorrhoid disease.[4,5] Medication for hemorrhoids is typically used for bleeding, pain, and swelling.[3]

A number of office-based interventions, such as rubber band ligation and infrared coagulation, are widely used and economically viable for the effective treatment of hemorrhoids resistant to medical treatments. Surgical procedures are effective in removing hemorrhoids, but can cause more pain and longer recovery time than office-based procedures.[2,5] Therefore, hemorrhoidectomy should be considered for recurrent or higher grade disease.[5] Internal hemorrhoids are traditionally graded I to IV according to the degree of prolapse.[5] Most grade I-II patients and patients with grade III internal hemorrhoidal disease for whom medical treatment has failed can be effectively treated with office-based

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procedures such as taping, sclerotherapy, and infrared coagulation (IRCHemorrhoidectomy should typically be offered to patients whose symptoms result from external hemorrhoids or combined internal and external hemorrhoids with prolapse (grade III-IV).[3-5]

Complications after surgical hemorrhoidectomy are low, the most common being post-procedural bleeding, with most larger series reporting an incidence of between 1% and 2%.[6] Acute urinary retention has been reported to occur between 1% and 15% and is the most common reason for surgical inability to discharge patients.[4,7]

Symptoms related to hemorrhoids are very common in the western hemisphere and other industrialized societies.[4] Although published prevalence estimates for hemorrhoids, which represent one of the most common medical and surgical diseases encountered in the United States, differ, more than 2.2 million outpatients per year; is the diagnosis of the third most common gastrointestinal pathology.[2,4] The overall prevalence in adults in Austria was reported as 39% by Riss et al.[1]

Bibliometrics is the analysis of scientific publications in the literature using various statistical methods.[8,9] Especially in recent years, in parallel with the increasing number of publications in the literature, bibliometric studies have been carried out on many important medical subjects.[8-14] Thanks to studies using bibliometric and statistical approaches, past and current trends, the most influential publications and journals, the most active authors and institutions can be determined about a subject or research area.

In addition, such studies give researchers the opportunity to dominate the literature in a short time.[8-14] Although the number of global studies on hemorrhoids has increased in recent years, there is still no bibliometric study in the literature. In this study, it was aimed to evaluate the scientific articles on hemorrhoids published between 1980 and 2021 holistically using bibliometric and statistical approaches. As a result of the analyzes, it was aimed to determine the most effective studies and journals, the most active countries, institutions and authors on hemorrhoids, to reveal cooperation between countries, and to identify past and current issues.

METHODS

The study is an open data study, does not contain human or animal material, and does not require ethics committee approval. All procedures were carried out in accordance with the ethical rules and the principles.

Web of Science (WoS) database (by Clarivate Analytics) was used for the literature review. The publication scan was performed only in the "title" section of the publications. All keywords related to hemorrhoid ("hemorrhoid*", "haemorrhoid*") were used for literature search in the WoS database. As a result of this search method, all articles containing any of the statements about hemorrhoids and other uses in the title were obtained and downloaded from the WoS database. The search process was determined as 1980-2021 (access date: 30.11.2021). Reproducibility codes (search findings may vary depending on different access dates) for researchers to access similar documents: (Title: (hemorrhoid*) or Title: (haemorrhoid*) Timespan: 1980-2021. Indexes: SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI). VOSviewer (Version 1.6.17, Leiden University's Center for Science and Technology Studies) package program was used for bibliometric network visualizations and citation analysis (15). The Exponential Smoothing estimator was used in the Microsoft Office Excel program to estimate the number of publications in the coming years based on past publication trends. Statistical analysis were performed with SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normal distribution of data was tested with the Kolmogorov-Smirnov test. The correlations between the publication productivity of the world countries on hemorrhoids and some economic development indicators (Gross Domestic Product (GDP), Gross Domestic Product per capita (GDP per capita)) of the countries (data obtained from the world bank) were investigated with Spearman's correlation coefficient in accordance with the data distribution (16). The statistically significant difference was considered to be $P<0.05$.

RESULTS

A total of 3203 publications were found in the literature review of the WoS database on hemorrhoids between 1980-2021. The distribution of these publications is Article (1863, 58.1%), Meeting Abstract (495, 15.4%), Letter (364, 11.3%), Review (165, 5.1%), Proceedings Paper (158, 4.9%), and the rest (n=158) were in other publication types (Editorial material, Book Chapter, Note, Correction, Early Access, News item, Book, Correction Addition, Discussion, Book review, Poetry, Reprint, Retracted publication). Bibliometric analyzes were carried out with 1863 articles from 3203 publications in total. 88% (1640) of these articles were in English, 5.2% (97) in German, 3.2% (60) in French, 1.5% (28) in Spanish, 1.1% (22) in Russian, and the rest in other languages. (Italian (6), Turkish (3), Japanese (2), Dutch (1), Hungarian (1), Korean (1), Portuguese (1), Ukrainian (1)) were published. The h-index of 1863 articles was 69, average citations per article 14.57, sum of times cited 27138 (without self citations: 13021).

Active Research Areas

The top 7 research areas with the most articles on hemorrhoids are Surgery (1028, 55.1%), Gastroenterology Hepatology (699, 37.5%), Medicine General Internal (284, 15.2%), Medicine Research Experimental (85, 4.5%), Pharmacology Pharmacy. (76, 4.0%), Integrative Complementary Medicine (23, 1.2%), and Radiology Nuclear Medicine Medical Imaging (22, 1.1%).

Development and Future Trend of Publications

The distribution of the number of published articles by years is shown in **Figure 1**. The estimation values of the results of the Exponential Smoothing estimation model, which is used to estimate the number of articles that can be published in 2021 and beyond, and the distribution of the number of published articles by years are shown in **Figure 1**. Since 2021 was not completed, it was excluded from the forecasting model. According to the estimation model results, it is estimated that 106 (Confidence Interval %: 83-128) articles will be published in 2021 and 113 (CI%: 81-145) articles will be published in 2025 (**Figure 1**).

Active Countries

The distribution of the number of articles by world countries is shown in **Figure 2**. Top 25 countries with the highest number of articles on hemorrhoids USA (250, 13.4%), Italy (210, 11.2%), UK (198, 10.6%), Germany (115, 6.1%), China (100, 5.3%), France (96, 5.1%), India (83, 4.4%), Japan (69, 3.7%), Turkey (62, 3.3%), Taiwan

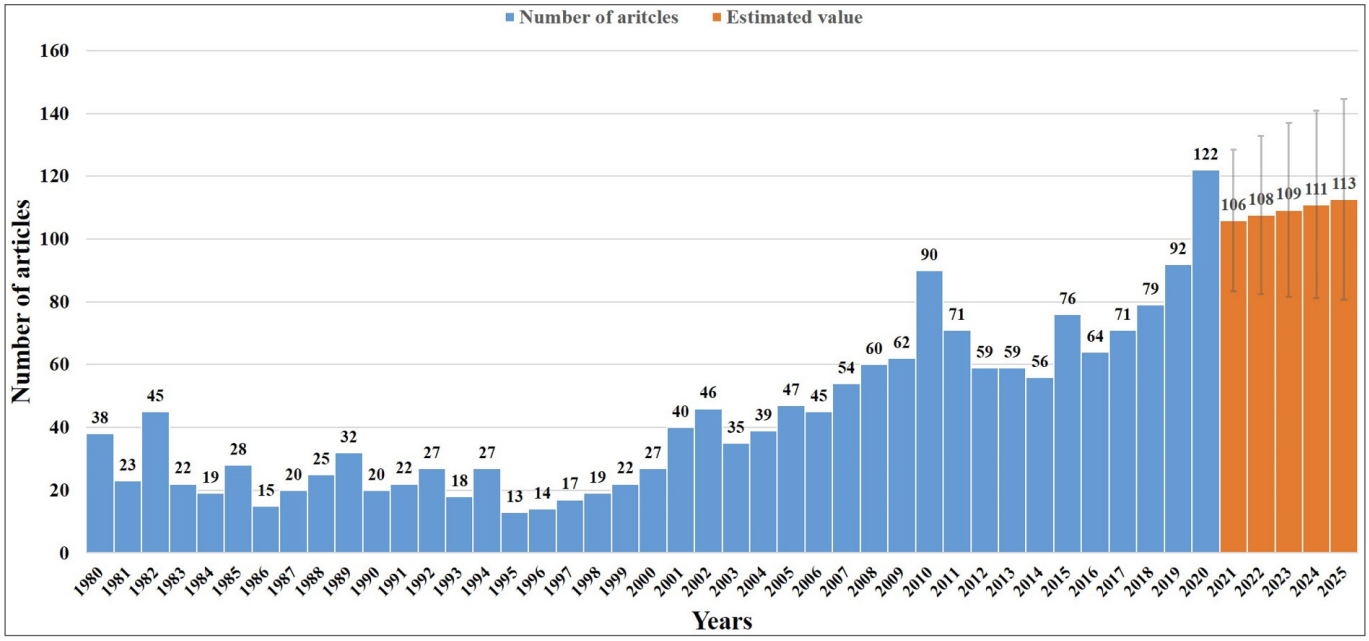

Figure 1. Distribution of articles on Hemorrhoids by years and estimation of articles in the coming years

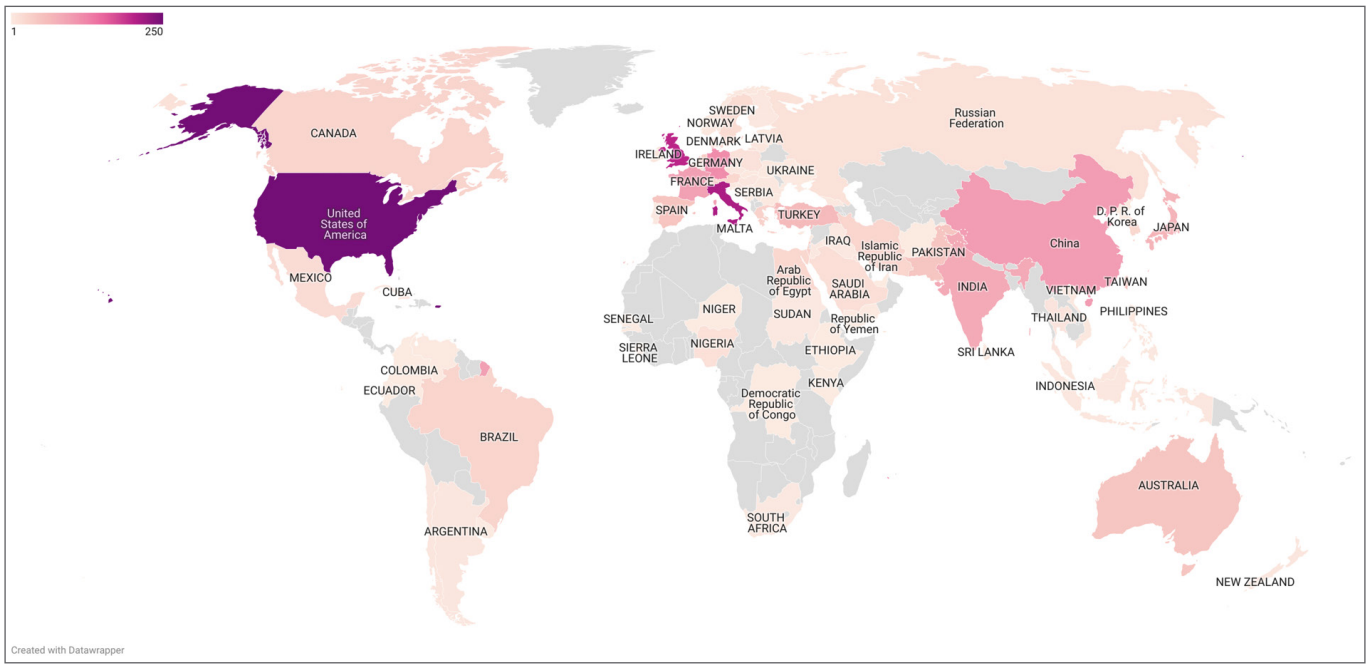

Figure 2. Top 20 countries in the world that have published the most articles on tracheostomy

(51, 2.7%), Spain (48, 2.5%), Australia (47 , 2.5%), Pakistan (47, 2.5%), Singapore (46, 2.4%), Netherlands (36, 1.9%), Israel (33, 1.7%), Switzerland (32, 1.7%), Greece (31, 1.6)), Brazil (28, 1.5), Canada (28, 1.5), Iran (27, 1.4%), Austria (24, 1.2%), Egypt (24, 1.2%), South Korea (24, 1.2%), Sweden (20, 1.0%). Network visualization map of cluster analysis, which was obtained as a result of cluster analysis among 35 countries that produced at least 5 articles from 103 countries producing publications on hemorrhoids and whose authors have international cooperation, is shown in **Figure 3.a.** According to the results of the analysis, 8 different clusters related to international cooperation were formed (Cluster 1: Belgium, Canada, France, India, Malaysia, Mexico, Russia, Thailand. Cluster 2: Denmark, Germany, Greece, Japan, Lithuania, Spain, Sweden. Cluster 3: Chile, Iran, Italy, Singapore, South Korea, Switzerland, USA Cluster 4: Netherlands, Poland, Turkey Cluster 5: Israel, China, Taiwan Cluster 6: England, Scotland, Wales Cluster 7: Australia, New zealand. Cluster 8: Austria, Nigeria). Total link strength scores showing the strength of cooperation were calculated for these 35 countries. The International collaboration density map created according to these scores is shown in **Figure 3.b.**

Correlation Analysis

There was a statistically positive and highly significant correlation between the GDP, and GDP per capita values of the world countries and the number of articles produced by the countries on Hemorrhoid (r=0.729, p<0.001; r=0.606, p<0.001).

Active Authors

The top 10 most active authors producing the most articles on hemorrhoids are Gupta PJ, respectively. (n=26), Eu KW. (18), Seow-Choen F. (17), Altomare DF. (15), HoYH. (14), Milito G. (13), Naldini G. (13), Ratto C. (13), Watson AJM. (13), Mascagni D. (11).

Active Institutions

The most active universities producing 10 or more articles on hemorrhoids are Singapore General Hospital (n=35), University of Rome La Sapienza (n=19), Tel Aviv University (18), University of Rome Tor Vergata (18), China Medical University (12), Raigmore Hospital (11), University Copenhagen (11), University Milan (11), University Illinois (10), Aristotle University Thessaloniki (9), Shanghai University of Traditional Chinese Medicine (9), University of California Los Angeles (9), University Palermo (9), and University of Sao Paulo (9).

Active Journals

1863 articles on hemorrhoids were published in 515 different journals. The first 35 most active journals producing 10 or more articles from these journals, the total number of citations received by the journals and the average number of citations per article are presented in **Table 1**. The citation network visualization map between these journals is presented in **Figure 4.**

Citation Analysis

The first 30 articles with the highest number of citations according to the total number of citations from 1863 articles published between 1980-2021 are presented in **Table 2**. The average number of citations received by the articles per year is given in the last column of **Table 2.**

Co-citation Analysis

There were a total of 14024 studies cited in the references section of all 1863 articles analyzed. The top 10 studies that received the most co-citations (more than 140 citations) were Longo (17) (NC: 227), Milligan (18) (NC:222), Thomson (19) (NC:219), Mehigan (20) (NC: 195), Macrae (21) (NC: 182), Johanson (22) (NC: 168), Morinaga (23) (NC:167), Rowsell (24) (NC:163), Cheetham (25) (Number of co-citations, NC: 141), Ganio (26) (NC: 140), were his works (17-26).

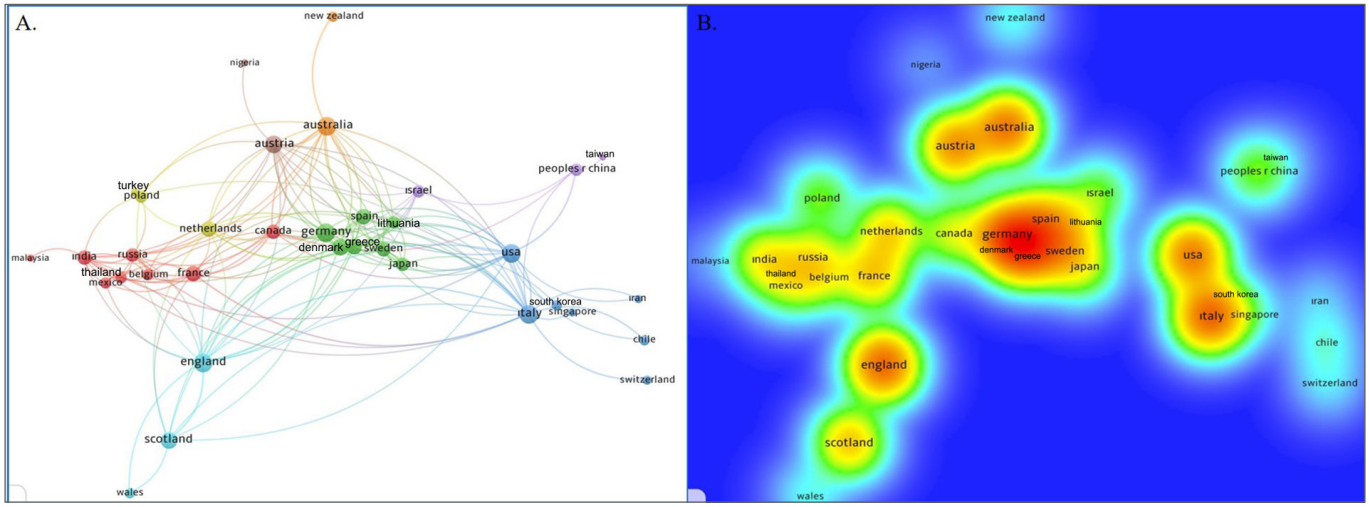

Figure 3. a. Network visualization map of cluster analysis on international collaboration between countries on Hemorrhoids. Footnote: Colors indicate clustering. The size of the circle indicates the large number of articles. b. Density map for international collaboration of countries on tracheostomy. Footnote: The strength of international collaboration score increases from blue to red (blue-green-yellow-red)

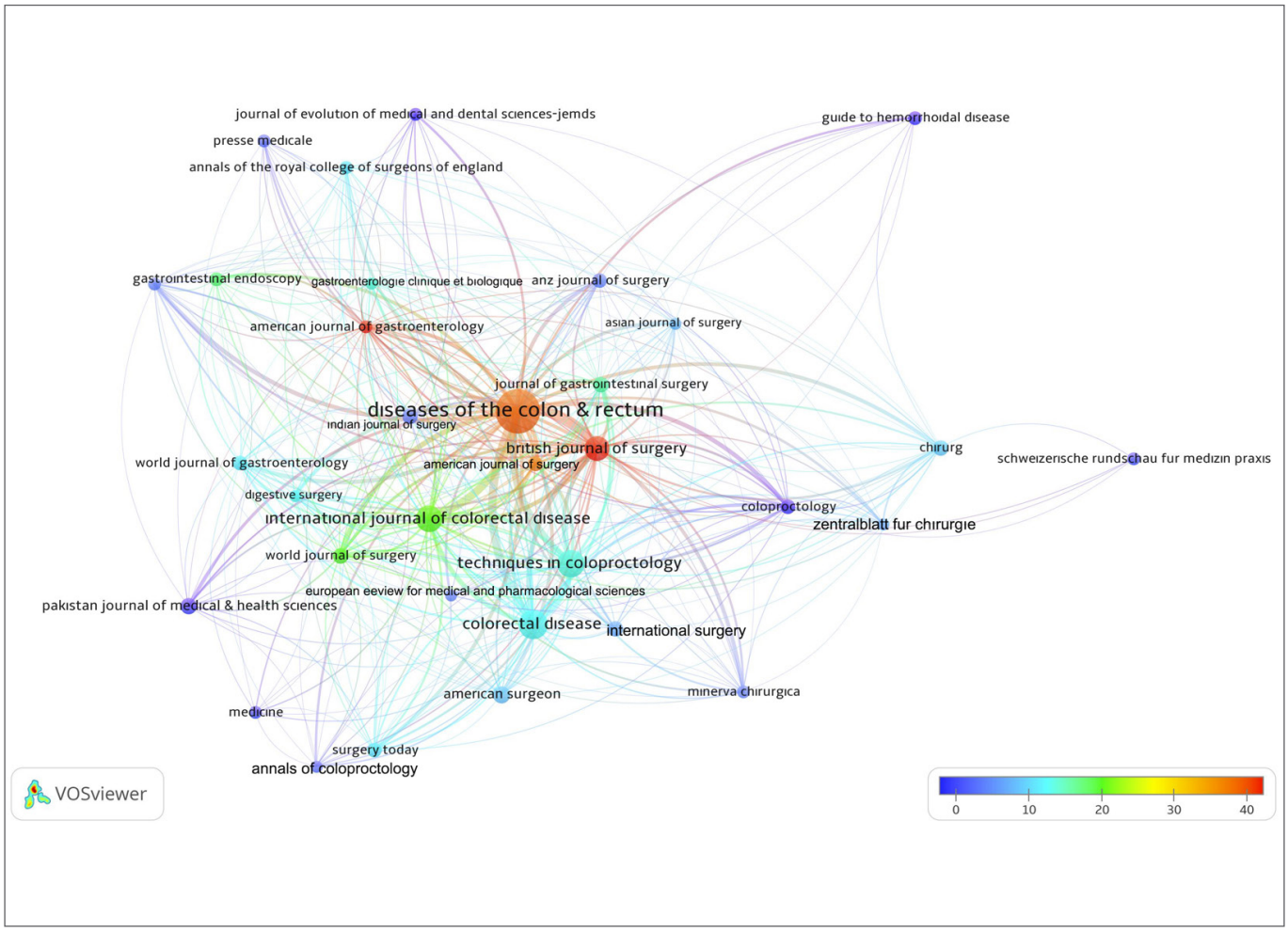

Figure 4. Network visualization map for citation analysis of active journals on Hemorrhoids. Footnote: The average number of citations per article by journals increases from blue to red (blue-green-yellow-red). The size of the circle indicates the large number of articles.

Table 1. The 35 most active journals that have published more than 10 articles on hemorrhoids

Journals	RC	C	AC	Journals	RC	C	AC
Diseases of the Colon & Rectum	228	8482	37.20	Guide to Hemorrhoidal Disease	14	1	0.07
Colorectal Disease	82	1106	13.49	American Journal of Gastroenterology	13	547	42.08
Techniques in Coloproctology	71	1018	14.34	Annals of the Royal College of Surgeons of England	13	142	10.92
International Journal of Colorectal Disease	67	1399	20.88	Annali Italiani Di Chirurgia	13	59	4.54
British Journal of Surgery	56	2674	47.75	Khirurgiya	13	3	0.23
American Surgeon	25	224	8.96	Journal of Evolution of Medical and Dental Sciences-Jemds	12	0	0.00
Pakistan Journal of Medical & Health Sciences	21	12	0.57	Medicine	12	17	1.42
Chirurg	19	182	9.58	Minerva Chirurgica	12	57	4.75
Journal of Gastrointestinal Surgery	19	310	16.32	Presse Medicale	12	40	3.33
World Journal of Surgery	19	384	20.21	Schweizerische Rundschau Fur Medizin Praxis	12	17	1.42
Indian Journal of Surgery	18	77	4.28	Annals of Coloproctology	11	34	3.09
International Surgery	18	129	7.17	Digestive Surgery	11	149	13.55
American Journal of Surgery	17	613	36.06	European Review for Medical and Pharmacological Sciences	11	51	4.64
Anz Journal of Surgery	17	76	4.47	Zentralblatt Fur Chirurgie	11	78	7.09
Coloproctology	17	6	0.35	Asian Journal of Surgery	10	83	8.30
World Journal of Gastroenterology	17	195	11.47	Gastroenterologie Clinique Et Biologique	10	145	14.50
Surgery Today	16	181	11.31	Prensa Medica Argentina	10	0	0.00
Gastrointestinal Endoscopy	15	267	17.80				

RC: Record Count, C: Number of Citation, AC: Average Citation Per Document

Table 2. The top 30 most cited articles on hemorrhoids by total number of citations

No	Article	Author	Journal	PY	TC	AC
1	The prevalence of hemorrhoids and chronic constipation - an epidemiologic-study	Johanson JF. et al.	Gastroenterology	1990	318	9.94
2	Stapling procedure for haemorrhoids versus milligan-morgan haemorrhoidectomy: randomised controlled trial	Mehigan BJ. et al.	Lancet	2000	296	13.45
3	Comparison of hemorrhoidal treatment modalities - a metaanalysis	Macrae HM. et al.	Diseases of The Colon & Rectum	1995	272	10.07
4	Circumferential mucosectomy (stapled haemorrhoidectomy) versus conventional haemorrhoidectomy: randomised controlled trial	Rowsell M. et al.	Lancet	2000	261	11.86
5	A novel therapy for internal hemorrhoids - ligation of the hemorrhoidal artery with a newly devised ınstrument (moricorn) ın conjunction wıth a doppler flowmeter	Morinaga K. et al.	American Journal of Gastroenterology	1995	238	8.81
6	Persistent pain and faecal urgency after stapled haemorrhoidectomy	Cheetham MJ. et al.	Lancet	2000	236	10.73
7	Postoperative complications after procedure for prolapsed hemorrhoids (pph) and stapled transanal rectal resection (starr) procedures	Pescatori M. et al.	Techniques in Coloproctology	2008	224	16
8	Prospective randomized multicentre trial comparing stapled with open haemorrhoidectomy	Ganio E. et al.	British Journal of Surgery	2001	223	10.62
9	Stapled hemorrhoidectomy - cost and effectiveness. Randomized, controlled trial ıncluding ıncontinence scoring, anorectal manometry, and endoanal ultrasound assessments at up to three months	Ho YH. et al.	Diseases of The Colon & Rectum	2000	208	9.45
10	Bupivacaine extended-release liposome ınjection for prolonged postsurgical analgesia ın patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial	Gorfine SR. et al.	Diseases of The Colon & Rectum	2011	202	18.36
11	Anal cancer ıncidence - genıtal warts, anal-fissure or fistula, hemorrhoıds, and smoking	Holly EA. et al.	Jnci-Journal of The National Cancer Institute	1989	196	5.94
12	Symptomatic hemorrhoids - current ıncidence and complications of operative therapy	Bleday R. et al.	Diseases of The Colon & Rectum	1992	188	6.27
13	Systematic review on the procedure for prolapse and hemorrhoids (stapled hemorrhoidopexy)	Tjandra Joe J. et al.	Diseases of The Colon & Rectum	2007	187	12.47
14	Randomized clinical trial of stapled versus milligan-morgan haemorrhoidectomy	Shalaby R. et al.	British Journal of Surgery	2001	175	8.33
15	Life threatening pelvic sepsis after stapled haemorrhoidectomy	Molloy RG. et al.	Lancet	2000	170	7.73
16	Stapled hemorrhoidopexy compared with conventional hemorrhoidectomy: systematic review of randomized, controlled trials	Nisar PJ. et al.	Diseases of The Colon & Rectum	2004	167	9.28
17	The prevalence of hemorrhoids in adults	Riss S. et al.	International Journal of Colorectal Disease	2012	156	15.6
18	Anorectal varices, hemorrhoids, and portal-hypertension	Hosking SW. et al.	Lancet	1989	151	4.58
19	A prospective, randomized, controlled multicenter trial comparing stapled hemorrhoidopexy and ferguson hemorrhoidectomy: perioperative and one-year results	Senagore AJ. et al.	Diseases of The Colon & Rectum	2004	141	7.83
20	Stapled vs excision hemorrhoidectomy - long-term results of a prospective randomized trial	Hetzer FH. et al.	Archives of Surgery	2002	135	6.75
21	Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy	Carapeti EA. et al.	Lancet	1998	134	5.58
22	Randomised controlled trial between stapled circumferential mucosectomy and conventional circular hemorrhoidectomy in advanced hemorrhoids with external mucosal prolapse	Boccasanta P. et al.	American Journal of Surgery	2001	133	6.33
23	Randomized clinical trial of stapled haemorrhoidopexy versus conventional diathermy haemorrhoidectomy	Ortiz H. et al.	British Journal of Surgery	2002	129	6.45
24	The pathogenesis of hemorrhoids	Haas PA. et al.	Diseases of The Colon & Rectum	1984	127	3.34
25	Stapled hemorrhoidopexy is associated with a higher long-term recurrence rate of ınternal hemorrhoids compared with conventional excisional hemorrhoid surgery	Jayaraman S. et al.	Diseases of The Colon & Rectum	2007	124	8.27
26	Randomized clinical trial of ligasure (tm) versus open haemorrhoidectomy	Palazzo FF. et al.	British Journal of Surgery	2002	122	6.1
27	Stapled hemorrhoidopexy versus milligan-morgan hemorrhoidectomy - a prospective, randomized, multicenter trial with 2-year postoperative follow up	Gravie, JF. et al.	Annals of Surgery	2005	113	6.65
28	Optimal nonsurgical treatment of hemorrhoids - a comparative-analysıs of ınfrared coagulatıon, rubber band ligation, and ınjectıon sclerotherapy	Johanson JF. et al.	American Journal of Gastroenterology	1992	112	3.73
29	A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation	Haas, E. et al.	American Surgeon	2012	109	10.9
30	A randomized, controlled trial of diathermy hemorrhoidectomy vs. Stapled hemorrhoidectomy in an ıntended day-care setting with longer-term follow-up	Cheetham MJ. et al.	Diseases of The Colon & Rectum	2003	109	5.74

PY: Publication year, TC: Total citation, AC: Average citations per year

Trending topics

2102 different keywords were used in all 1863 articles on hemorrhoids. Among these keywords, the most used 75 different keywords (used in at least 7 different articles) are shown in **Table 3**. The cluster network visualization map obtained as a result of the clustering analysis performed between these keywords is shown in **Figure 5**. The trend visualization network map obtained as a result of the analyzes carried out to determine current topics and the most cited topics is presented in **Figure 6** and citation network visualization map **Figure 7**.

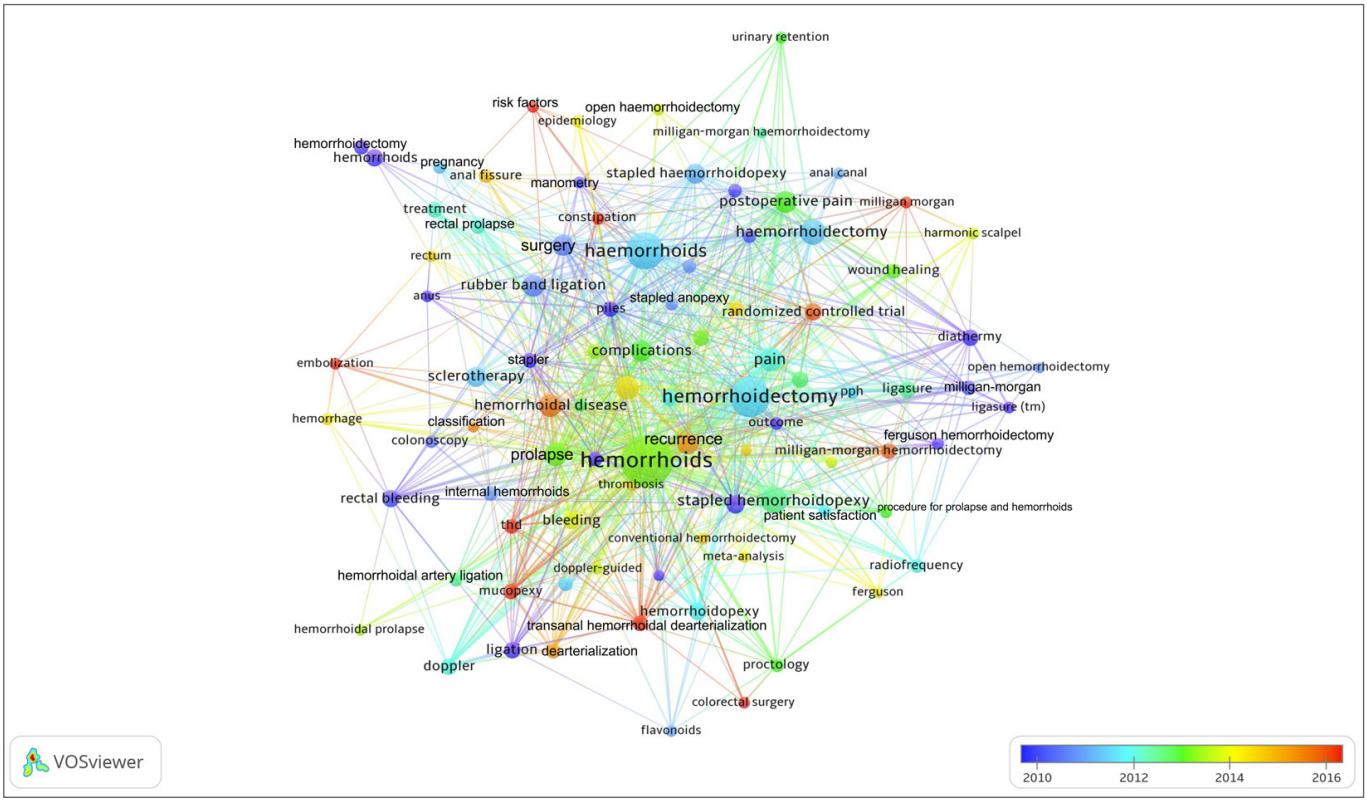

Figure 6. Network visualization map for trends on Hemorrhoids. Footnote: In the indicator given in the lower right corner of the figure, the topicality of the article increases from blue to red (blue-green-yellow-red). The size of the circle indicates the number of uses of the keyword.

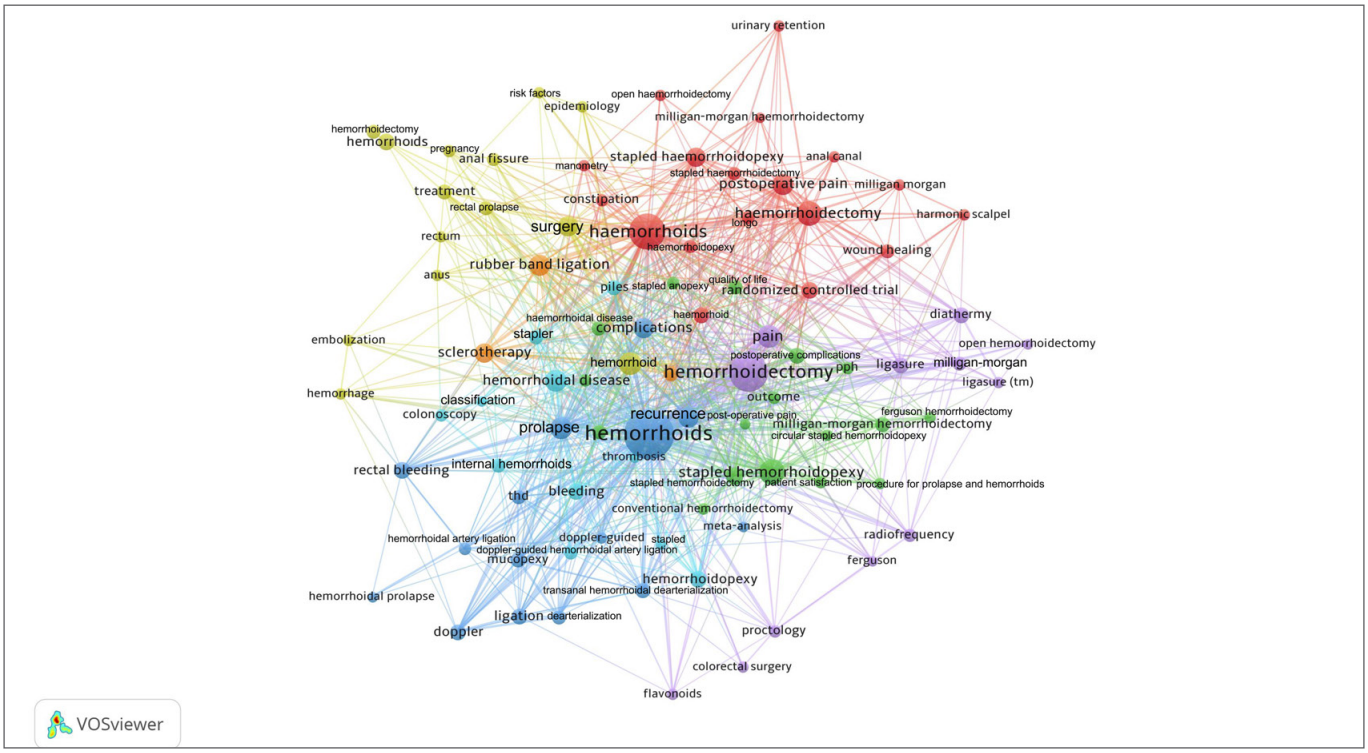

Figure 5. Network visualization map for cluster analysis based on keyword analysis on Hemorrhoids. Footnote: Colors indicate clustering. Keywords in the same cluster are of the same color. The size of the circle indicates the number of uses of the keyword.

Table 3. The 75 most frequently used keywords in articles about hemorrhoid

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
hemorrhoids (or haemorrhoids)	646	mucopexy	17	pregnancy	10
hemorrhoidectomy (or haemorrhoidectomy)	283	transanal hemorrhoidal dearterialization	17	anal canal	9
stapled hemorrhoidopexy (or haemorrhoidopexy)	99	treatment	17	anus	9
hemorrhoidal disease (or haemorrhoidal disease)	63	quality of life	16	doppler-guided	9
complications	54	rectal prolapse	16	embolization	9
pain	54	open hemorrhoidectomy (or haemorrhoidectomy)	15	ferguson hemorrhoidectomy	9
postoperative pain (or post-operative pain)	49	THD	15	hemorrhage	9
prolapse	45	wound healing	15	urinary retention	9
rubber band ligation	43	dearterialization	14	circular stapled hemorrhoidopexy	8
stapled hemorrhoidectomy (or haemorrhoidectomy)	39	internal hemorrhoids	14	colorectal surgery	8
surgery	39	stapler	14	conventional hemorrhoidectomy	8
recurrence	36	surgical technique	14	epidemiology	8
sclerotherapy	34	anal fissure	12	flavonoids	8
milligan-morgan hemorrhoidectomy (or haemorrhoidectomy)	24	doppler-guided hemorrhoidal artery ligation	12	harmonic scalpel	8
bleeding	23	longo	12	ligasure (TM)	8
hemorrhoidopexy (or haemorrhoidopexy)	23	radiofrequency	12	manometry	8
milligan-morgan (or milligan morgan)	22	colonoscopy	11	procedure for prolapse and hemorrhoids	8
randomized controlled trial	22	constipation	11	rectum	8
rectal bleeding	22	hemorrhoidal artery ligation	11	risk factors	8
doppler	21	outcome	11	classification	7
ligation	21	PPH	11	ferguson	7
postoperative complications	20	proctology	11	hemorrhoidal prolapse	7
diathermy	19	stapled anopexy	11	meta-analysis	7
ligasure	19	haemorrhoidal artery ligation	10	stapled	7
piles	18	patient satisfaction	10	thrombosis	7

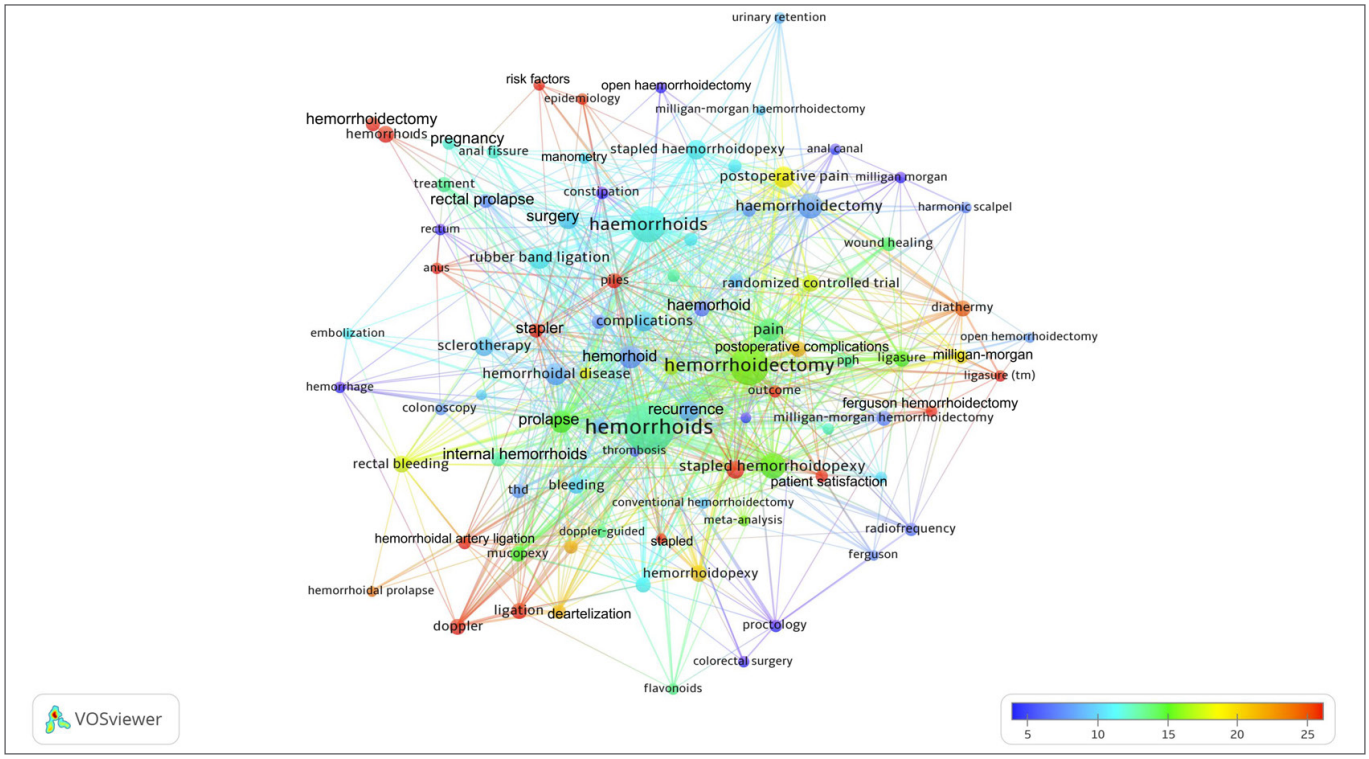

Figure 7. Network visualization map of the most frequently cited topics on Hemorrhoids. Footnote: In the indicator given in the lower right corner of the figure, the number of citations received by the topic increases from blue to red (blue-green-yellow-red). The size of the circle indicates the number of uses of the keyword.

DISCUSSION

An average of 28 articles were published on hemorrhoids between 1980 and 2006. Between 2007 and 2020, an average of 73 articles were published. A remarkable upward trend was observed in 2019 and 2020. A total of 92 articles were published in 2019 and 122 articles were published in 2020. When the Exponential Smoothing estimation results were evaluated, it was seen that the number of articles on Hemorrhoids would continue with an increasing trend.

When the publication distribution of the world countries is examined, it is seen that 18 of the first 25 countries that are most active in article productivity on hemorrhoids are developed countries, while the other 7 (India, Turkey, China, Brazil, Iran, Egypt, Pakistan) are developing countries. Although these 7 countries are developing, it is known that they are countries with large economies. According to the results of the correlation analysis in our study, a highly significant correlation was found between article productivity and economic development indicators. The reason for this is that the economic size of the countries is effective in the productivity of the article on hemorrhoids. Similar to our study results, it has been stated that economic power is effective in article productivity in bibliometric studies conducted on some medical subjects in the literature. When evaluated with the density map created according to the total cooperation score between the countries, the countries with the most intensive cooperation were England, Italy, Australia, USA, Germany, Austria, Denmark, Scotland, France, Greece, Netherlands, Spain, respectively. When the co-authorship cooperation of countries on hemorrhoids is examined, it seems that cooperation based on geographical countries is effective in the production of articles (England, Scotland, Wales), (Netherlands, Poland), (Italy, Switzerland), (Germany, Denmark, Spain, Sweden, Greece, Lithuania), (Canada, Mexico), (France, Belgium, Russia, India, Thailand, Malaysia), (Australia, New zealand), (China, Taiwan) are among the countries that do not have geographical proximity although they are in the same clusters (USA, Iran, Chile, South korea, Singapore), (Canada, France), (Germany, Japan), (Austria, Nigeria) etc. joint work has been done.

The journals that publish the most articles on hemorrhoids are Diseases of the Colon & Rectum, Colorectal Disease, Techniques in Coloproctology, International Journal of Colorectal Disease, British Journal of Surgery, American Surgeon, Pakistan Journal of Medical & Health Sciences, Chirurg, Journal of Gastrointestinal Surgery. and the World Journal of Surgery. It can be suggested that authors who want to publish on hemorrhoids should primarily consider these journals. When the citation analyzes of the journals are evaluated, the most effective journals according to the average number of citations per article they publish are British Journal of Surgery, American Journal of Gastroenterology, Diseases of the Colon & Rectum, American Journal of Surgery, International Journal of Colorectal Disease, World Journal of Surgery, Gastrointestinal. Endoscopy, Journal of Gastrointestinal Surgery, Gastroenterologie Clinique Et Biologique and Techniques in Coloproctology. Researchers who want their articles to be cited more can be recommended to consider these journals first. When the analyzed articles were evaluated according to the total number of citations they received, Johanson et al.'s[22] study titled "The prevalence of hemorrhoids and chronic constipation an epidemiologic study" was determined to be the most cited study. Mehigan et al.[20] article titled "Stapling procedure for haemorrhoids versus Milligan-Morgan haemorrhoidectomy: randomized controlled trial" published in the Lancet was determined to be the second most effective study. Macrae et al.[21] The article titled "Comparison of hemorrhoidal treatment modalities - a meta analysis" published in Diseases of the Colon & Rectum was determined as the third most influential study. The fourth most influential study is Rowsell et al.[24] published in the Lancet, titled "Circumferential mucosectomy (stapled haemorrhoidectomy) versus conventional haemorrhoidectomy: randomised controlled trial". The fifth most influential study is Morinaga et al.[23] published in the American Journal of Gastroenterology, titled "A novel therapy for internal hemorrhoids - ligation of the hemorrhoidal artery with a newly devised instrument (moricorn) in conjunction with a doppler flowmeter". Cheetham et al.[25] article titled "Persistent pain and faecal urgency after stapled haemorrhoidectomy" published in the Lancet was determined as the sixth most effective study. When the studies are evaluated according to the average number of citations per year, the most influential first article is Davis et al.[27] titled "The American society of colon and rectal surgeons clinical practice guidelines for the management of hemorrhoids" published in Diseases of the Colon & Rectum. The second most influential article is Gorfine et al.[28] published in Diseases of the Colon & Rectum. titled "Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial". The third most influential study is Pescatori et al.[29] published in Techniques in Coloproctology.[29] The fourth most influential article is Riss et al.[1] published in the International Journal of Colorectal Disease titled "The prevalence of hemorrhoids in adults". The fifth most influential study is Mehigan et al.[20] The sixth most influential article is Brown et al.[30] published in the Lancet titled "Haemorrhoidal

artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids (HubBLe): a multicentre, open-label, randomized controlled trial". According to the co-citation numbers of all analyzed articles, Longo,[17] Milligan,[18] Thomson,[19] Mehigan,[20] Macrae,[21] Johanson,[22] Morinaga,[23] The studies of Rowsell,[24] Cheetham,[25] and Ganio[26] were identified as the most influential. It can be recommended that clinicians and researchers interested in this subject should first read these publications.

When the keyword analysis findings were evaluated as a result of the cluster analysis, it was seen that the hemorrhoids subjects were divided into clusters in 7 different colors (red, blue, green, yellow, orange, purple, turquoise). The most cited keywords are doppler, ligation, stapled hemorrhoidectomy, diathermy, piles, anus, stapler, hemorrhoidectomy, risk factors, epidemiology, stapled, hemorrhoidal artery ligation, patient satisfaction, ferguson hemorrhoidectomy, outcome and ligasure (tm), hemorrhoidal prolapse and determined as postoperative complications. According to the results of the analysis made to determine the trend topics, it has been determined that the keywords studied in recent years are THD, mucopexy, transanal hemorrhoidal dearterialization, colorectal surgery, embolization, constipation, risk factors, Milligan-Morgan, classification, recurrence and randomized controlled trial.

As a result of the literature review on hemorrhoids, no bibliometric study was found. In the literature, only Hureibi et al.[31] identified the 100 most cited studies on benign anorectal disease . Our research is the first comprehensive bibliometric study on hemorrhoids. Only WoS database was used in the literature review of our study. Pubmed and Schopus databases were not preferred due to the inability to perform citation and co-citation analysis. In addition, since studies published in journals with low impact levels are included in the Scopus database, it was not preferred. The WoS database indexes the articles published in journals with a higher impact factor than other databases, and comprehensive citation analyzes can be performed when data is downloaded from the WoS database.[13,14] In recent years, WoS has been preferred more in bibliometric analyzes.[8-14]

CONCLUSION

In this comprehensive bibliometric study on hemorrhoids, a summary information of 1863 articles published between 1980-2020 was shared. It has been determined that the trend topics in hemorrhoid research are THD, mucopexy, transanal hemorrhoidal dearterialization, colorectal surgery, embolization, constipation, risk factors, Milligan-Morgan, classification, recurrence, and randomized controlled trial. This article can be a useful resource for scientists and clinicians regarding the past, present and future of hemorrhoids global outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent: The study is an open data study, does not contain human or animal material, and does not require informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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A bibliometric study of vascularized fibular grafting technique

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ABSTRACT

Aims: Vascularized fibula graft (VFG) technique is one of these "gold standard" techniques in bone regeneration. Although there have been several bibliometrics studies in orthopedics, there haven't been any on VFGs. By identifying the gaps in previous research, we sought to provide light on the scientific evolution of VFGs and provide direction for future investigations.

Methods: In this bibliometric study, the Web of Science (WOS) database was used to access publications on VFG published between 1986-2022. A literature search was performed with selected keywords. The dataset obtained was downloaded from the WOS database as an output. This output was analyzed with VOSviewer and Biblioshiny tools.

Results: A total of 430 documents on VFG included the study. A mean of 11.9 articles/year was published on VFG. The first article on VFG published in 1986. Since 2005, there has been an increasing trend in the number of articles and citations. The year with the highest number of both publications (n=32) and citations (n=756) was 2021. The publications on VFG have cited a total of 7300 times, an average of 16.98 citations per publication. Total 51 countries contributed to publications on the VFG between 1986-2022. The United States of America (USA) was identified as the global leader in terms of the number of publications (n=91, 21.163%), followed by Japan (n=58, 13.488%) and China (n=56, 13.023%). The USA had 91 manuscripts and 2162 citations with an H-index:29 and Japan had 58 manuscripts and 1145 citations with an H-index:22.

Conclusion: The literature on VFG is quite limited. Most of the publications are from developed countries. Studies should be supported for this method that can be used in the treatment of many diseases, especially in developing countries.

Keywords: Publications, bibliometric analysis, vascularized fibular grafting

INTRODUCTION

Bone regeneration is a complicated, well-coordinated physiological process of bone formation that is involved in ongoing remodeling throughout life and can be observed during normal fracture repair.[1,2]

There are many methods that are considered the "gold standard": For example, autologous bone grafting, allograft implantation, and the use of growth factors, osteoconductive scaffolds, osteoprogenitor cells, and distraction osteogenesis are just some of the current techniques used to improve the impaired or "inadequate" bone regeneration process. Vascularized fibula graft (VFG) is one of these "gold standard" techniques.[3]

VFGs, in contrast to other bone-grafting techniques, call for the preservation and reconnection of a vascular pedicle from the donor site to the graft site.[4]

Vascularized fibula graft transfer technique is a well-known technique for treating large bone abnormalities brought on by infection, tumor excision, early stages of osteonecrosis, or trauma.[4,5] It avoids the creeping substitution process that traditional bone transplants go through, resulting in better recovery and increased strength.4 Also free VFG is a biological reconstruction technique that can promote the growth of new bone and nourish the cartilage in the femoral head's subchondral region.[6]

The VFG technique dates back to the 1960s, but its first applications began after microvascular anastomosis procedures were developed.[4] Taylor et al.[7] reported the first case study describing the VFG technique in the year 1975. In this report, a tibial defect was repaired utilizing a vascularized graft from the opposing fibula.[5] Since then, the indications for VFG have grown to include fixing skeletal defects brought on by trauma, congenital pseudoarthrosis, tumors, and infections.[4,8,9] VFG recipient sites can be upper or lower extremities and this technique can be used in both adult and pediatric patients.[4]

Intensive scientific research is being conducted in tissue engineering and gene therapy to reduce the disadvantages of the latest methods, to develop bone graft implants with biomechanical properties as similar as possible to normal bone structure, and to accelerate the bone regeneration process.[2]

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Bibliometric studies are research methods that examine the results of scientific outputs in a field of science or research topic and guide further studies. With this technique, which is used in many fields including medicine, many scientific advances and gaps can be identified.[10-17] Although many studies have been conducted in orthopedics, no similar study was found in the literature on VFGs.[18,19] In this bibliometric study, our aim was to reveal the scientific development of VFGs and to guide future studies by identifying the missing points.

METHODS

The study is an open data bibliometric study, does not contain human or animal material, and does not require ethics committee approval, and informed consent. All procedures were carried out in accordance with the ethical rules and the principles.

This study is a bibliometric study of the literature on vascularized fibular grafting technique. In this study, the Web of Science (WOS) electronic bibliometric database was used to access publications on the relevant topic.

As the WOS database is constantly updated, we conducted a literature search in the WoS database on a single day, February 15, 2023.

Inclusion/Exclusion Criteria

We adopted a comprehensive search strategy to access VFG's publication records. Language, country/region were not applied. Since the first publication was published in 1986, we chose 1986 as the search start year. Since 2023 was not completed, we did not include publications in 2023. In summary, we chose 1986-2022 as the search years. We did not exclude by document type. In addition, publications in all sub-indexes of the WOS core collection were included in the study.

Search Terms

A literature search was performed with selected keywords (vascularized fibular graft OR vascularized fibular grafting OR Vascularized Fibular Bone Grafting) in the TITLE section of the WOS database search engine.

Bibliometric Methods and Visualization Tools

Then, the dataset obtained was downloaded from the WOS database as an output. This output was transferred to Excel 2019, VOSviewer_1.6.18 visualization tool, and an open-source data visualization software tool Biblioshiny (version 2.0) were used to examine the development and trends in article themes.[20]

Bibliometric data such as countries with the highest number of publications in the relevant subject, types of publications, number of publications over the years, number of citations, institutions where the most publications were published, authors who published the most publications, trending topics, dominant keywords of publications were analyzed. In addition, detailed visualization of collaborations between countries was made using Vos viewer.

RESULTS

A total of 430 documents on VFG published until the end of 2022 were selected and included in the analysis. A mean of 11.9 articles/year was published on VFG. The first article on VFG published in 1986. The development of VFG's publications over time is depicted in **Figure 1** together with citations. A general upward trend in publications was observed, with small downward fluctuations in some years.

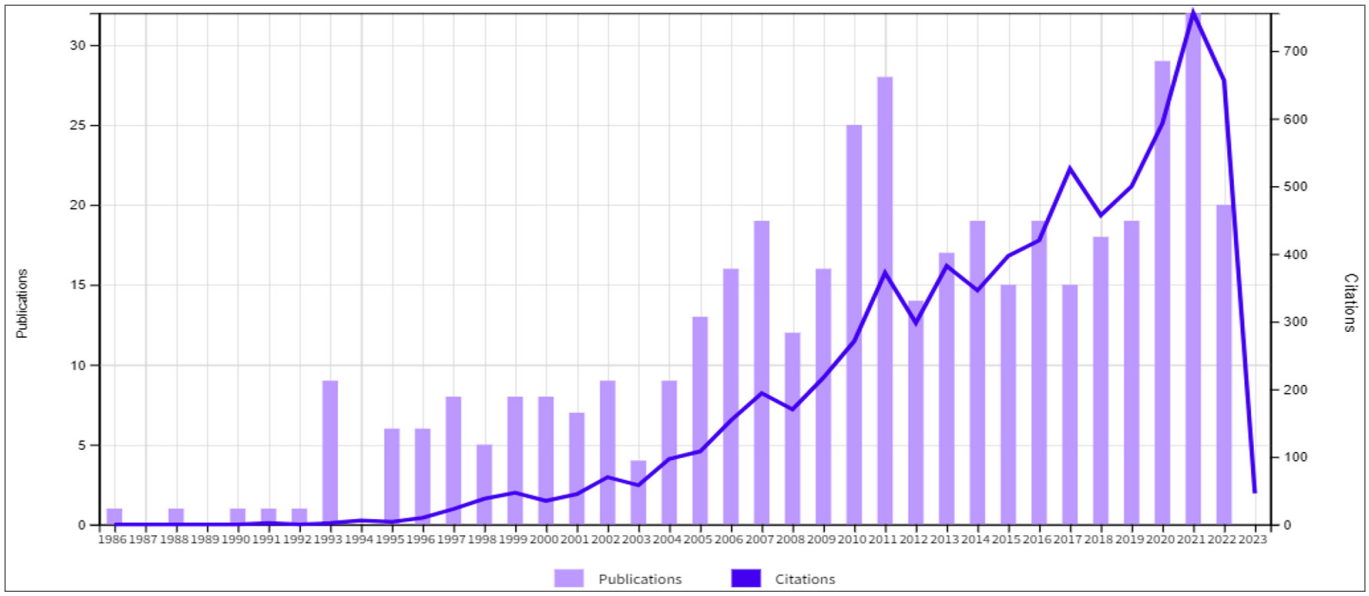

Figure 1. Annual publication and citation numbers of the VFG publications between 1986-2022*

* Downloaded from the WoS database. Although the research year is until the end of 2022, 2023 is also seen in this dataset. 2023 citation numbers are not yet calculated in WoS as the year is not over.

Since 2005, there has been an increasing trend in the number of articles. 2021 is the year with the highest number of publications with 35 publications (7.442%). Since 2013, at least 15 publications have been published every year (**Figure 1**). The annual number of citations of VFG publications is irregular but has never fallen below 100 per year since 2005 (**Figure 1**). The year with the highest number of both publications (n=32) and citations (n=756) was 2021. In 2022, there was a decrease in the number of publications (n=20) and citations (n=656) (**Figure 1**).

95.814% of the publications were in English. 85.349% were indexed in Science Citation Index Expanded (SCI-EXPANDED), 12.558% in Emerging Sources Citation Index (ESCI), 4.651% in Conference Proceedings Citation Index - Science (CPCI-S) and 1.163% in Book Citation Index - Science (BKCI-S). The publications on VFG have cited a total of 7,300 times, an average of 16.98 citations per publication. The average value of the H indexes was 45.

Total 51 countries contributed to publications on the VFG between 1986-2022. The United States of America (USA) was identified as the global leader in terms of the number of publications (n=91, 21.163%), followed by Japan (n=58, 13.488%) and China (n=56, 13.023%) (**Table 1**). The USA contributed 91 manuscripts and 2162 citations with an h-index of 29 and 23.76 citations per publication in the VFG from 1986 to 2022. Japan contributed 58 manuscripts and 1145 citations with an H-index of 22 and 19.74 citations per publication in the VFG in the same period.

Table 1. Countries with the most publications on VFG between 1986 and 2022

Ranking	Countries/Regions	n	%
1	Usa	91	21.163
2	Japan	58	13.488
3	China	56	13.023
4	France	32	7.442
5	Italy	30	6.977
6	India	24	5.581
7	Egypt	20	4.651
8	England	19	4.419
9	Germany	17	3.953
10	Turkey	15	3.488
11	Australia	10	2.326
12	Greece	10	2.326
13	Switzerland	10	2.326
14	Netherlands	7	1.628
15	Pakistan	7	1.628
16	Spain	7	1.628
17	Taiwan	7	1.628
18	Singapore	6	1.395
19	South Korea	6	1.395
20	Austria	5	1.163
21	Canada	5	1.163
22	Indonesia	5	1.163
23	Israel	4	0.930
24	Brazil	3	0.698
25	Iran	3	0.698

*Showing 25 out of 51 countries; no data about 1 record

The publications on VFG were published in 25 research areas, the most common being surgery (63.023%) and orthopedics (52.326%). Some publications were published in more than one research area (**Table 2**).

Table 2. Top research areas of the VFG publications

Research Areas	n	% of 430
Surgery	271	63.023
Orthopedics	225	52.326
General internal medicine	31	7.209
Oncology	30	6.977
Pediatrics	21	4.884
Neurosciences neurology	12	2.791
Dentistry oral surgery medicine	11	2.558
Emergency medicine	10	2.326
Research experimental medicine	9	2.093

There was 430 documents and 359 articles on VFG published between 1986-2022. 1665 authors contributed the VFG literature. Annual growth rate of the publications was 3.01.

%14 documents were single-authored. International co-authorships rate was %11.83. Main information on VFG literature is given in **Table 3**.

Table 3. Main information on VFG literature published between 1986-2022.

Description	Results
Timespan	1986-2022
Sources (journals, books, etc)	145
Documents	430
Annual growth rate %	3.01
Document average age	11.9
Average citations per doc	16.93
References	6073
Document contents	
Keywords plus (ID)	625
Author's keywords (DE)	691
Authors	
Authors	1665
Authors of single-authored docs	14
Authors collaboration	
Single-authored docs	14
Co-authors per doc	4.94
International co-authorships %	11.83
Document types	
Article	359
Book chapter	5
Early access	2
Proceedings paper	15
Editorial material	5
Letter	1
Meeting abstract	1
Proceedings paper	5
Review	38

The publications were published in 146 different journals. The journals with the most publications on VGF were the Journal of bone and joint surgery (n=22), Microsurgery (n=22), and Journal of Reconstructive Microsurgery (n=20). **Table 4** summarizes the journals that publish the most on VGF.

Table 4. The list of journals that publish the most on VGF

Publication Titles	n	%	Journal impact factor (five year)
Journal of Bone and Jointsurgery British Volume	22	5.116	3.479
Microsurgery	22	5.116	2.405
Journal of Reconstructive Microsurgery	20	4.651	2.492
Clinical Orthopaedicsand Related Research	17	3.953	5.885
Journal of Bone and Jointsurgery American Volume	16	3.721	6.955
Journalofhand Surgeryamerican Volume	12	2.791	2.809
Journal of Plastic Reconstructive and Aesthetic Surgery	12	2.791	3.215
Orthopaedics Traumatology Surgery Research	11	2.558	2.847
Plasticand Reconstructive Surgery	11	2.558	5.348
Annalsofplastic Surgery	10	2.326	1.988

The authors from 550 affiliations contributed the VGF research. The authors with the most publications in the VFG were affiliated with institutions in the USA. Mayo Clinic from the USA was the most productive affiliation on VGF research with 32 publications. Sapporo Medical University from Japan ranked 2nd with 11 publications and followed by Duke University from the USA (n=10), the University of Pennsylvania from the USA (n=10) and the University of California, Davis (UC Davis, UCD, or Davis) from the USA (n=9). The number of publications of institutions according to years is schematized in **Figure 2**.

The article published by Capanna and colleagues in Orthopedic Clinics of North America in 2007 was the most cited article on VFG (n=148 and with an average of 8.71 citations per year.).[21] The summary list of the top 25 most cited articles on VFG published between 1986 and 2022 is given in **Table 5**.

Figure 3a and **Figure 3b** provide an overview of the use of these keywords and present a chronological analysis of the keywords provided by the article's writers. Three distinct periods were separated from the life span in order to calculate the frequency of keywords throughout time. The term "resection" was used in the most research (n=108). These studies also received the most citations after they were published. The majority of articles containing this term were published after 2000s. The second most common term over the past 20 years has consistently been "reconstruction," and it is also the most utilized keyword. 'Graft', 'defects', 'flap', 'osteosarcoma', 'bone', 'vascularized fibular graft', 'tumor resection','management', 'allograft', 'children', and 'replacement' are other noteworthy keywords in terms of their frequency of occurrence during the last ten years. **Figure 3c** is the keyword frequency tree.

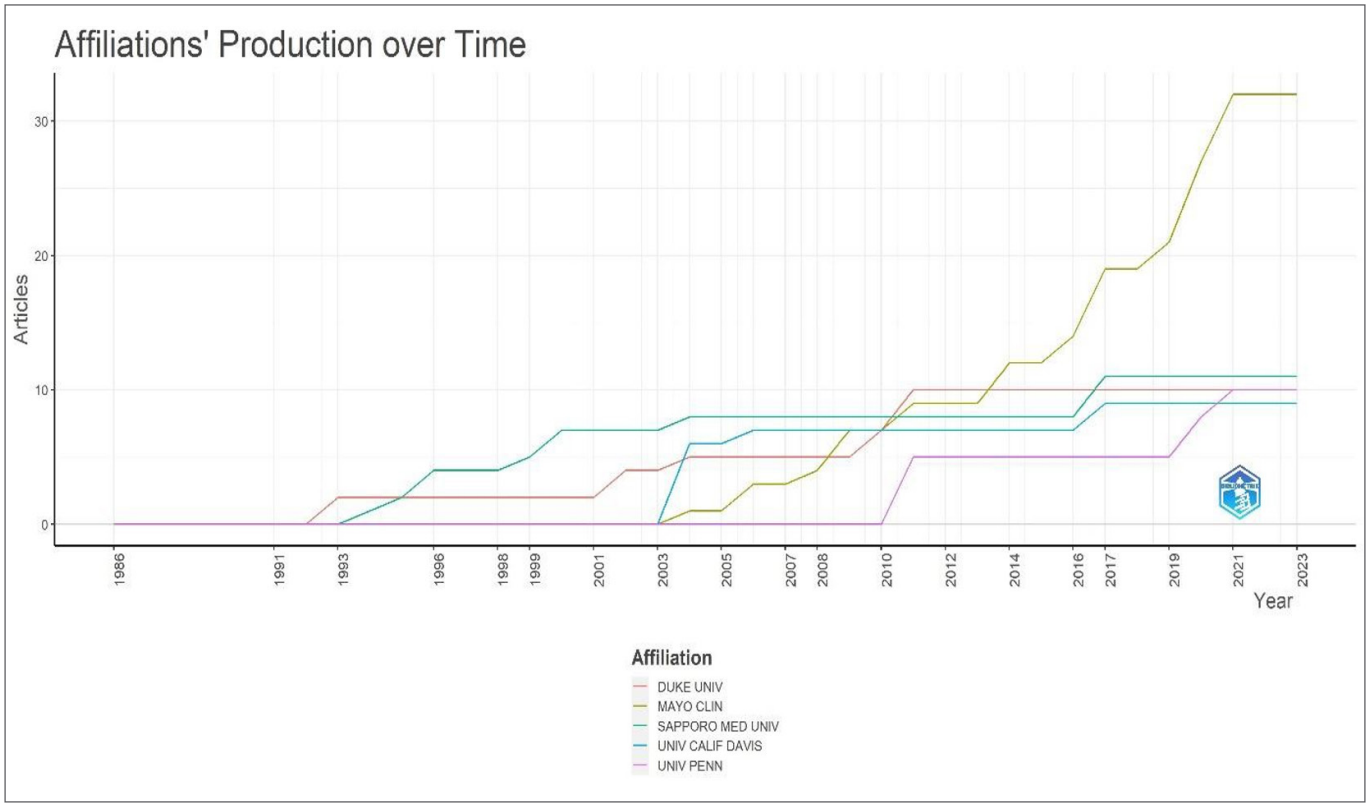

Figure 2. Annual production of mostly publishing affiliations on VFG

Table 5. Summary list of the top 25 most cited manuscipts on VFG published between 1986 and 2022

Ranking	Title	Authors	Source Title	Publication Year	DOI	Total citations	Average per year
1	A new reconstructive technique for intercalary defects of long bones: the association of massive allograft with vascularized fibular autograft. Long-term results and comparison with Alternative techniques	Capanna, et al.	Orthopedic Clinics of North America	2007	10.1016/j.ocl.2006.10.008	148	8.71
2	Limb salvage for neoplasms of the shoulder girdle - intermediate reconstructive and functional Results	OConnor, et al.	Journal of Bone and Joint Surgery-American Volume	1996	10.2106/00004623- 199612000-00011	137	4.89
3	Free vascularised fibular grafting for reconstruction After tumour resection	Hsu, et al.	Journal of Bone and Joint Surgery-British Volume	1997	10.1302/0301- 620X.79B1.6818	119	4.41
4	Arthrodesis of the ankle with a free vascularized autogenous bone graft-reconstruction of segmental loss of bone secondary to osteomyelitis, Tumor, or trauma	Bishop, et al.	Journal of Bone and Joint Surgery-American Volume	1995	10.2106/00004623- 199512000-00011	97	3.34
5	The use of massive bone allograft with intramedullary free fibular flap for limb salvage in a pediatric and adolescent Population	Moran, et al.	Plastic and Reconstruc Tive Surgery	2006	10.1097/01.prs.0000227682.7 1527.2b	95	5.28
6	Free vascularized fibular grafts for reconstruction of skeletal defects	Malizos, et al.	Journal of The American Academy of Orthopaedic Surgeons	2004	10.5435/00124635- 200409000-00010	92	4.6
7	Vascularize d fibula transfer for lower Limb Reconstruction	Beris, et al.	Microsurgery	2011	10.1002/micr.20841	89	6.85
8	The use of free fibular flap for functional mandibular Reconstruction	Peled, et al.	Journal of Oral and Maxillofacial Surgery	2005	10.1016/j.joms.2004.06.052	84	4.42
9	Precision tumour resection and reconstruction using image- Guided computer navigation	Wong, et al.	Journal of Bone and Joint Surgery-British Volume	2007	10.1302/0301- 620X.89B7.19067	79	4.65
10	Vascularized proximal fibular epiphyseal transfer for distal radial Reconstruction	Innocenti, et al.	Journal of Bone and Joint Surgery-American Volume	2004	10.2106/00004623- 200407000-00021	71	3.55
11	Vascularized fibular graft after excision of giant- cell tumor of the distal radius: wrist arthroplasty Versus partial wrist arthrodesis	Minami, et al.	Plastic and Reconstructive Surgery	2002	10.1097/00006534- 200207000-00020	70	3.18
12	The treatment of giant- cell tumors of the distal part of the Radius	Vandergrie, et al.	Journal of Bone and Joint Surgery-American Volume	1993	10.2106/00004623- 199306000-00011	69	2.23
13	Technical procedures for template-guided surgery for mandibular reconstruction based on digital Design and manufacturing	Liu, et al.	Biomedical Engineering Online	2014	10.1186/1475-925X-13-63	68	6.8
14	Vascularize d fibular grafts for reconstruc Tion of the femur	Yajima, et al.	Journal of Bone and Joint Surgery-British Volume	1993	10.1302/0301- 620X.75B1.8421008	67	2.16
15	Treatment of segmental defects of the humerus with an osteoseptocutane Ous fibular transplant	Heitmann, et al.	Journal of Bone and Joint Surgery-American Volume	2002	10.2106/00004623- 200212000-00014	61	2.77
16	Vascularized free fibular transfer combined with autografting for the management of fracture nonunions Associated with radiation therapy	Duffy, et al.	Journal of Bone and Joint Surgery-American Volume	2000	10.2106/00004623- 200004000-00009	60	2.5
17	Reconstruction and limb salvage after resection for malignant bone tumour of the proximal humerus - a Sling procedure Using a free Vascularised fibular graft	Wada, et al.	Journal of Bone and Joint Surgery-British Volume	1999	10.1302/0301- 620X.81B5.9430	59	2.36
18	Free vascularized fibular graft reconstruction of large skeletal Defects after tumor resection	Eward, et al.	Clinical Orthopaedics and Related Research	2010	10.1007/s11999-009-1053-x	58	4.14
19	Long bone reconstruction with vascularized Bone grafts	Pederson, et al.	Orthopedic Clinics of North America	2007	10.1016/j.ocl.2006.10.006	58	3.41
20	Methods of reconstruction for bone defect after tumor excision: a review of Alternatives	Nishida, et al.	Medical Science Monitor	2008		56	3.5
21	Free vascularized fibular graft salvage of complications of long-bone allograft after tumor Reconstruction	Friedrich, et al.	Journal of Bone and Joint Surgery-American Volume	2008	10.2106/JBJS.G.00551	56	3.5
22	Reconstruction of large posttraumatic skeletal defects of the forearm by Vascularized free fibular graft	Adani, et al.	Microsurgery	2004	10.1002/micr.20067	56	2.8
23	Intercalary segmental reconstruction of long bones after malignant bone tumor resection using primary methyl methacrylate cement spacer interposition and secondary bone grafting: the induced membrane Technique	Villemagne, et al.	Journal of Pediatric Orthopaedics	2011	10.1097/BPO.0b013e31821ff a82	55	4.23
24	Hypertrophy after free vascularized fibular transfer to The lower limb	El-Gammal, et al.	Microsurgery	2002	10.1002/micr.10066	54	2.45
25	Vascularized fibular graft for bone reconstructıon of the extremıtıes after tumor resectıon In limb-saving procedures	Minami, et al.	Microsurgery	1995	10.1002/micr.1920160204	54	1.86

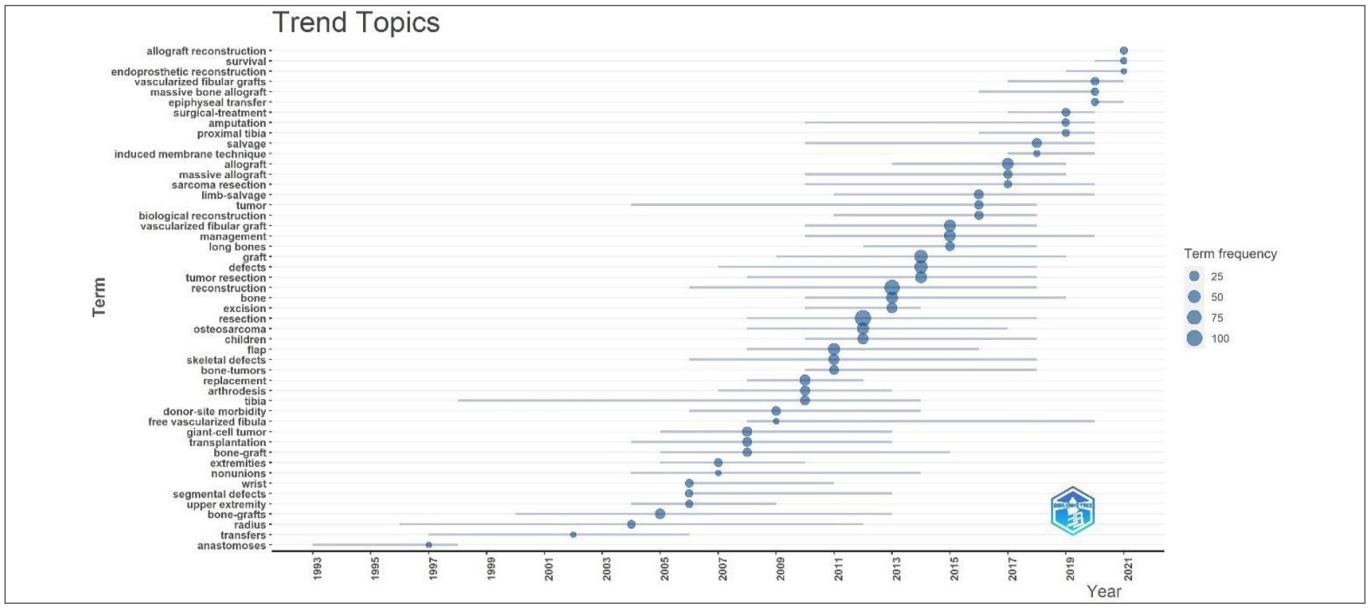

Figure 3a. Trend topics

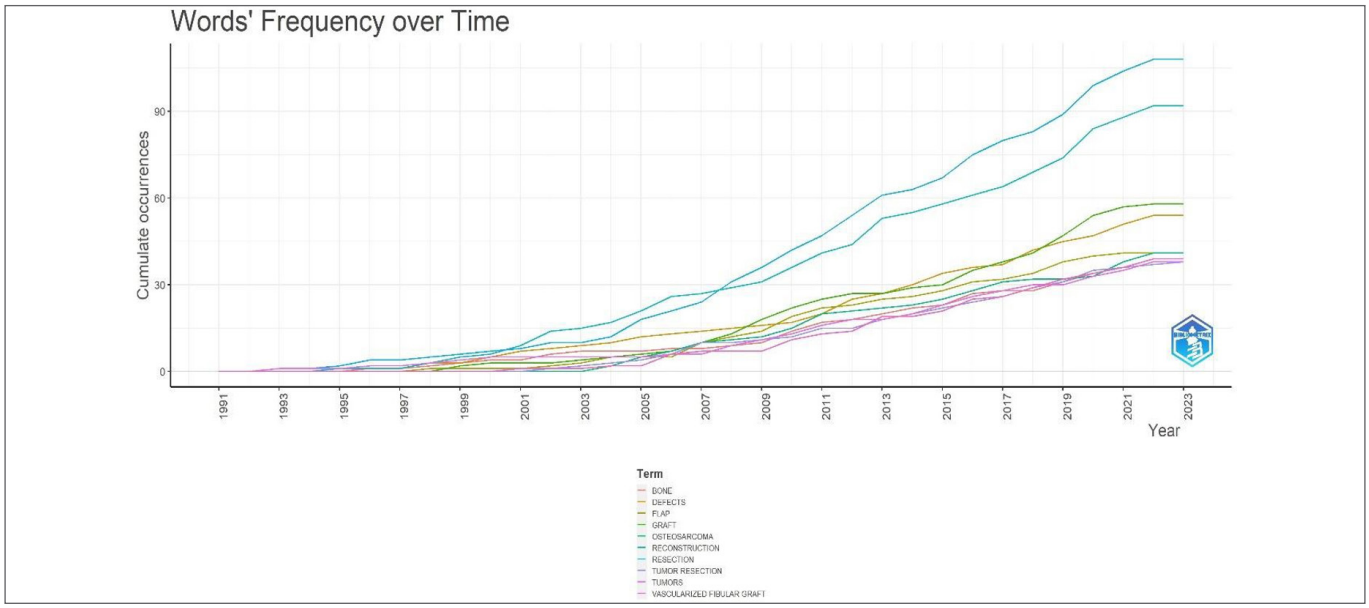

Figure 3b. Word's frequency over time

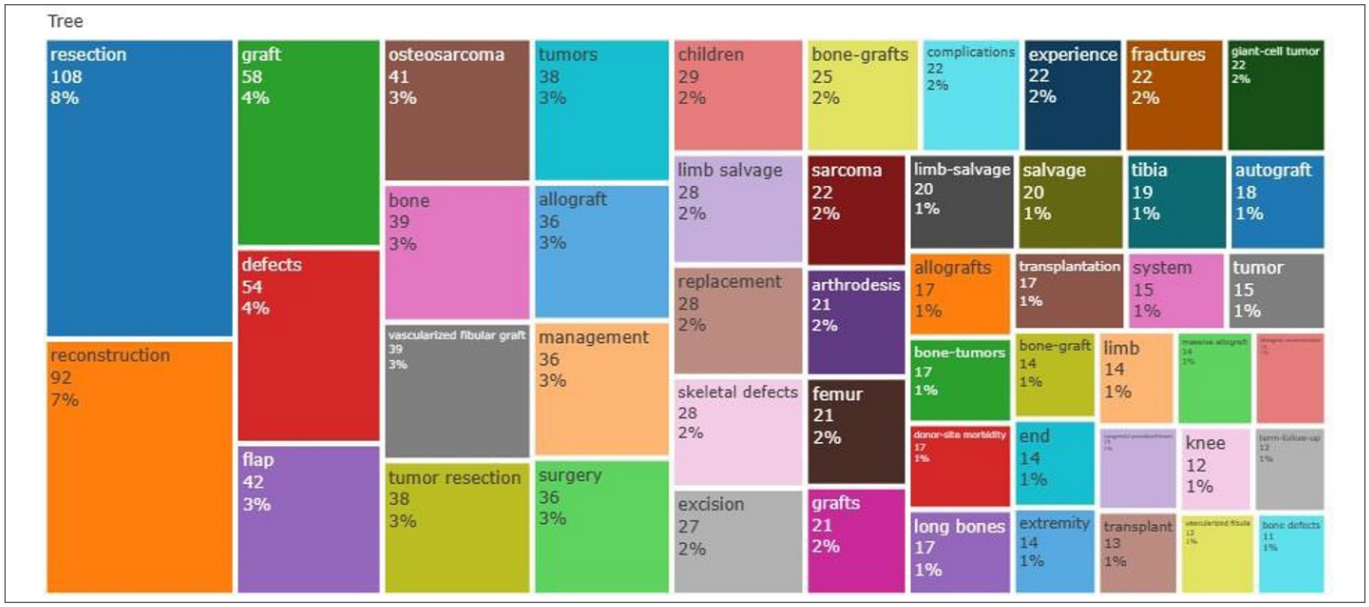

Figure 3c. Keyword frequency tree

Using VOSviewer, we produced two visual network maps for co-citation among institutions and countries (**Figure 4** and **Figure 5**). The network of co-citations throughout institutions and countries is represented by each colors. An item is more commonly co-referenced or cited if the circle is larger.

Among 531 institutions, 39 of them had occurred a minimum of three times. There were 39 items, 7 clusters, and 203 links, and the total link strength was 355.

Among 54 countries, 26 of them had occurred a minimum of three times. There were 26 items, five clusters, and 198 links, and the total link strength was 1537.

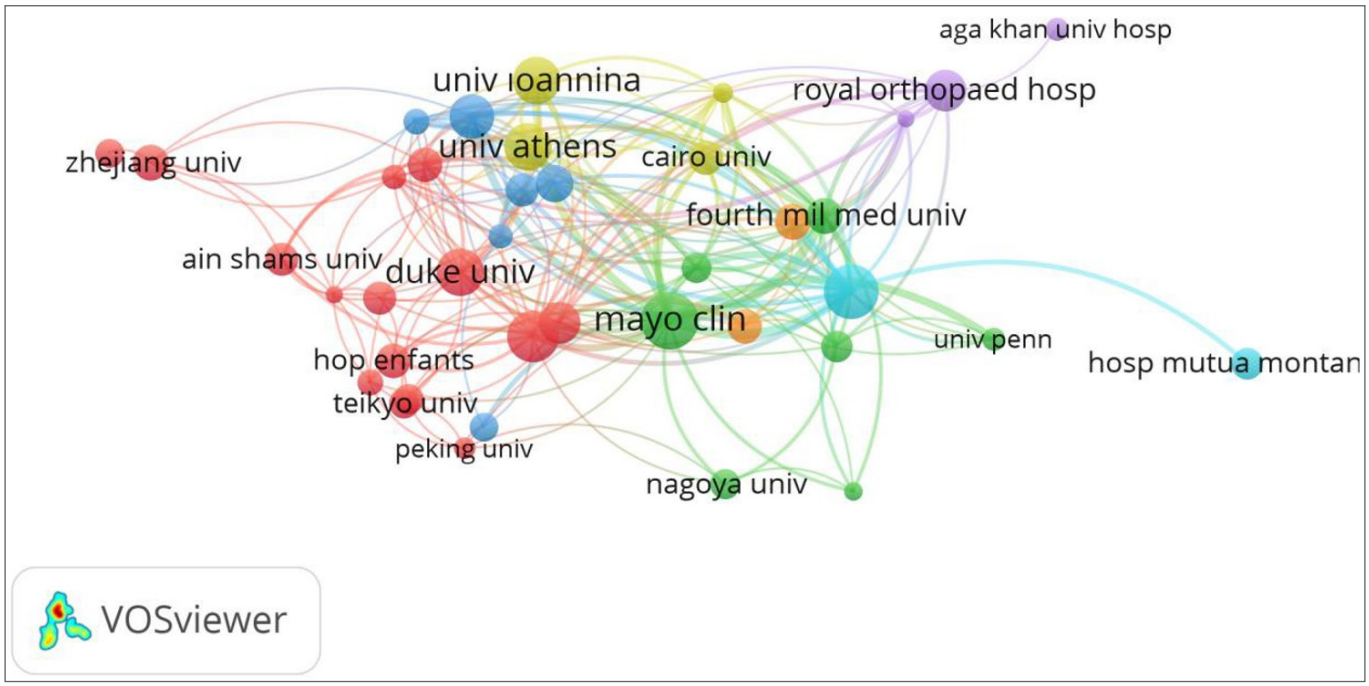

Figure 4. Citation analysis between institutions

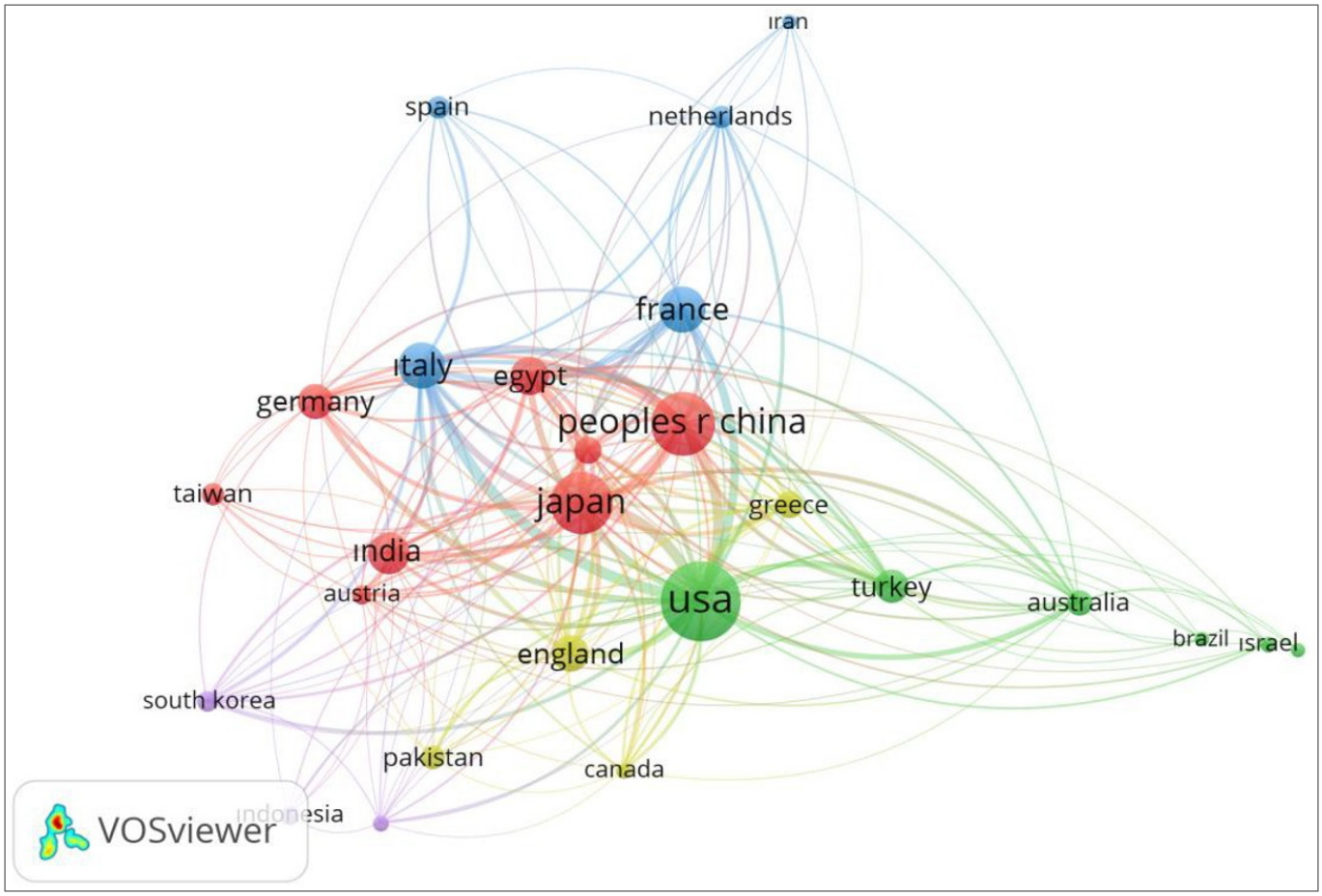

Figure 5. Citation analysis between countries

DISCUSSION

In this study, a comprehensive bibliometric analysis of the literature on VFG was conducted using the WoS database. This is the first bibliometric analysis of the literature on VFG. For this reason, it contains some guiding information for future studies on this subject. This bibliometric analysis carried out as part of this study's design demonstrated a non-linear behavior in the amount of citations and publications received by articles published in VFG. The first article on VFG in WoS databse was published in 1986. The publications showed an overall rising tendency, with minor downward variations in a few years. The number of articles has been trending upward since 2005. With 35 articles (7.442%), 2021 has the most publications overall. Every year since 2013, at least 15 publications have been released. Although inconsistent, the annual number of citations for VFG papers has never been lower than 100 since 2005.

A total of 51 countries contributed to publications on VFG between 1986 and 2022. This shows that the topic of VFG has attracted global interest. Although publications were frequently published from developed countries such as the USA, Japan, and European countries, developing countries (such as Egypt, Turkey, and Pakistan) also contributed to the VFG topic.

The USA was identified as the global leader in terms of the number of publications (n=91, 21,163%), followed by Japan (n=58, 13,488%) and China (n=56, 13,023%). From 1986 to 2022, the USA contributed 91 articles and 2162 citations to the VFG, with 23.76 citations per publication and an h-index of 29. Japan contributed 58 articles and 1145 citations to the VFG during the same period, with an h-index of 22 and 19.74 citations per publication. This finding shows that the USA is the leading country in VFG publications in terms of both numbers of publications and citations. In addition, our country citation analysis results show that there is collaboration between countries with the most publications. The authors with the most VFG publications were connected to American academic centers. With 32 publications, the Mayo Clinic in the USA was the most productive affiliation on VGF research. With 11 publications, Sapporo Medical University in Japan came in second, ahead of Duke University in the USA (n=10), the University of Pennsylvania (n=10), and the University of California, Davis (UC Davis, UCD, or Davis) in the USA (n=9). Our inter-institutional citation analysis showed that these institutions were also the institutions where the most cited publications were published. There were also links between institutions in the same color groups regarding attribution of each other.

An article's impact is determined by the number of citations. A high-quality paper is likely to receive more citations, as is generally agreed upon, but determining the paper's quality can be difficult. While this is true, poorly designed research can still be cited in manuscripts. While this is true, poorly designed research can also be cited by other authors.[22]

This study analyzed the most cited articles in VFG and found that most of them were from the field of clinical trials, and surgery (orthopedics/plastic surgery). Our current analysis showed that VFG application studies on surgical technique, Limb salvage and tumor received more citations. According to Tahamtan et al., there are a number of variables that might affect the frequency of citations, and they divided these variables into three categories: "Article- related factors," "Author-related factors," and "Journal-related factors." That is why we investigated the journals that publish the most publications on this topic and their impact factors in our study. These journals may also give ideas to authors who plan to publish articles on VFG.[23]

When examining the literature for research, keywords are a crucial tool that can be used in place of phrases and sentences. In fact, keywords frequently offer more relevant information.[24] Many previously published bibliometric analyses have included information about keywords.[25-27] We conducted a detailed analysis of these keywords using the Biblioshiny program. We examined the mostly selected keywords by year and the most frequently used keywords in a very detailed way. Three distinct periods were separated from the life span in order to calculate the frequency of keywords throughout time. The term "resection" was used in the most research (n=108). These studies also received the most citations after they were published. The majority of articles containing this term were published after 2000s. The second most common term over the past 20 years has consistently been "reconstruction," and it is also the most utilized keyword. 'Graft', 'defects', 'flap', 'osteosarcoma', 'bone', 'vascularized fibular graft', 'tumor resection', 'management', 'allograft', 'children', and 'replacement' are other noteworthy keywords in terms of their frequency of occurrence during the last ten years.

In our study, VFG-related publications were most commonly published in surgery (63.023%) and orthopedics (52.326%). Specific to these fields, tumor and surgical techniques were predominant in this publications. Large tumor resection flaws provide a challenge for skeletal reconstruction. Free VFG gives the chance for quick autograft implantation in extremities wounded by adjuvant radiation or chemotherapy. Despite the high likelihood of complications, free VGF reconstruction provides a durable solution for treating

significant skeletal abnormalities following tumor removal without raising the risk of amputation, local recurrence, or metastasis.[28,29] In connection with the results of these studies, the effectiveness of this method in the treatment of tumors in the field of orthopedics is an important keyword. the results of the keyword analysis in our study also prove this.

Limitations

Further research might alleviate some of the shortcomings of this study. A considerable discussion of the content coverage of VFG publications, for instance, was not included in the study because it concentrated primarily on the presentation and visualization of bibliometric and scientometric indicators. Consequently, a scoping review that considers the conceptualization and definition of the VFG topic could be a good starting point for future research. The fact that this study does not provide information regarding how the literature on VFG has evolved is another disadvantage. While bibliometric and scientometric indicators can be employed for these goals, they are insufficient for judging the caliber of knowledge generated. One database was only searched, which is another drawback. As a result, it doesn't encompass the entirety of the VFG literature.

CONCLUSION

Although the VFG surgical technique is a featured and popular technique in orthopedic surgery, the number of publications reported for VFG remains insufficient in the orthopedic and surgical literature. Future studies should consider including more publications and database outputs (such as Pubmed/Scopus). In addition, the inclusion of other outcomes, including the content of publications, would be helpful for researchers.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study is an open data bibliometric study, does not contain human or animal material, and does not require ethics committee approval.

Informed Consent: The study is an open data bibliometric study, does not require informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The association of anemia and high neutrophil-lymphocyte ratio with decreased survival in patients with laryngeal cancer treated with radiotherapy

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ABSTRACT

Aims: We aimed to examine the prognostic value of inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and anemia on oncological outcomes in patients with laryngeal squamous cell carcinomas (LSCC) treated with radiotherapy.

Methods: 213 LSCC patients analyzed retrospectively. Inflammatory markers were established by examining blood samples taken within 7 days before treatment. Patients were categorized into two groups: low and high according to NLR, PLR, and SII threshold values. In addition, to evaluate the effect of hemoglobin (Hb) level, the threshold value of each inflammatory marker and Hb level were combined, and 3 groups were formed (3 groups for NLR, 3 groups for PLR, and 3 groups for SII). The relationship between inflammatory markers and overall survival (OS), disease-free survival (DFS), and local regional recurrence-free survival (LRRFS) was investigated.

Results: In univariate analysis, high NLR, PLR, SII, and low Hb (<13 g/dl) level were associated with worse survival (all p<0.022), except for PLR and Hb for LRRFS. OS and DFS were significantly better in patients in each group A with a low inflammatory index and high Hb (all p<0.013). In the multivariate analysis, high NLR and group CNLR (high NLR with low Hb) were statistically significant predictors of decreased OS (HR 1.85, 95% CI 1.05-3.28, p=0.033; HR 2.61, 95% CI 1.14-5.97, p=0.022) and DFS (HR 1.81, 95% CI 1.11-2.96, p=0.017; HR 3.32, 95% CI 1.20-9.16, p=0.028).

Conclusion: NLR may serve as a potential prognostic biomarker in LSCC, and its predictive ability is further enhanced when NLR is combined with Hb level.

Keywords: Anemia, laryngeal squamous cell carcinoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, radiotherapy, systemic immune-inflammation index

INTRODUCTION

Laryngeal squamous cell carcinomas (LSCC) are the most frequently seen cancers among head and neck cancers (HNC).[1] Currently, the two main treatment modalities used to treat LSCC in the absence of distant metastases are surgical excision and radiotherapy (RT).[2,3] It has been stated in systemic reviews that surgery and RT are similarly effective in the management of early-stage LSCC, and there is no difference in terms of local control rates.[4] Moreover, in early-stage LSCC, RT is preferred as it gives satisfactory results in terms of sound quality.[5] In addition, after prospective randomized studies showed that there is no difference in survival between chemoradiotherapy (CRT) and surgery in advanced-stage LSCC, this approach, which can provide larynx preservation, has become a standard treatment in selected advanced stages.[6,7] With definitive RT, it is possible to obtain better psychosocial and functional results by preserving voice and swallowing function instead of the worsened quality of life caused by surgery. Although it varies according to the stage of the tumor, the site of the disease, and the patient's preference, RT is a frequently preferred modality since it enables laryngeal preservation. Moreover,

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in the presence of adverse features, the necessity of adjuvant RT or adjuvant CRT in the postoperative setting is still valid.[8]

The response to RT may differ between patients; unfortunately, recurrence can be encountered over time. Host-related factors and tumor characteristics are factors that affect treatment response and survival. While age, gender, and performance status constitute the host-related factors, stage, lymphovascular invasion (LVI), perineural invasion (PNI), p53 mutations are some of the tumor-related factors.[9,10] While these are not entirely sufficient to predict survival, they can help to some extent determine the prognosis. Therefore, it is of great importance to search for reliable prognostic markers to predict survival.

Data from the literature suggest that anemia affects the prognosis of patients with HNC treated with RT.[11] The hemoglobin (Hb) level is an indicator of the oxygen-binding capacity of the blood. Low Hb levels are thought to be associated with hypoxia, resulting in resistance to RT, and thus with a poor prognosis.[11,12]

A growing body of evidence in recent years has demonstrated that systemic inflammation plays a crucial role in tumorigenesis and progression, so many researchers have extensively focused on investigating the relationship between cancer prognosis and inflammation-based parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), which reflects the balance of host inflammatory and immune status.[13-16]

To the best of our knowledge, these indices have been shown to predict oncological outcomes in various tumor types, but fewer are reported for LSCC.[12,14-16-20] These simple hematological parameters can be useful in determining the prognosis of LSCC in daily practice. We hypothesized whether the predictive effect could be enhanced by combining low Hb levels, which are an indicator of hypoxia, and high NLR, PLR, and SII values, which are thought to be associated with tumorigenesis and progression, thus we aimed to examine the prognostic value of inflammatory markers (NLR, PLR, SII) and anemia on overall survival (OS), disease-free survival (DFS) and local regional recurrence free survival (LRRFS) in LSCC patients treated with RT.

METHODS

Ethics

This study was approved by the institutional review board of our institute and was conducted in accordance with the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients. The study was initiated with the approval of the Samsun University Clinical Researches Ethics Committee (Date: 2023, Decision No: 10/11).

Study Population

LSCC patients referred to the Radiation Oncology Clinic of Samsun University Samsun Training and Research Hospital between January 2012 and December 2017 and who received RT were reviewed retrospectively. Patients older than 18 years old with a histopathological diagnosis of LSCC, treated with definitive RT/CRT or adjuvant RT/CRT were included. Patients who used steroid therapy or have had acute or chronic inflammatory diseases or hematological disorders and a second malignancy were excluded. Blood samples were taken within one week before RT start or oncologic surgery.

Clinical Data Collection

A retrospective chart review was performed. The data, including patient demographics, laboratory parameters, imaging reports, clinicopathological characteristics, treatment, and oncological outcomes were extracted through the patient archive files and electronic medical records system. Hb, neutrophil, lymphocyte, platelet counts, C-reactive protein (CRP), uric acid, and albumin levels were recorded by examining the blood samples taken within 7 days before the treatment. NLR is defined as the absolute neutrophils count divided by lymphocyte count, and PLR is defined as the absolute platelet count divided by lymphocyte count. SII was defined according to this formula: platelet counts × neutrophil counts/lymphocyte counts. Anemia was defined as a Hb level of <13 g/dL.

After determining the optimal cut-off values for NLR, PLR, and SII, the patients were divided into two groups, low and high, according to these values. In addition, to evaluate the effect of Hb level (13 g/dL), the threshold values of each inflammatory marker and Hb level were combined, and three groups were formed. Patients were grouped as follows for NLR: Group ANLR, low NLR and high Hb, Group BNLR, low NLR and low Hb or high NLR and high Hb, Group CNLR, high NLR and low Hb. Patients were grouped as follows for PLR: Group APLR, low PLR and high Hb, Group BPLR, low PLR and low Hb or high PLR and high Hb, Group CPLR, high PLR and low Hb. Patients were grouped as follows for SII: Group ASII, low SII and high Hb; Group BSII, low SII and low Hb or high SII and high Hb; Group CSII, high SII and high Hb.

Treatment and Follow-up

Patients were treated with definitive RT/CRT or adjuvant RT/CRT. In early-stage tumors, usually the hypofractionated regimen (63 Gy in T1N0 tumors and 65.25 Gy in T2N0 tumors with 2.25 Gy fraction (fx) per day) was preferred; otherwise, they were treated with a conventional scheme of 66-70 Gy with 2 Gy fx per day. Patients were treated with the 3-dimensional conformal RT technique. On the other hand, advanced-stage LSCC patients were treated with the intensity-modulated RT technique. With a daily fraction of

2 Gy, a total of 70 Gy was given for definitive RT, while a total of 60-66 Gy was given as adjuvant. In some patients who underwent definitive treatment, 69.96 Gy (2.12 Gy/fx to 69.96 Gy; 1.8 Gy/fx to 59.4 Gy; 1.64 Gy/fx to 54.12 Gy) was administered in 33 fractions using the simultaneous integrated boost technique. Concomitant chemotherapy was administered with definitive RT in the advanced-stage and with adjuvant RT in the presence of risk factors. During RT, intravenous chemotherapy (35-40 mg/m² cisplatin) once a week or once every 21 days (75-100 mg/m² cisplatin) was administered.

Patients were followed up with laryngoscopic and physical examinations for 4-6 weeks after RT, and every 3 months during the first 2 years, every 6 months for the next 3 years, and annually thereafter. Radiological imaging, including computed tomography and/or positron emission tomography, was performed at the initial follow-up to assess treatment response and in subsequent follow-ups in the presence of clinical suspicion based on physical examination and/or laryngoscopy findings. Based on clinical, radiological, and/or histological findings, loco-regional recurrence was defined as primary tumor regrowth or cervical lymph node involvement; detection of any metastasis in solid organs was accepted as distant metastasis.

Statistical Analysis

The endpoints of the study were OS, DFS, and LRRFS. OS was defined as the interval between the date of diagnosis and death from any cause until the last follow-up. DFS was defined as the interval between the date of diagnosis and the date of occurrence of local, regional, or/and distant failure, whichever comes first, or death until the last follow-up. LRRFS was defined as the interval between the date of diagnosis and the detection of loco-regional recurrence or death from any cause until the last follow-up. Patients were followed up regularly from the date of diagnosis to May 2018, or the date of death.

Continuous variables are presented as the medians, and categorical variables are presented in order of frequency. Receiver Operating Characteristics (ROC) curve analysis was used to determine the optimal cut-off point for NLR, PLR, and SII for prediction of survival. Chi-squared and Fisher's exact tests were used for comparisons between NLR, PLR, SII, and clinicopathological characteristics. The Kaplan-Meier method and log-rank test were utilized to analyze and compare the survival rates. Cox proportional hazards models were used for univariate and multivariate analyses. The hazard ratios (HR) with 95% confidence intervals (CI) and p values were reported. All statistical analyses were performed using SPSS 25.0 statistical software (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant. Bonferroni correction was used to adjust p-value for parameters categorized into 3 groups (p<0.017).

RESULTS

Patient Characteristics

Clinicopathological characteristics of the 213 LSCC patients included in our study, 159 of whom received definitive RT and 54 received adjuvant RT, are shown in **Table 1**.

Table 1 Clinicopathological characteristics

Variable	N (%)
Age (median)	61 (26-87)
Gender	
Female	4 (1.9)
Male	209 (98.1)
Localization	
Glottic	148 (69.5)
Supraglottic	63 (29.6)
Subglottic	2 (0.9)
Anterior commissura invasion	
-	62
+	56
Unknown	95
Subglottic extension	
-	93
+	25
Unknown	95
T stage	
T1	91 (42.7)
T2	34 (18.3)
T3	36 (16.9)
T4	47 (22.1)
N stage	
N0	164 (77)
N1	20 (9.4)
N2	24 (11.3)
N3	5 (2.3)
Stage	
1	91 (42.7)
2	31 (14.6)
3	31 (14.6)
4	60 (28.7)
Surgery	
-	159 (74.6)
+	54 (25.4)
Lymphovascular invasion	
-	18 (33.3)
+	36 (66.7)
Perineural invasion	
-	43 (79.6)
+	11 (20.4)
Extracapsular extension	
-	48 (88.9)
+	6 (11.1)
Treatment	
Definitive RT	121 (56.8)
Definitive CRT	38 (17.8)
Adjuvant RT	24 (11.2)
Adjuvant CRT	30 (14.2)
RT Schedule/Dose	
Hypofraction	
Stage 1 (63 Gy)	52 (24.5)
Stage 2 (65.25 Gy)	10 (4.7)
Conventional, definitive	
Stage 1 (66-70 Gy)	39 (18.3)
Stage 2 (68-70 Gy)	20 (9.3)
Stage 3 (70 Gy)	17 (8)
Stage 4 (70 Gy)	21 (9.9)
Conventional, adjuvant	
Stage 2 (66 Gy)	1 (0.4)
Stage 3 (60-66 Gy)	14 (6.6)
Stage 4 (60-70 Gy)	39 (18.3)
RT Technique	
Conformal	121 (56.8)
IMRT	86 (40.4)
SIB	6 (2.8)
Chemotherapy schema	
Once a week (35-40 mg/m²)	56 (26.3)
Once every 21 days (75-100 mg/m²)	12 (5.6)

CRT: Chemoradiotherapy; IMRT: Intensity-modulated radiotherapy; RT: Radiotherapy; SIB: Simultaneous integrated boost

Cut-off Values of Inflammatory Markers and Grouping with Hemoglobin Levels

ROC analysis determined the optimal cut-off values of NLR, PLR, and SII to predict survival as 2.34 (area under the curve (AUC):0.608, sensitivity 64%, specificity 53%, p=0.018), 122 (AUC:0.624, sensitivity 66%, specificity 54%, p=0.007) and 564 (AUC:0.631, sensitivity 70%, specificity 55%, p=0.004), respectively (**Figure 1**). According to these determined threshold values, the patients were categorized into two groups: low and high. According to these determined threshold values, the patients were categorized into two groups: low and high. The threshold values used to estimate the relationship between each inflammatory index and OS were also used for DFS and LRRFS, as in the study of Cho et al.[21]

Patients with high PLR and SII tended to have a more advanced T classification and stage than those in the low PLR and SII groups (p=0.007, p=0.004; p=0.016, p=0.018), and patients with high PLR also had an advanced stage of N (p=0.009). Patients over 60 years of age were mostly detected in the high NLR group (p=0.040). The presence of PNI was found more frequently in the high SII group (p=0.010), and subglottic extension was more common in both the high SII and high PLR groups (p=0.022, p=0.010). The relationship between clinicopathological features and NLR, PLR, and SII is detailed in **Table 2**.

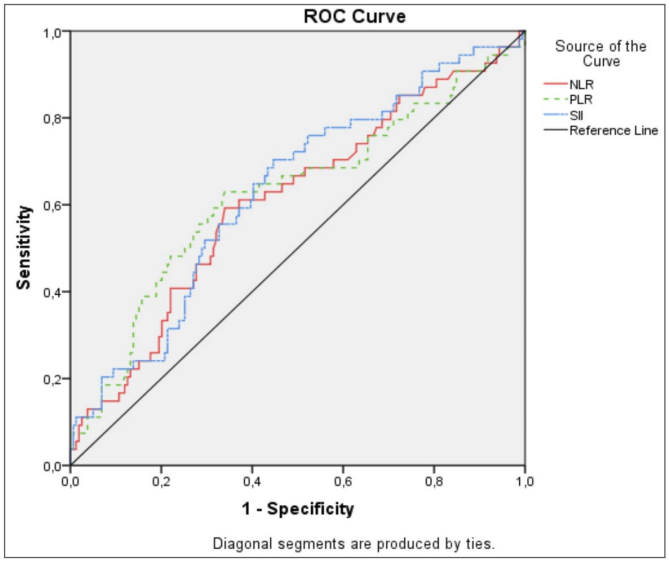

Figure 1. Receiver operating characteristic (ROC) curve analysis for NLR, PLR and SII

Table 2. The relationship with clinicopathological features and NLR, PLR and SII

Variable	NLR			PLR			SII		
	<2.34 102 (n,%)	≥2.34 111 (n,%)	p	<122 100 (n,%)	≥122 113 (n,%)	p	<564 100 (n,%)	≥564 113 (n,%)	p
Age									
<60	53 (55.8)	42 (44.2)	0.040	48 (50.5)	43 (49.5)	0.408	51 (53.7)	44 (46.3)	0.097
≥60	49 (41.5)	69 (58.5)		52 (44.1)	66 (55.9)		49 (41.5)	69 (58.5)	
Gender									
Female	0 (0)	4 (100)	0.053	2 (50)	2 (50)	0.902	1 (25)	3 (75)	0.375
Male	102 (48.8)	107 (51.2)		98 (46.9)	111 (53.1)		99 (47.1)	110 (52.6)	
Anterior commissura invasion									
-	21 (33.9)	41 (66.1)	0.063	21 (33.9)	41 (66.1)	0.260	21 (33.9)	41 (66.1)	0.135
+	29 (51.8)	27 (48.2)		25 (44.6)	31 (55.4)		27 (48.2)	29 (51.8)	
Subglottic extension									
-	43 (46.2)	50 (53.8)	0.116	42 (45.2)	51 (54.8)	0.010	43 (46.2)	50 (53.8)	0.022
+	7 (28)	18 (72)		4 (16)	21 (84)		5 (20)	20 (80)	
T stage									
T1-2	67 (51.5)	63 (48.5)	0.207	71 (54.6)	59 (45.4)	0.007	70 (53.8)	60 (46.2)	0.016
T3-4	35 (42.2)	48 (57.8)		29 (34.9)	54 (65.1)		30 (36.1)	53 (63.9)	
N stage									
N0-1	90 (48.9)	94 (51.1)	0.550	93 (50.5)	91 (49.5)	0.009	90 (48.9)	94 (51.1)	0.166
N2-3	12 (41.4)	17 (58.6)		7 (24.1)	22 (75.9)		10 (34.5)	19 (65.5)	
Stage									
1-2	62 (50.8)	60 (49.2)	0.335	68 (55.7)	54 (44.3)	0.004	66 (54.1)	56 (45.9)	0.018
3-4	40 (44)	51 (56)		32 (35.2)	59 (64.8)		34 (37.4)	57 (62.6)	
Lymphovascular invasion									
-	10 (55.6)	8 (44.4)	0.777	9 (50)	9 (50)	0.061	9 (50)	9 (50)	0.255
+	18 (50)	18 (50)		8 (22.2)	28 (77.8)		12 (33.3)	24 (66.7)	
Perineural invasion									
-	20 (46.5)	23 (53.5)	0.179	12 (27.9)	31 (72.1)	0.263	13 (30.2)	30 (69.8)	0.010
+	8 (72.7)	3 (27.3)		5 (45.5)	6 (54.5)		8 (72.7)	3 (27.3)	
Extracapsular extension									
-	25 (52.1)	23 (47.9)	0.923	15 (31.3)	33 (68.8)	0.917	18 (37.5)	30 (62.5)	0.667
+	3 (50)	3 (50)		3 (33.3)	4 (66.7)		3 (50)	3 (50)	

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index

On the other hand, as in the study of Sung et al.,[22] three groups were formed according to each inflammatory index and Hb level (13 g/dL). In brief, patients were grouped as follows for NLR: Group ANLR, NLR <2.34 and Hb ≥13 g/dL; Group BNLR, NLR <2.34 and Hb <13 g/dL or NLR ≥2.34 and Hb≥13 g/dL; Group CNLR, NLR ≥2.34 and Hb <13 g/dL. Patients were grouped as follows for PLR: Group APLR, PLR <122 and Hb ≥13 g/dL; Group BPLR, PLR <122 and Hb <13 g/dL or PLR ≥122 and Hb ≥13 g/dL; Group CPLR, PLR ≥122 and Hb<13 g/dL. Patients were grouped as follows for SII: Group ASII, SII <564 and Hb ≥13 g/dL; Group BSII, SII <564 and Hb <13 g/dL or SII ≥564 and Hb ≥13 g/dL; Group CSII, SII ≥564 and Hb <13 g/dL.

Factors that Affect Overall Survival

With a median follow-up of 31 (5-79) months, the 5-y OS was 68.9% for all patients. The 5-y OS was significantly better in patients with the low NLR, PLR and SII groups, compared to patients with the high NLR, PLR and SII groups, with ratios 76.8% vs 60.7%; 77.7% vs 60.6%; and 83.1% vs 58.1%, respectively (p=0.008, p=0.014, p=0.001) (**Tables 3** and **4**).

The 5-y OS rates for groups ANLR, BNLR, and CNLR were 81.7%, 65.7%, and 49.6%; for groups APLR, BPLR, and CPLR were 79.8%, 70.7, and 51.1%; for groups ASII, BSII, and CSII were 83.1%, 65.7%, and 48.4%, respectively, and there was a significant difference between the groups (p=0.001, p=0.005, p=0.001) (**Table 3** and **4**). A significant survival difference was observed between group A patients compared to Group B and C patients (p=0.006, p<0.001; p=0.003, p<0.001) for NLR and SII subgroups, but the difference was significant between groups A and C, but not with group B for PLR (p=0.001; p=0.035).

In terms of clinicopathological parameters, age (p< 0.001), T stage (p=0.010), N stage (p<0.001), stage (p=0.005), anemia (p=0.004) were found statistically significant in univariate analysis (Tables 3 and 4). However, the multivariate analysis demonstrated that age (HR=3.89, 95% CI: 2.05-7.39, p<0.001), N stage (HR=3.33, 95% CI: 1.63-6.83, p=0.001), NLR (HR=1.85, 95% CI: 1.05-3.28, p=0.033), and NLR with Hb (HR=2.61, 95% CI: 1.14-5.97, p=0.022) were independent prognostic factors of OS in LSCC patients (**Table 3**, **Figure 2**).

Factors that Affect Disease Free Survival

The 5-y DFS was 61.5% for all patients. Patients with high NLR, PLR, and SII had lower DFS than those with low NLR, PLR, and SII (p=0.003, p=0.022, p=0.001), indicating that high NLR, PLR, and SII are significantly worse prognostic factors for DFS (**Table 3**). 5-y DFS rates were 71.5% vs 50.9%, 71% vs 52.3%, and 73.4% vs 50.1% for low and high groups, respectively (**Table 4**). Also, improved DFS rates were demonstrated in patients in the groups ANLR, APLR, and ASII (p=0.001, p=0.013, p=0.001), as presented in **Table 4** (**Figure 3**).

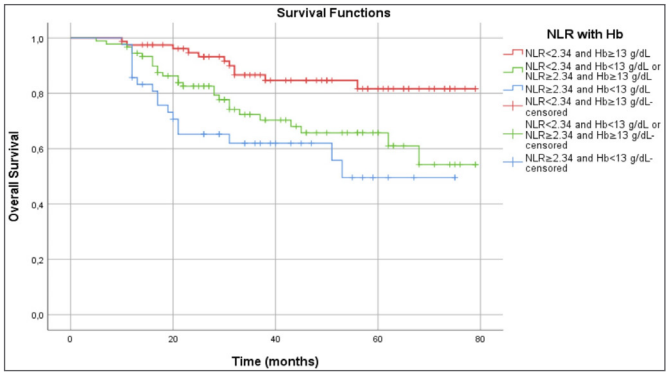

Figure 2. Kaplan-Meier graph of OS according to NLR with Hb

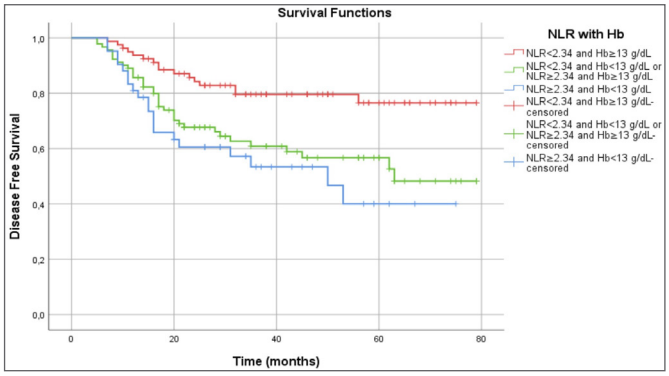

Figure 3. Kaplan-Meier graph of DFS according to NLR with Hb

Furthermore, age (p=0.001), T stage (p=0.011), N stage (p<0.001), stage (p=0.010), and anemia (p=0.016) were associated clinicopathological parameters with DFS in univariate analysis (Table 3). In multivariate analysis, age (HR=2.58, 95%CI: 1.54-4.31, p<0.001), N stage (HR=3.19, 95%CI: 1.80-5.66, p<0.001), NLR (HR=1.81, 95%CI: 1.11-2.96, p=0.017), and NLR with Hb (HR=3.32, 95%CI: 1.20-9.16, p=0.028) remained as prognostic for DFS (**Table 3**).

Factors that Affect Local Regional Recurrence Free Survival

The 5-y LRRFS was 62.4% for all patients. As presented in Table 4, increased LRRFS rates were found in patients with low NLR and SII groups (p=0.008, p=0.002). Also, improved LRRFS rates were demonstrated in patients in the groups ANLR and ASII (p=0.003, p=0.002) (**Table 4**, **Figure 4**).

Age (p<0.001) and N stage (p=0.001) were significant clinicopathological factors affecting LRRFS in univariate analysis (**Table 3**). In multivariate analysis, age (HR=2.78, 95%CI: 1.61-4.79, p<0.001) and N stage (HR=2.87, 95%CI: 1.63-5.05, p<0.001) remained as prognostic for LRRFS.

Table 3. Univariate and multivariate cox regression analysis for overall survival, disease free survival and local regional recurrence free survival

Variable	OS Univariate		DFS Univariate		LRRFS Univariate	
	HR (95% Cl)	p	HR (95% Cl)	p	HR (95% Cl)	p
Age <60 vs ≥60	3.40 (1.81-6.38)	<0.001	2.34 (1.41-3.88)	0.001	2.66 (1.56-4.55)	<0.001
Gender Female vs male	1.00 (0.13-7.31)	0.993	0.66 (0.16-2.73)	0.570	0.61 (0.15-2.52)	0.494
Anterior commissura invasion -/+	1.06 (0.45-2.52)	0.884	0.86 (0.42-1.75)	0.681	0.73 (0.34-1.55)	0.415
Subglottic extension -/+	0.59 (0.23-1.55)	0.286	0.88 (0.37-2.05)	0.768	0.79 (0.33-1.87)	0.592
T stage T1-2 vs T3-4	1.98 (1.16-3.40)	0.010	1.80 (1.13-2.86)	0.011	1.50 (0.93-2.40)	0.089
N Stage N0-1 vs N2-3	3.35 (1.86-6.02)	<0.001	3.15 (1.87-5.29)	<0.001	2.51 (1.44-4.36)	0.001
Stage 1-2 vs 3-4	2.13 (1.23-3.69)	0.005	1.81 (1.14-2.90)	0.010	1.53 (0.94-2.48)	0.077
LVI No vs Yes	2.19 (0.62-7.70)	0.220	2.96 (0.86-10.18)	0.084	2.48 (0.71-8.65)	0.153
PNI No vs Yes	0.22 (0.03-1.71)	0.151	0.38 (0.08-1.67)	0.205	0.21 (0.02-1.58)	0.131
ECE No vs Yes	1.43 (0.32-6.32)	0.637	1.92 (0.55-6.64)	0.301	1.27 (0.29-5.61)	0.746
Hemoglobin ≥13 vs <13	0.46 (0.27-0.80)	0.004	0.56 (0.35-0.90)	0.016	0.63 (0.39-1.04)	0.070
NLR <2.34 vs ≥2.34	2.08 (1.19-3.66)	0.008	2.02 (1.24-3.28)	0.003	1.93 (1.17-3.18)	0.008
PLR <122 vs ≥122	2.00 (1.13-3.53)	0.014	1.73 (1.07-2.81)	0.022	1.62 (0.99-2.67)	0.050
SII <564 vs ≥564	2.56 (1.39-4.51)	0.001	2.31 (1.40-3.81)	0.001	2.19 (1.31-3.66)	0.002
NLR with Hb	1.47 (1.18-1.84)	0.001	1.38 (1.14-1.67)	0.001	1.30 (1.06-1.59)	0.003
Group A vs B		0.006		0.003		0.002
Group A vs C		<0.001		<0.001		0.005
Group B vs C		0.145		0.321		0.846
PLR with Hb	1.40 (1.13-1.73)	0.005	1.29 (1.07-1.56)	0.013	1.22 (1.00-1.49)	0.040
Group A vs B		0.035		0.031		0.025
Group A vs C		0.001		0.005		0.026
Group B vs C		0.160		0.358		0.835
SII with Hb	1.48 (1.19-1.84)	0.001	1.38 (1.14-1.67)	0.001	1.30 (1.07-1.59)	0.002
Group A vs B		0.003		0.001		0.001
Group A vs C		<0.001		<0.001		0.002
Group B vs C		0.190		0.405		0.926
	Multivariate		**Multivariate**		**Multivariate**	
	HR (%95 Cl)	**p**	**HR (%95 Cl)**	**p**	**HR (%95 Cl)**	**p**
Age <60 vs ≥60	3.89 (2.05-7.39)	<0.001	2.58 (1.54-4.31)	<0.001	2.78 (1.61-4.79)	<0.001
N Stage N0-1 vs N2-3	3.33 (1.63-6.83)	0.001	3.19 (1.80-5.66)	<0.001	2.87 (1.63-5.05)	<0.001
NLR <2.34 vs ≥2.34	1.85 (1.05-3.28)	0.033	1.81 (1.11-2.96)	0.017	1.66 (0.98-2.82)	0.056
NLR with Hb	2.61 (1.14-5.97)	0.022	3.32 (1.20-9.16)	0.028	1.85 (0.85-4.01)	0.116
Group A vs B		0.056		0.013		
Group A vs C		0.006		0.021		

CI: Confidence interval; DFS: Disease free survival; ECE: Extracapsular extension; Hb: Hemoglobin; HR: Hazard ratio; LRRFS: Local regional recurrence free survival; LVI: Lymphovascular invasion; OS: Overall survival; PNI: Perineural invasion; RT: Radiotherapy. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index

Table 4. Survival outcomes according to NLR, PLR, SII and Hb level

		NLR		PLR		SII		Hb		NLR with Hb			PLR with Hb			SII with Hb		
		NLR <2.34	NLR ≥2.34	PLR <122	PLR ≥122	SII <564	SII ≥564	Hb ≥13	Hb <13	Group ANLR	Group BNLR	Group CNLR	Group APLR	Group BPLR	Group CPLR	Group ASII	Group BSII	Group CSII
OS	Median, (months) 95% CI	NR	68 -	NR	NR	NR	68 -	NR	NR	NR	NR	53 -	NR	NR	NR	NR	NR	53 -
	2-y	90.7	77.2	89.7	78.4	90.7	77.4	89.4	70.1	94.7	82.6	65.2	92.6	83	68.9	94.8	81.1	68.3
	5-y	76.8	60.7	77.7	60.6	83.1	58.1	75.1	55.1	81.7	65.7	49.6	79.8	70.7	51.1	83.1	65.7	48.4
	p	0.008		0.014		0.001		0.004			0.001			0.005			0.001	
DFS	Median, (months) 95% CI	NR	62 (45.93-78.06)	NR	62 (40.45-80.54)	NR	62 (42.75-81.24)	NR	53 -	NR	63 -	50 (25.91-74.10)	NR	63	50 (21.79-78.20)	NR	63	50 (23.91-76.09)
	2-y	79.6	66.1	78.3	67.3	83.5	62.6	76.8	62.3	84.3	67.7	60.6	81.4	69.2	62.4	86.3	63.8	61.1
	5-y	71.5	50.9	71	52.3	73.4	50.1	67.7	47.7	76.5	56.7	40	73.8	58.5	44	76.8	57.9	40.3
	p	0.003		0.022		0.001		0.016			0.001			0.013			0.001	
LRRFS	Median, (months) 95% CI	NR	62 (43.68-80.31)	NR	68 -	NR	62 (39.5-84.47)	NR	NR	NR	68 (35.10-100.89)	53 -	NR	68 -	NR	NR	68 -	53 -
	2-y	80.4	68.8	80.3	69.2	84.5	65.2	78.5	64.8	85.4	69.2	64.3	83.7	69.8	65.9	89.6	65.3	65
	5-y	71.9	51.4	70.8	54.5	73.6	51.4	67.1	52.3	77.2	54.7	47.4	73.5	58.1	50.3	77	56.7	47.2
	p	0.008		0.050		0.002		0.070			0.003			0.040			0.002	

CI: Confidence interval; DFS: Disease free survival; Hb: Hemoglobin; LRRFS: Local regional recurrence free survival; NLR: Neutrophil-to-lymphocyte ratio; NR: Not reached; OS: Overall survival; PLR: Platelet-to-lymphocyte ratio; SII: Systemic immune-inflammation index

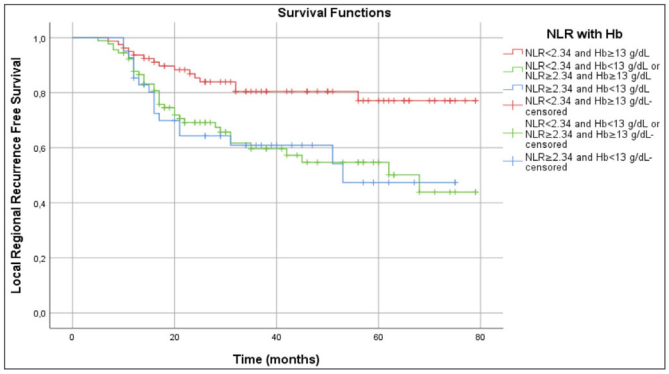

Figure 4. Kaplan-Meier graph of LRRFS according to NLR with Hb

DISCUSSION

In this study, we investigated whether hematological parameters have a prognostic effect on survival in patients with LSCC treated with RT. Our findings demonstrated that high levels of pretreatment NLR, PLR, and SII and low Hb levels were associated with worse survival (except for PLR and Hb for LRRFS) in univariate analysis. In addition, the analysis of the subgroups determined according to Hb level and inflammatory indices showed that survival was significantly better in patients in each group A with low inflammatory index and high Hb. In the multivariate analysis, high NLR and group CNLR were statistically significant predictors of worse OS and DFS. We found that the predictive ability increased even more when the inflammatory index was combined with the Hb level.

Over the past decades, systemic inflammation indices have been extensively investigated for patient classification and survival prediction in various tumor types.[14-16] NLR, PLR and SII have been shown to predict survival in many studies and reliable results have been obtained with meta-analyses, but fewer studies have been reported in terms of LSCC.[14-16,20,23,24] Currently available data include retrospective studies of systemic inflammation indices such as NLR, PLR, and SII in LSCC. Surgery was used as the treatment option in most of these series, and survival outcomes were associated with surgery. For example, Fu et al.[23] reported that preoperative NLR was correlated with survival in a retrospective series of 420 advanced LSCC patients who underwent total laryngectomy, with a hazard ratio of 1.42. The threshold for NLR was 2.59, with 5 y-OS 63% in the low NLR group and 52.8% in the high NLR group. In the large series of Mao et al.[24] patients were divided into three subgroups according to their PLR scores as low (119.55), moderate (>119.55 and 193.55), and high (>193.55). The 5-y cancer specific survival rates were found to be 75.3%, 68.4%, and 53.9%, respectively, according to the groups. The 5-y-survival rates found in these two studies are similar to ours study in terms of NLR and PLR. In these series, adjuvant RT was probably given after surgery based on the pathological characteristics of the patients but was not specified in the methodology of these studies. In some

studies, in which systemic inflammatory indices were evaluated preoperatively, it was stated that adjuvant RT/CRT was applied to some of the patients. Although the number of patients was not high, in the study published by Li et al.[24] in 2021, approximately two-thirds of the 147 patients underwent adjuvant RT. In this study, NLR, PLR, and SII were evaluated together; the 5 y- OS rates were 79.7% vs 36.4%, 70.5% vs 28.8%, and 72.2% vs 29.6% for the low and high groups; the 5 y- PFS rates were 71.2% vs 31.9%, 64.8% vs 22%, and 65% vs 25%, respectively. It was shown that preoperative NLR, PLR, and SII contributed significantly to both OS and progression free survival (PFS).

Studies investigating the effect of systemic inflammatory index on survival in patients undergoing definitive RT in LSCC were mostly mentioned in the HNC studies. Bojaxhiu et al.[26] reported that high NLR is an indicator of poor OS in patients with HNC using RT as the main treatment modality, and this predictive feature was still valid for LSCC when subgroup analysis was performed by site of primary disease. Similar to the results of other studies, NLR was found to be predictive for OS and PFS in a series of 125 advanced-stage patients undergoing definitive CRT (HR: 1.51; HR: 1.79).[27] Cho et al.[21] evaluated the outcomes of 621 patients and reported that 5 y- OS (83.8% vs 50.9%) and PFS (75.8 vs 39.2%) were better in the low NLR group in HNC. More recently, high NLR values in LSCC have been shown to be associated with reduced OS, DFS, and PFS, based on the results of a published meta-analysis involving 12 retrospectively designed 3710 patients undergoing surgery and/or RT (HR:1.76; HR:1.66; HR:1.72).[20]

In our study, while most of the patients were treated with definitive RT/CRT, adjuvant RT/CRT was applied in to approximately one-fourth of them. Since it would be more accurate to compare the results of studies designed similarly to our study, we focused on studies that included patients who underwent definitive RT and patients who received RT after surgery. Atasever Akkas et al.[28] evaluated 118 patients; the 5 y- OS rates were 69% vs 41%, 64% vs 55%, and 76% vs 34% for the low and high groups; the 5 y- DFS rates were 69% vs 35%, 64% vs 49%, and 69% vs 33%, respectively. They found a relationship between NLR, PLR, and SII and survival in patients with LSCC in the univariate analysis, while SII was significantly correlated with OS in the multivariate analysis (HR:10.54). Recently, Kotha et al.[29] showed that high NLR is a poor prognostic marker for OS and cause specific survival in a more homogeneous group of 1047 patients with advanced-stage disease (HR: 1.31; HR: 1.46). In our study, NLR, PLR, and SII were associated with both OS, DFS, and LRRFS (excluding PLR) in univariate analysis, but only NLR remained significant for OS and DFS in multivariate analysis. As mentioned above, regardless of the type of treatment, it was observed that prognostically significant results were obtained with NLR, as in our study, and in most of the studies.

As in other cancers, the threshold values determined for systemic immune inflammation biomarkers in studies reported for LSCC are specific to each study and cannot be used or valid in any other study. Currently, it is not known which values should be accepted as reference points for these markers, but their predictive effect is evident.

As a result of experimental and clinical studies, it is known that tumor hypoxia and anemia negatively affect the efficacy of RT in solid tumors, including HNC.[30] Years ago, in a randomized study to examine the radiosensitizing effect of Misonidazole, it was determined that high Hb levels increased local control rates, especially in hypopharyngeal cancer.[21] Subsequent studies have reported lower recurrence-free survival rates for LSCC in patients with anemia before and/or after RT compared to those without.[32-34] In addition, in another study evaluating the difference between the Hb levels detected preoperatively, pre-RT, and during RT, it was shown that OS was adversely affected by the decline of Hb levels during RT.[35]

Although the accepted threshold value for anemia varied in the aforementioned studies, 12-14.5 g/dl was preferred in males. In our study, which was dominated by male patients, we accepted values below 13 g/dl as anemia. Consistent with the literature, we found that anemia was associated with a shorter OS as well as DFS. In order to evaluate the hypothesis whether the predictive effect can be strengthened by combining low Hb level, we further categorized the patients into three groups for each inflammatory index. When we reanalyzed according to these groups, we found that the predictive effect was increased when NLR was combined with Hb in multivariate analysis.

Recent data have demonstrated the prognostic impact of systemic inflammatory indices, which are not yet used in risk scoring. In a retrospective study, Pogorzelski et al.[36] aimed to evaluate chemotherapy response and survival in metastatic HNC and presented their data on prognostic scoring, which they defined using NLR, Hb, age, and ECOG performance status parameters, which they found statistically significant in multivariate analyzses. The median value determined for each value in the patients included in the study was accepted as the threshold value for NLR, Hb, and age. High NLR, low Hb, advanced age, and poor performance were each determined as positive factors, and prognostic scores from 0 to 4 were defined by summing them numerically. It was found that OS and PFS were shortened in patients with a high prognostic clinical score. In our study, we grouped patients by combining Hb level and systemic inflammatory index without considering other parameters, and the best OS and DFS were detected in the group with both low NLR and high Hb levels.

Studies evaluating the combined prognostic effect of hematological parameters obtained from routine blood samples are few in LSCC. In a series of 68 patients with LSCC who underwent induction chemotherapy, the effect of Hb and NLR values at the beginning and at the end of treatment on both response to chemotherapy and survival was investigated.[37] In this study, the authors evaluated parameters separately. Anemia or high NLR at baseline did not alter chemotherapy response but worsened OS. Similarly, when hematological parameters were evaluated separately in our study, it was shown that survival decreased with anemia and high systemic inflammatory index.

The Hb level was added to the inflammatory indices in Hb, albumin, lymphocyte, platelet (HALP) score, which is thought to reflect the immune and nutritional status. There are meta-analyses showing that a low HALP score is associated with reduced survival in solid tumors, but no study involving HNC has yet been identified.[38,39]

The strengths of this study are as follows. In our study, systemic inflammatory indices such as NLR, PLR, and SII were evaluated together. Since studies on systemic inflammatory indices in LSCC are few, we have contributed to the literature by obtaining significant results with a relatively large number of patients. The effect of Hb level, which had a previously proven predictive effect, was also investigated. In addition, we were able to show that the prognostic efficiency of hematological parameters increased when patients were divided into groups by combining both hematological parameters.

However, this study had several limitations. First, the data were collected retrospectively, and all patients were treated at a single institution. Second, the patients in our cohort consisted of a highly heterogeneous group with based on the stage and the different treatment options applied. Third, because of its retrospective design, it was difficult to accurately determine whether patients were taking drugs that could alter hematological parameters, such as statins, nonsteroidal anti-inflammatory drugs, or iron supplements. Therefore, prospective studies will be more helpful in revealing the prognostic effect of hematological parameters on survival with a more homogeneous patient population in LSCC.

CONCLUSION

According to the results of our study, the predictive ability increased, even more, when the NLR was combined with the Hb level. The development of straightforward and reliable prognostic markers is essential to validate hematological parameters for patient risk stratification, response to therapy, and prediction of survival.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Samsun University Clinical Researches Ethics Committee (Date: 2023, Decision No: 10/11)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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A new model for estimating in-hospital mortality in patients with pulmonary embolism: PATHOS score

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ABSTRACT

Aims: Pulmonary embolism (PE) is a major contributor to the death rate associated with cardiovascular diseases. The objective of this research is to evaluate the efficacy of the PATHOS score in predicting in-hospital mortality in patients diagnosed with pulmonary embolism (PE) in emergency departments (ED).

Methods: The data of patients who were visited in the ED of a third-level healthcare facility, and diagnosed with PE between 2022 and 2023 were analyzed. To examine the value of the PATHOS score in predicting mortality, through the use of Receiver Operating Characteristic (ROC) analysis, the Area Under the Curve (AUC) was determined.

Results: The study was completed with 111 patients. Of these patients, 52 (46.8%) were male and 59 (53.2%) were female. The mean age of the patients was 67.67±16.49. When the cut-off value of PATHOS score in identifying in-hospital mortality was >2, the sensitivity was 70.8%, the specificity was 71.3%, and the positive predictive value was 41.2% and the negative predictive value was 81.9%.

Conclusion: In this study, we concluded that the PATHOS score may be an effective tool for in-hospital mortality estimation of patients diagnosed with PE in the ED. However, this score needs further evaluation in large-scale and multicenter studies.

Keywords: Mortality, pulmonary embolism, scoring systems

INTRODUCTION

Pulmonary embolism (PE) is a disease that occurs as a result of the sudden blockage of one of the pulmonary arteries and its branches. It is a life-threatening clinical condition, arising due to a complete or partial blockage of the pulmonary artery by materials like thrombus or non-thrombus entities (air, fat, etc.), which mostly originate from the deep veins of the lower extremities.[1-3] The most common cause of PE is deep vein thrombosis (DVT) and these two disease conditions are also referred to together as venous thromboembolism (VTE).[4]

PE, which is a significant health problem commonly seen in the community, has an annual average incidence rate of approximately 23-269/100,000, varying by country. Its prevalence increases exponentially with age. In terms of causes of mortality, pulmonary embolism (PE) ranks third worldwide among acute cardiovascular syndromes, following myocardial infarction and stroke.[5]

Various clinical scoring systems have been developed to assess the prognosis of PE patients and to determine treatment strategies. However, these scores are generally complex and time-consuming, and they do not sufficiently account for certain clinical conditions. This situation could lead to difficulties in appropriately directing patient care.[6-8]

Scoring systems are widely used in the daily practice of emergency departments (ED), and these systems serve as helpful tools in the process of managing critically ill patients.[9-12] The recently developed PATHOS score is a simple and useful predictive model created to estimate in-hospital mortality of PE patients.[13] This score aims to facilitate the decision-making process regarding prognosis by considering patients' clinical features and laboratory results.

The objective of this research is to assess the effectiveness of the PATHOS score in estimating the likelihood of in-hospital death among patients diagnosed with PE in the ED.

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METHODS

The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 16/05/2023, Decision No: 2340). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[14]

Study Population and Design

This study was designed as retrospective and observational, and was conducted in the emergency department (ED) of a tertiary hospital. Every patient above the age of 18 who arrived at the ED, between May 2022 and May 2023 and were diagnosed with PE were included in the study. Patients under 18 years of age, patients diagnosed with a condition other than PE, patients transferred from another hospital, and patients for whom the PATHOS score could not be calculated were not included in the study. The information of all patients was recorded into a dataset using the hospital's electronic database. The dataset used for the evaluation includes the patients' demographic features (age, gender, etc.), laboratory results (platelet count, troponin levels, etc.), comorbid diseases, and clinical features (heart rate, oxygen saturation, systolic blood pressure, etc.). The PATHOS score consists of 6 variables, and the presence of each variable is scored with +1 point. These variables are as follows; platelet count < 100 or > 400 $\times 10^3/\mu L$, age > 80 years, troponin level > cutoff, heart rate > 100 pulses per minute, SpO_2 <90%, systolic blood pressure < 100 mmHg.[13] The main outcome measure of the study was the incidence of in-hospital mortality due to any cause.

Statistical Analysis

The statistical evaluations were conducted with SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The descriptive statistics were expressed as the mean and standard deviation, as well as the percentage distribution. The conformity of the data to normal distribution was checked with the Kolmogorov-Smirnov test. Pearson Chi-Square test was used for comparing distributions in comparing sociodemographic, clinical, and laboratory finding characteristics between those who died and those who survived. Student's t-test was used for comparing continuous variables. The analysis of the Receiver Operating Characteristic (ROC) was employed to determine the Area Under the Curve (AUC) to investigate the value of the PATHOS score in predicting mortality. A p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

After excluding 3 patients transferred from another hospital and 4 patients for whom the PATHOS score could not be calculated, the study was completed with 111 patients. Of these patients, 52 (46.8%) were male and 59 (53.2%) were female. The average age of the patients was 67.67±16.49. The patients were categorized into two groups: those who survived and those who did not, and then various features were compared (**Table 1**). The average age of the non-survivor group was 76.75±10.51, while the average age of the survivor group was 65.17±17.01. The statistical analysis revealed that the average age of non-survivors was statistically significantly higher than that of survivors (p:0.045) (**Table 1**). The average systolic blood pressure of the non-survivor group was 110.83±21.61 mmHg, while the average systolic blood pressure of the survivor group was 124.33±23.92 mmHg. The statistical analysis showed that the average systolic blood pressure of non-survivors was statistically significantly lower than that of survivors (p:0.019) (**Table 1**). The average PATHOS score of the non-survivor group was 2.88±0.99, while the average PATHOS score of the survivor group was 1.87±1.20. The statistical analysis revealed that the average PATHOS score of non-survivors was statistically Substantially greater compared to those who survived (p<0.001) (**Table 1**).

As a result of the ROC analysis of PATHOS score in predicting in-hospital mortality among PE patients, the area under the curve was 0.733 (95% CI 0.640-0.812), the Youden index was 0.421 (p<0.001). When the cut-off value of PATHOS score in identifying in-hospital mortality was >2, the sensitivity was 70.8%, the specificity was 71.3%, and the positive predictive value was %41.2 and the negative predictive value was %81.9 (**Table 2**, **Figure 1**).

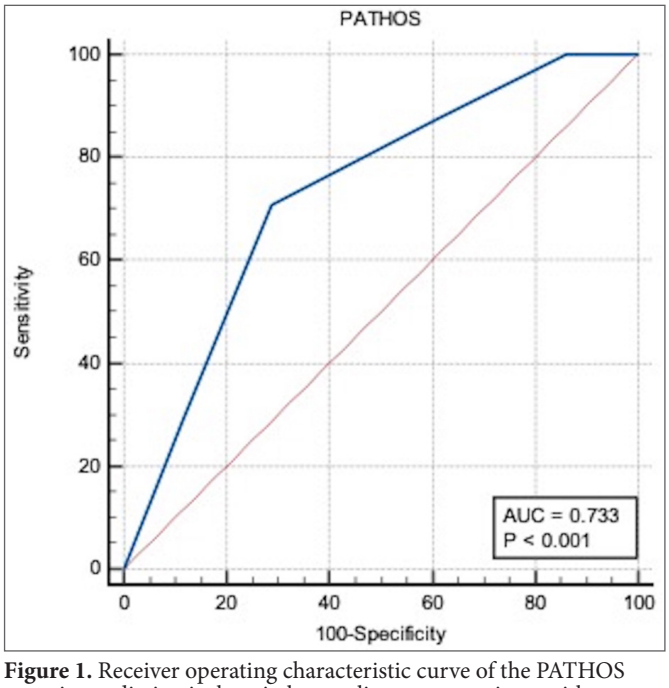

Figure 1. Receiver operating characteristic curve of the PATHOS score in predicting in-hospital mortality among patients with pulmonary embolism.

Table 1. General characteristics of the patients included in the study

	Non-survivor		Survivor		Total		p value
	n(%)	Mean±SD	n(%)	Mean±SD	n(%)	Mean±SD	
Gender							
Male	15 (62.5)		37 (42.5)		52 (46.8)		0.107
Female	9 (37.5)		50 (57.5)		59 (53.2)		
Age,years		76.75±10.51		65.17±17.01		67.67±16.49	
≤80	13 (54.1)		66 (75.9)		79 (71.2)		0.045
>80	11 (45.9)		21 (24.1)		32 (28.8)		
SBP (mmHg)		110.83±21.61		124.33±23.92		121.41±24.01	
≥100	17 (70.8)		79 (90.8)		96 (86.5)		0.019
<100	7 (29.2)		8 (9.2)		15 (13.5)		
DBP (mmHg)		65.87±13.44		75.87±14.06		73.71±14.47	
Heart rate (ppm)		109.12±21.59		106.65±20.91		107.18±20.98	
≥100	9 (37.5)		37 (42.5)		46 (41.4)		0.816
<100	15 (62.5)		50 (57.5)		65 (58.6)		
HT	11 (45.8)		33 (37.9)		44 (39.6)		0.490
DM	2 (8.3)		16 (18.4)		18 (16.2)		0.352
CAD	7 (29.2)		17 (19.5)		24 (21.6)		0.400
CHF	5 (20.8)		15 (17.2)		20 (18)		0.765
Asthma	1 (4.2)		10 (11.5)		11 (9.9)		0.451
COPD	7 (29.2)		13 (14.9)		20 (18)		0.135
WBC (10^3u/L)		14558.33±6561.47		11061.03±3773.65		11817.21±4714.56	
HGB (g/L)		12.34±1.89		13.46±9.79		13.22±8.71	
PLT (10^3u/L)		281.95±135.55		251.26±110.81		257.9±116.63	
≥100 / ≤400	19 (79.2)		75 (86.2)		94 (84.7)		0.521
<100 / >400	5 (20.8)		12 (13.8)		17 (15.3)		
Urea (mg/dL)		52.41±19.33		46.01±23.64		47.4±22.85	
Creatinine (mg/dL)		0.96±0.24		1.019±0.45		1.01±0.42	
SPO_2		85.50±5.90		89.31±7.36		88.49±7.23	
≥90	7 (29.2)		46 (52.9)		53 (47.7)		0.364
<90	17 (70.8)		41 (47.1)		58 (52.3)		
Troponin		4.16±10.90		2.25±11.04		2.66±10.99	
≤0.14	13 (54.2)		56 (64.4)		69 (62.2)		0.476
>0.14	11 (45.8)		31 (35.6)		42 (37.8)		
PATHOS score		2.88±0.99		1.87±1.20		2.09±1.23	<0.001

SBP: systolic blood pressure, DBP: diastolic blood pressure, HT: hypertension, DM: diabetes mellitus, CAD: chronic arterial disease, CHF: congestive heart failure, COPD: chronic obstructive pulmonary disease, WBC: white blood cell, HGB: hemoglobin, PLT: platelet

Table 2. Diagnostic values and cut-off level of the PATHOS score to predict in-hospital mortality among patients with pulmonary embolism

	AUC	Cut-Off	Sensitivity	Specificity	+LR	-LR	PPV	NPV	Youden Index
PATHOS score	0.733 (0.640-0.812)	>2	70.8	71.3	2.5	0.8	41.2	81.9	0.421

AUC: Area under the curve, LR: likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value

DISCUSSION

In this study, we examined the effectiveness of the PATHOS score in predicting in-hospital mortality in patients diagnosed with PE who presented to the ED. According to the study results, the PATHOS score demonstrated acceptable discriminatory power, as evidenced by an AUC of 0.73. PE is among the primary causes of death related to cardiovascular conditions.[15] It constitutes a significant burden in global health services and the clinical outcomes of patients are often significantly affected.[16] As per the PE guidelines issued by the European Society of Cardiology (ESC) in 2020, the use of scoring systems for patient mortality prediction has been recommended.[17] Using scoring systems in PE is crucial for several reasons. Scoring systems help in classifying patients according to their risk of adverse events or death. This allows physicians to guide treatment decisions based on the severity of the patient's condition. Patients with a higher risk score might need more aggressive treatment and monitoring. Scoring systems are used as a tool to decide the appropriate level of care (outpatient, inpatient, or intensive care) and whether thrombolytic therapy is indicated. They aid in balancing the risks and benefits of different treatment approaches. By stratifying patients, these scoring systems help healthcare providers efficiently allocate resources, ensuring that patients who are at higher risk receive the appropriate level of care.

These scoring systems provide a standardized method for comparing patient populations in research studies. It allows for more robust and reliable data in clinical trials and epidemiological studies. Lastly, scoring systems can provide prognostic information, assisting physicians in predicting the likely course and outcome of the disease

This study aimed to facilitate the application of more individual and targeted approaches in PE treatment. For this purpose, the validation of the PATHOS score, created in 2023, was worked on. The study was completed with 1358 patients diagnosed with PE who presented to the ED of two university hospitals in Italy. In the derivation cohort, the AUC value of the PATHOS score was found to be 0.827, while in the validation cohort, the AUC value was calculated as 0.74. In the analysis of all patients, the best cutoff was found to be >2. At this cutoff, the sensitivity was 60%, the specificity was 81%, the positive predictive value was 30%, and the negative predictive value was 94%.[13] In our study, the AUC value was 0.733, which gave a similar result to the validation cohort. However, at cutoff >2, the sensitivity was 70.8%, the specificity was 71.3%, the positive predictive value was 41.2%, and the negative predictive value was 81.9%. In our study, the AUC value was found to be lower than the derivation cohort of the original study, and the negative predictive value was relatively lower from the total group. There may be several reasons for this. The first is differences in sample size. Sample size can affect the reliability of a study's results and statistical power. Since the sample used in this study was smaller than the original study, this could be a reason for AUC differences.[18] Secondly, the patient population can be considered. Demographic or clinical differences in the patient population may also lead to AUC differences.

For instance, this difference may occur if patients are different in terms of age, gender, ethnicity, underlying diseases, or severity of PE.[19] Lastly, there can be random errors in any study, and these errors can affect the results. This is especially true for smaller samples.[20]

Limitations of this study include its single-centered and retrospective design. These factors restrict the applicability of the results and enhance the likelihood of selection bias. Lastly, the PATHOS score is still a new score and requires further validation studies.

CONCLUSION

In this study, we concluded that the PATHOS score could be an effective tool in predicting in-hospital mortality in patients diagnosed with PE in the ED. However, this score needs to be evaluated more in comprehensive and multi-centered studies. Additionally, more study should be done on integrating additional prognostic factors into the score to enhance the effectiveness of the PATHOS score in identifying high-risk patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 16.05.2023, Decision no: 2340).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Original Article

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Increased prevalence of gastric pathologies in patients with total hip and total knee prostheses: a retrospective endoscopic study

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ABSTRACT

Aims: The objective of this retrospective study was to evaluate the prevalence of *Helicobacter pylori* (*H. pylori*) positivity, gastric atrophy, and intestinal metaplasia in patients with dyspeptic complaints who had undergone total hip and knee replacement surgeries, compared to a control group without prosthesis.

Methods: The study group consisted of 51 patients with dyspeptic complaints and total knee and hip prosthesis, while the control group comprised 75 patients with similar complaints but without prosthesis. Endoscopic gastric biopsies were obtained from all participants, and the presence of *H. pylori*, gastric atrophy, and intestinal metaplasia were evaluated.

Results: The prevalence of *H. pylori* positivity, gastric atrophy, and intestinal metaplasia were significantly higher in patients who underwent total knee and hip replacement compared to the control group without prosthesis.

Conclusion: The results of this study suggest that patients who undergo total hip and knee replacement surgeries may be at higher risk for developing gastric pathologies, such as *H. pylori* infection, gastric atrophy, and intestinal metaplasia. Therefore, it is recommended that physicians who care for these patients monitor them closely for these conditions and consider endoscopic surveillance as part of their management plan.

Keywords: Total knee arthroplasty, total hip arthroplasty, *H. pylori*, atrophy, intestinal metaplasia

INTRODUCTION

Total hip and total knee replacements are common orthopedic surgeries performed to relieve pain and improve mobility in patients suffering from joint diseases such as osteoarthritis, rheumatoid arthritis, or post-traumatic arthritis.[1-3] Despite the successful outcomes of these surgeries, they may be associated with certain complications such as infections, implant loosening, dislocation, or fractures. Moreover, these procedures may also have systemic effects on other organs in the body, including the gastrointestinal tract.[4,5]

Dyspepsia is a common gastrointestinal complaint characterized by pain or discomfort in the upper abdomen, bloating, nausea, and early satiety.[6] It may result from various causes, such as gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), functional dyspepsia, or gastric malignancies.[7] *H. pylori* is a gram-negative bacterium implicated in the pathogenesis of several gastrointestinal diseases, such as gastritis, PUD, and gastric cancer.[8] Moreover, chronic *H. pylori* infection may lead to gastric atrophy and intestinal metaplasia, precursors of gastric malignancies.[9,10]

Recent studies have suggested that patients who undergo total hip or total knee replacements may be at an increased risk of developing dyspeptic symptoms and gastric pathologies.[11,12] However, the evidence is still limited, and further research is needed to explore the potential association between these surgeries and gastrointestinal disorders. Therefore, in this retrospective study, we aimed to evaluate the prevalence of *H. pylori* positivity, gastric atrophy, and intestinal metaplasia in patients who underwent total hip and total knee replacements and compare it to a control group with similar dyspeptic complaints but without prosthesis.

The findings of this study may shed light on the possible systemic effects of joint replacements on the gastrointestinal tract and highlight the importance of early detection and management of gastric pathologies in these patients.

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METHODS

The study was carried out with the permission of the Giresun Training and Research Hospital Clinical Researches Ethics Committee (Date: 13.02.2023, Decision No: 03). Informed consent from the patients was not needed as the study was designed as retrospectively. The study was conducted in line with the ethical principles of the Declaration of Helsinki and its later amendments.

A total of 51 patients with total knee arthroplasty (TKA) and total hip arthroplasty (THA) and 75 patients without prosthesis who presented to our general surgery clinic due to the complaint of abdominal pain were included in this study. The patients were divided into two groups the TKA/THA group and the control group. Following a physical examination and laboratory investigations, all patients underwent gastric endoscopy, and endoscopic specimens were then sent to the pathology laboratory for biopsy examinations. Patients with known gastrointestinal disorders, malignancies and those with missing data were excluded from the study.

Patients' demographics, such as age and gender, laboratory parameters and biopsy findings, were recorded and compared between the groups.

Statistical Analysis

Data obtained in this study was statistically analyzed using the SPSS version 24.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) package software. The normality of the variables was tested using the Kolmogorov-Smirnov method. An Independent t-test among the parametric tests was used to compare the variables between the two groups. Continuous variables are expressed as mean±standard deviation, while categorical variables are expressed as frequency and percentage (n, %). $p<0.05$ values were considered statistically significant.

RESULTS

A total of 51 patients with TKA/THA and 75 prosthesis-free patients who presented to our clinic with abdominal pain were included in the study. The mean age was 64.4±13.2 years in the TKA/THA group and 62.4±12.8 years in the control group. There was no statistically significant difference between the two groups in terms of age (p=0.322).

Eight (15.7%) patients were male, and 43 (84.3%) were female in the TKA/THA group, while 11 (14.67%) patients were male and 64 (85.33%) patients were female in the control group. No statistically significant difference was found between the groups in terms of gender (p=0.887).

When laboratory parameters were examined, the mean hematocrit value was statistically significantly lower in the TKA/THA group compared to the controls (p=0.026). Similarly, the mean creatinine, alanine transaminase (ALT) and albumin levels were statistically significantly lower in the TKA/THA group compared to the control group (p=0.005, p=0.037, p=0.001; respectively). No statistically significant difference was found between the two groups in terms of the other laboratory parameters (for all, p>0.05) (**Table 1**).

Table 1. Laboratory values of the groups

	TKA/THA		Control		p†
	Mean	±SD	Mean	±SD	
Hemoglobin	12.5	1.7	13	1.9	0.054
Hematocrit	37.9	4.7	19.7	5.3	0.026
MCV	84.5	6.6	86.3	5.4	0.101
WBC	6.9	2.4	7.4	2.4	0.105
Lymphocyte	2.1	0.7	2.2	0.7	0.619
Platelet	269.8	80.2	250.5	67.6	0.284
Glucose	123.3	43.4	113.6	35	0.144
Urea	35.4	15	38.8	25.6	0.907
Creatinine	0.8	0.2	0.9	0.4	0.005
AST	18.9	6.4	20.6	8.6	0.130
ALT	16.2	8.1	19.7	13.3	0.037
Albumin	4.3	0.5	4.5	0.5	0.001

Descriptive statistics were shown as * mean ±SD or ** median (25th - 75th) percentiles. † Mann Whitney U test, MCV: mean corpuscular volüme, WBC: white blood cell, AST: Aspartate transaminase, ALT: alanine transaminase

When the results of the gastric biopsy were examined, the incidence of *H. pylori*, atrophy and intestinal metaplasia were statistically significantly higher in the TKA/THA group compared to the control group (p=0.030, p=0.024, p=0.035; respectively) (**Table 2**).

Table 2. Biopsy results according to the groups

Parameter	TKA/THA		Control		p†
	n	%	n	%	
H. pylori					0.030
No	16	31.4	37	49.33	
Yes	35	68.6	38	50.67	
Atrophy					0.024
No	30	58.8	57	76.00	
Yes	21	41.2	18	24.00	
Intestinal metaplasia					0.035
No	32	62.7	59	78.67	
Yes	19	37.3	16	21.33	

† Mann Whitney U test

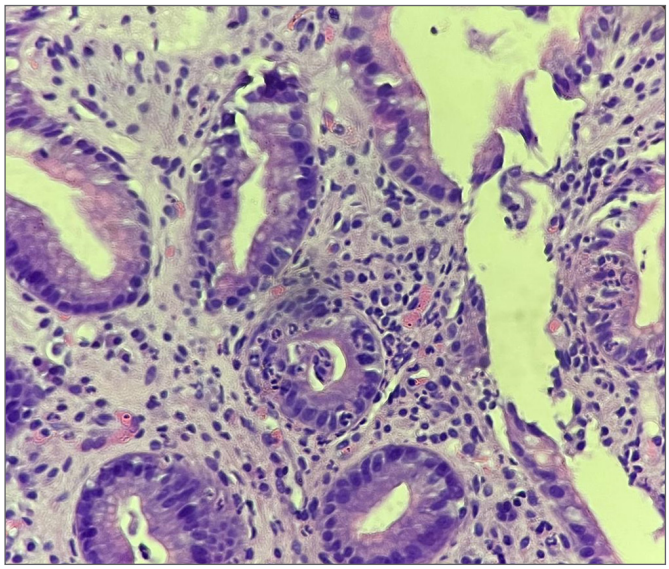

Figure 1. Gastric biopsy showing intraepithelial neutrophils. Magnification 400×

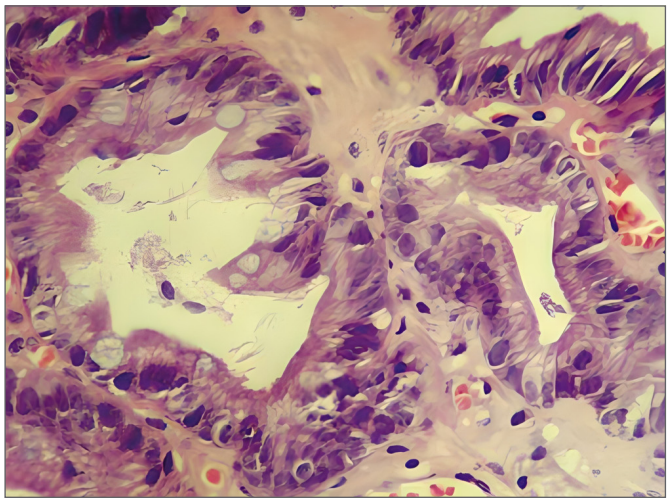

Figure 2. Gastric biopsy showing intestinal metaplasia. Magnification 400×

DISCUSSION

Our retrospective endoscopic study demonstrated that patients with total hip and knee prostheses had a significantly higher prevalence of *H. pylori* positivity, gastric atrophy, and intestinal metaplasia than those without prostheses. These findings suggest a potential association between joint replacements and gastric pathologies, which may have important clinical implications.

The exact mechanisms underlying this association have yet to be fully understood, but several hypotheses have been proposed. First, joint replacements may change the immune response and increase the susceptibility of the gastrointestinal tract to *H. pylori* infection, which may lead to chronic inflammation, mucosal damage, and the development of gastric atrophy and intestinal metaplasia.[13,14] Second, joint replacements may cause changes in the gut microbiota and disrupt the balance between useful and harmful bacteria, which may also contribute to developing dyspeptic symptoms and gastric pathologies.[15] Third, joint replacements may release metal ions and wear debris, which may have toxic effects on the gastric mucosa and aggravate existing gastric lesions.[16]

Several studies in the literature report complications after TKA/THA procedures. Adenikinju et al.[17] stated that although rare, gastrointestinal complications following TKA/THA can result in detrimental outcomes, significant morbidity, and mortality. Thus, a raised awareness of these complications is warranted. In a study by Bekeris et al.[18] gastrointestinal complications were observed in 1.03% of patients undergoing THA and 0.79% of patients undergoing TKA procedures.

In a study by Heo et al.[19] complications at six months following TKA/THA procedures were investigated. According to this study, each 1 kg/m² increase in BMI value was associated with increased odds for re-operation. In the same survey, non-procedure-related major complications following TKA/THA procedures included cardiovascular complications, stroke and pulmonary embolism, while no gastrointestinal complications were mentioned.

In a study by Hnepa et al.[20] NSAID-induced gastrointestinal lesions are a relevant internal medicine problem due to unclear pathogenic mechanisms. They should be taken into account by physicians of all specialities. The authors recommended that examination and diagnosis of the gastrointestinal tract should be regularly performed to prevent NSAID-induced complications. Patients undergoing TKA/THA procedures are known to receive NSAIDs for an extended period, and therefore, these patients tend to develop gastrointestinal complications. Moreover, prolonged use of NSAIDs further increases the risk of gastrointestinal bleeding.[21]

In a study by Massaglia et al.[22] investigating gastrointestinal complications following TKA/THA, the most common complications were constipation followed by diarrhoea, malabsorption, haemorrhage, and *Clostridium difficile*.

It has been reported that significant muscle atrophy develops after TKA/THA, resulting in decreased strength and impaired mobility.[23] Chronic *H. pylori* infection induces chronic inflammation in the gastric mucosa, resulting in atrophy and intestinal metaplasia and increasing the risk of developing gastric adenocarcinoma.[24]

Regardless of the underlying mechanisms, the implications of our findings are significant. Patients who undergo joint replacements should be aware of the potential risk of developing dyspeptic symptoms and gastric pathologies and undergo regular endoscopic screening to detect

and manage abnormalities. Furthermore, orthopedic surgeons should consider the possible systemic effects of joint replacements on other organs, including the gastrointestinal tract, and take appropriate measures to minimize the risk of complications.

The clinical management of dyspepsia in patients with joint replacements may be challenging, as the treatment options may be limited by the presence of the prosthesis and the risk of complications such as bleeding or perforation. However, a multidisciplinary approach involving gastroenterologists, orthopedic surgeons, and primary care physicians may help optimize the management of dyspeptic symptoms and prevent the progression of gastric pathologies.

Study Limitations

The main limitations of our study include its retrospective design, the relatively small sample size, and the lack of data on the duration and type of joint replacements, as well as the use of NSAIDs and other medications. In addition, other gastrointestinal complications could also be investigated. Although we compared blood parameters and found significant differences between the groups, we could not attribute these findings to a specific reason. Moreover, the study did not investigate the potential impact of joint replacements on other gastrointestinal pathologies such as GERD, PUD, or gastric cancer. However, as a strength, this is the first study in the literature investigating the results of gastric biopsy in patients undergoing TKA/THA procedures. Our results will be guiding for further studies to be conducted on this issue.

CONCLUSION

Our retrospective study suggests that patients who undergo total hip and total knee replacements may have an increased risk of developing dyspeptic symptoms and gastric pathologies such as *H. pylori* positivity, gastric atrophy, and intestinal metaplasia. Healthcare providers should be aware of these potential systemic effects of joint replacements and be prepared to screen and evaluate patients for dyspeptic symptoms and gastric pathologies. In addition, these findings highlight the importance of close monitoring and managing gastrointestinal symptoms in patients with joint replacements and the need for further research to explore the potential mechanisms and preventive measures for these complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Giresun Training and Research Hospital Clinical Researches Ethics Committee (Date: 13.02.2023, Decision No: 03).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Evaluation of ultrafiltrated fluid overloaded patients: a single center study

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ABSTRACT

Aims: Fluid overloaded patients with heart or renal insufficiency have poor quality of life and increased morbidity and mortality. In this study, we aimed to investigate the factors affecting the prognosis in patients who presented with fluid overload and were ultrafiltered.

Methods: Three groups of patients were compared: Group 1: Patients with chronic kidney disease and ejection fraction ≤ 40%; Group 2: Patients with chronic kidney disease and ejection fraction > 40%; Group 3: Patients with ejection fraction ≤ 40% but without chronic kidney disease. Patients were also evaluated regarding mortality.

Results: Group 1, 2 and 3 consisted of 14, 62 and 16 patients: respectively. There were statistically significant results for 24-hour urine volume (p=0.040), proteinuria (p=0.010), ultrafiltration volume/weight at hospitalization (p<0.001), ejection fraction (p<0.001), left ventricular hypertrophy (p=0.040), uric acid (p<0.001), hemoglobin (p<0.001), dialysis dependency after hospital discharge (p<0.001) and mortality (p<0.001) when three groups were compared. However, there was no statistically significant result for ultrafiltration volume (p=0.100). Compared to survived patients those who did not survived were significantly older (p<0.001), had lower ejection fraction (p=0.010), creatinine (p<0.001), sodium (p=0.020), ferritin (p=0.040), proteinuria (p=0.010). They also had statistically significantly higher hemoglobin (p<0.001), creatinine clearance (p<0.001), uric acid (p<0.001) levels. However, the percentage of patients using loop diuretics at hospitalization (p=0.040) was higher in the group who survived.

Conclusion: Patients with HF were more prone to hypervolemia and mortality. The ultrafiltration volume/weight at hospitalization and serum uric acid levels were also significantly higher in these patients. Patients with chronic kidney disease had significantly higher proteinuria, creatinine and lower hemoglobin levels. The rate of loop diuretic usage at hospitalization was significantly higher in the survived group.

Keywords: Dialysis, ejection fraction, heart failure, loop diuretics, left ventricular hypertrophy, mortality, ultrafiltration

INTRODUCTION

Patients followed for cardiorenal syndrome are prone to fluid overload and they have higher risk of morbidity and mortality.[1] Unfortunately, hospitalizations are inevitable for some of these patients. Ultrafiltration (UF) is applied to patients whose volume overload cannot be controlled with intravenous diuretics and water restriction. Removal of excess fluid with UF relieves symptoms of congestion, improves exercise capacity and cardiac filling pressures.[2,3] It also has favorable effects on pulmonary function and neurohormone levels.[4-6]

The current definition of cardiorenal syndrome does not add diagnostic and prognostic value to the separate evaluation of heart failure (HF) and kidney disease. It is also hard to document if the inciting event is HF or renal failure in cardiorenal syndrome.[7] So, with this study we did not define the type of this syndrome, rather we aimed to investigate the factors affecting the prognosis in patients who presented with fluid overload and were ultrafiltered in a tertiary hospital.

METHODS

For this study, approval was obtained from İstanbul Haydarpaşa Numune Training and Research Hospital Ethics Committee (Date: 28.05.2019, Decision No: 771). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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One hundred forty-two patients who were ultrafiltrated in the emergency dialysis unit between January 2012 and May 2017 were evaluated retrospectively. Post-renal obstruction, pregnancy, hypervolemia after surgery, UF after switch from peritoneal dialysis to hemodialysis (HD), malignancy and cirrhosis were the exclusion criteria. Fifty patients were excluded and finally the study population consisted of 92 patients.

The decision of UF was taken by the patients' own doctors. Most of the patients were ultrafiltrated with temporary dialysis catheters. In stage 5 chronic kidney disease (CKD) patients previously created arteriovenous fistulas were used. HD was performed with high-flux membranes and heparin was used as an anticoagulant. The rate of fluid removal was adjusted considering the hemodynamic and volume status of the patients.

Data include demographic data, comorbid diseases, complete blood count, creatinine, albumin, electrolytes, uric acid (UA), C-reactive protein (CRP) and thyroid stimulating hormone (TSH), hospitalization time, cardiac ejection fraction (EF), left ventricular hypertrophy (LVH), 24-hour urine volume and proteinuria, UF volume during hospitalization, dialysis dependency after hospital discharge.

Three groups of patients were compared:

- **Group 1:** Patients with CKD (estimated glomerular filtration rate (eGFR) < 60 ml/min) and cardiac EF ≤ 40%
- **Group 2:** Patients with CKD and cardiac EF > 40%
- **Group 3:** Patients with EF ≤ 40% but without CKD

Survived and non-survived patients were also compared.

Statistical Analysis

The statistical analysis was carried out by Statistical Package for Social Sciences for Mac ver. 20.0 (SPSS Inc., Chicago, IL). Data were expressed as mean±standard deviation for normally distributed data, while median (minimum-maximum) were used for non-normally distributed data. The normality tests were conducted with both Shapiro-Wilk and Kolmogorov Smirnov tests and when both tests produced p values >0.05, the distribution was assumed normal.

Statistical comparisons of individual groups were based on independent samples t test and One-way ANOVA for continuous and normally distributed variables. When the distribution was not normal, Mann-Whitney U and Kruskal-Wallis tests were implemented. If One-way ANOVA and Kruskal-Wallis revealed any differences, the source of differences was investigated with Post-hoc tests Tukey HSD and Mann-Whitney U and the means having difference were allocated a letter a and b in **Table 1.** Relationship between two categorical variables were investigated with Chi-square test of independence. If Chi-square test revealed statistical difference, Post-hoc tests between groups were conducted with adjusted residuals analysis and statistical significance of these difference were indicated with letters k and l.

In addition, mortality related factors were investigated with ROC Curve Analysis. A value of p<0.05 was considered to be statistically significant.

Table 1. Comparison of groups regarding clinical and laboratory data

Parameters	Group 1 (n=14)	Group 2 (n=62)	Group 3 (n=16)	p
Age (year)	63.8±12	62.7±14	70.4±12.5	0.138
Male (n, %)	11 (17.2)	42 (65.6)	11 (17.2)	0.727
Hospitalization time (days)	14.5 (5-34)	11.5 (1-45)	17.0 (2-32)	0.439
Survival time (days)	100.5 (16-880)	554 (23-1331)	65 (2-1585)	0.090
24-hour urine volume (ml)	350 (0-4000)[a]	865 (0-4500)[a,b]	400 (0-1480)[b]	0.040*
Proteinuria (g/24 hour)	2.33 (0.13-15.73)[a]	2.31 (0.17-25.67)[b]	0.21 (0.08-0.64)[a,b]	0.010*
Ultrafiltration volume (kg)	10.32±5.8	9.64±4.8	12.6±5.1	0.100
Ultrafiltration volume /weight at hospitalization (%)	10[a]	10[b]	15[a,b]	<0.001*
Ejection fraction (%)	35 (20-40)[a]	60 (45-70)[a,b]	30 (25-40)[b]	<0.001*
LVH (n, %)	3 (11.1)[k]	23 (85.2)[k,l]	1 (3.7)[l]	0.040*
Sodium (mmol/l)	136 (118-143)	137 (118-144)	135.5 (101-138)	0.672
Potassium (mEq/L)	4.8±0.8	4.8±0.9	4.5±0.8	0.273
Uric acid (mg/dl)	9.3±2.4	7.5±2.5[a]	11.4±3.6[a]	<0.001*
Albumin (g/dl)	2.8±0.7	2.8±9.7	2.9±9.5	0.310
Hemoglobin (g/dl)	10.3±2.1[a]	9.0±1.8[a,b]	10.7±1.7[b]	<0.001*
CRP (mg/dl)	3.5 (2.8-8.5)	2.7 (1.26-15.59)	2.15 (1.0-6.3)	0.240
TSH (mIU/l)	1.3 (0.3-16.50)	1.3 (0.2-18.7)	1.94 (0.2-28.2)	0.500
Dialysis dependency (n, %)	10 (15.6)[k]	49 (76.6)[k,l]	5 (7.8)[l]	<0.001*
Mortality (n, %)	6 (12.2)[k]	27 (55.1)[k]	16 (32.7)	<0.001*

*: statistically significant difference at 0.05 significance level. CRP: C-reactive protein; LVH: Left ventricular hypertrophy; TSH: Thyroid stimulating hormone; a, b: Letters indicating statistical difference based on Tukey's HSD and Mann-Whitney U test; k, l: Letters indicating statistical difference based on Adjusted Residuals; Each percentage in this table represents row percentage.

RESULTS

Comparison of three groups regarding clinical and laboratory data is shown in **Table 1**. Group 1, 2 and 3 consisted of 14, 62 and 16 patients; respectively. There were statistically significant results for 24-hour urine volume (p=0.040), proteinuria (p=0.010), UF volume/weight at hospitalization (p<0.001), EF (p<0.001), LVH (p=0.040), UA (p<0.001), hemoglobin (p<0.001), dialysis dependency after hospital discharge (p<0.001) and mortality (p<0.001) when three groups were compared. However, there was no statistically significant result for age (p=0.138), gender (p=0.727), hospitalization time (p=0.439), survival time (p=0.090), total UF volume during hospitalization (p=0.100), sodium (p=0.672), potassium (p=0.273), albumin (p=0.310), CRP (p=0.240) and TSH (p=0.500). Statistically significant results between groups are shown with letters in **Table 1.**

Comparison of the survived and non-survived groups is shown in **Table 2.** Compared to survived patients those who did not survived were significantly older (p<0.001), had lower EF (p=0.010) and rate of loop diuretic usage at hospitalization (p=0.040), creatinine (p<0.001), sodium (p=0.020), ferritin (p=0.040), 24-hour proteinuria (p=0.010). On the other hand, results for hemoglobin (p<0.001), creatinine clearance (p<0.001), UA (p<0.001) were significantly higher for patients who did not survive. However, there were no statistically significant results for gender (p=0.070), hospitalization time (p=0.410), UF volume (p=0.700), UF volume/weight at hospitalization (p=0.990), dialysis dependency after hospital discharge (p=0.610).

ROC curve was drawn to determine the effect level and cut-off value of age, hemoglobin, creatinine clearance and uric acid variables in non-survived group (**Figure 1**) (**Table 3**). The area under the curve in the ROC curve drawn for the age variable of non-survived group is 0.833. The area under the ROC curve was statistically significant (p=0.001). The cut-off value for age was found to be 63.5 years. The sensitivity of this value is 82.4%, and the specificity is 80%. The area under the curve in the ROC curve drawn for the hemoglobin variable of non-survived group is 0.745. The area under the ROC curve was statistically significant (p=0.018). The cut-off value for hemoglobin was found to be 8.81 g/dl. The sensitivity of this value is 76.5%, and the specificity is 67%. The area under the curve in the ROC curve drawn for the creatinine clearance variable of non-survived group is 0.739. The area under the ROC curve was statistically significant (p=0.021). The cut-off value for creatinine clearance was found to be 7.82 ml/min. The sensitivity of this value is 70.6%, and the specificity is 54%. The area under the curve in the ROC curve drawn for the UA variable of non-survived group is 0.789. The area under the ROC curve was statistically significant (p=0.011). The cut-off value for UA was found to be 8.00 mg/dl. The sensitivity of this value is 70.6%, and the specificity is 73.3%.

Table 2. Comparison of survived and non-survived group

Parameter	Survived group (n=43)	Non-survived group (n=49)	p
Age (years)	57.39±13.53	70.18±10.97	<0.001*
Male (n,%)	30 (46.9)	34 (53.1)	0.070
Patients' groups (n,%) • CKD & EF ≤40% • CKD & EF >40% • EF ≤40 no CKD	 8 (57.1) 35 (56.5) 0 (0)	 6 (42.9) 27 (43.5) 16 (100)	 <0.001*
Hospitalization time (days)	14.5±10.8	16.2±9.4	0.410
Ejection fraction (%)	54.4±13.0	46.3±12.7	0.010*
Ultrafiltration volume (kg)	10.5±5.3	10.1±5.0	0.700
Ultrafiltration volume /weight at hospitalization (%)	11.8±5.3	11.7±5.0	0.990
Proteinuria (g/24 hour)	5.94±4.79	2.62±4.97	0.010*
Hemoglobin (g/dl)	8.8±1.8	10.2±1.9	<0.001*
Creatinine (mg/dl)	6.6±2.7	4.42±2.8	<0.001*
Creatinine clearance (ml/min)	7.9±4.1	14.7±9.4	<0.001*
Sodium (mmol/L)	136.7±5.0	133.6±7.3	0.020*
Ferritin (uq/l)	404.6±496.6	227.4±277.0	0.040*
Uric acid (mg/dl)	7.2±2.6	9.6±3.0	<0.001*
Loop diuretic usage (n, %) (At hospitalization)	27 (64.3)	15 (35.7)	0.040*
Dialysis dependency (n, %)	29 (45.3)	35 (55.7)	0.610

*: statistically significant difference at 0.05 significance level; Each percentage in this table represents row percentage

Table 3: ROC Curve Analysis Results

Parameter	Cut-off	Sensitivity (%)	Specificity (%)	Area Under Curve (95% Confidence Interval)	p
Age	63.5	82.4	80	0.833 (0.671-0.952)	0.001 *
Hemoglobin	8.81	76.5	67	0.745 (0.564-0.888)	0.018 *
Creatinine clearance	7.82	70.6	54	0.739 (0.559-0.886)	0.021 *
Uric acid	8.00	70.6	73.3	0.789 (0.641-0.938)	0.011 *

*: statistically significant difference at 0.05 significance level

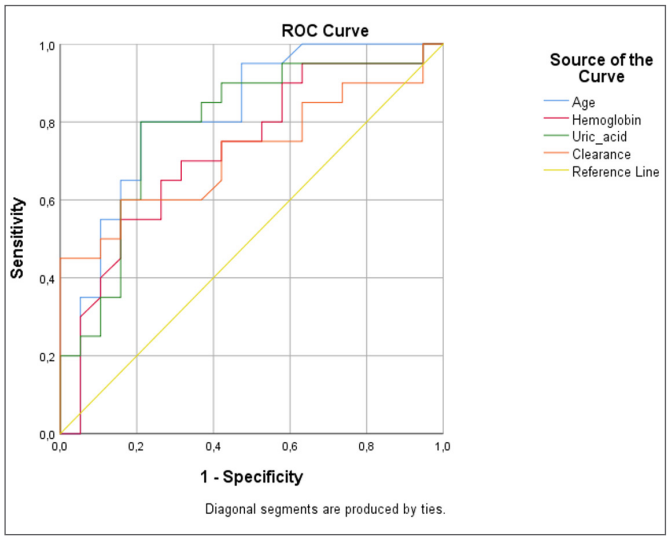

Figure 1: ROC Curve of age, hemoglobin, creatinine clearance, and uric acid variables in non-survived group

DISCUSSION

In this study, we aimed to investigate the factors affecting the prognosis in patients who presented with fluid overload and were ultrafiltered. One of the main findings of this study was serum UA. The patients in group 3 had significantly higher UA levels than patients in group 2. The non-survived patients also had significantly higher levels of UA levels than survived group. The non-survived group included patients with significantly lower EF and all group in group 3 were in the non-survived group. The National Health and Nutrition Examination Survey also demonstrated hyperuricemia in nearly half of the patients with HF.[8] In HF, anaerobic metabolism in tissues due to low oxygen availability increases the levels of serum lactic acid which in turn intensifies the reabsorption of UA in the kidney leading to an increase in serum UA levels.[9] Diets low in sodium and reduction in renal UA excretion with declining GFR are also causes of hyperuricemia in patients with HF.[10,11] Serum UA also rises in response to the institution of diuretics.[10] It is also demonstrated that there is an inverse relation between EF and serum UA.[12] A recent meta-analysis by Huang et al.[13] showed that hyperuricemia was associated with an increased risk of incident HF. They showed that for every 1 mg/dl increase of serum UA, the risk of all-cause mortality and the composite endpoint in HF increased by 4 % and 28%: respectively.[13]

In this study, the EF was significantly lower in non-survived group compared to survived group and all patients in group 3 died. Regarding EF, a metaanalysis by Jørgensen et al.[14] showed a significantly lower risk of mortality in HF patients with improved EF, compared to patients with persistently reduced EF, with an estimated risk ratio of 0.34.

In this study there was also significantly lower level of proteinuria in group 3 and the survived group had significantly higher level of proteinuria compared to non-survived group. A study by Albright et al.[15] demonstrated that there can be modest proteinuria in patients with HF and successful treatment of HF reverse the proteinuria. Intrinsic renal disease should be thought in these patients when the proteinuria exceeds 1 g/day, and the proteinuria does not reverse with successful HF therapy. When the intrinsic renal disease in group 1 and 2 was considered, the significantly higher proteinuria was expected in these groups compared to group 3.

There were also statistically significant results in favor of survived group regarding CKD characteristics. Because more patients with CKD rather than HF are in the survived group, the results were more related to characteristics of CKD patients. First of all, the serum creatinine level was higher, and the creatinine clearance was lower in the survived group. In the survived group, the mean hemoglobin level was also lower. Again, when three groups were compared, the hemoglobin level was statistically lower in patients in group 2 compared to group 1 and 3. As a complication of CKD, the prevalence of anemia increases as the stage of CKD increases[16] and lower hemoglobin levels in patients with CKD is expected. Again, the statistically higher ferritin levels in survived group can be because of iron replacement for anemia management during CKD follow up.

For CKD patients, the prevalence of LVH increases as the renal function of patients decreases and rises to 90% after the initiation of dialysis.[17] Systolic hypertension, elevated pulse pressure with fluid overload and increased arterial stiffness play role in LVH development in patients with advanced CKD.[18] In our study the number of patients with LVH was also statistically higher in group 2 and the hemoglobin level was also lower in these patients. Despite significantly higher level of ferritin in the survived patients; the hemoglobin level was significantly lower, that one can think the need of erythropoietin in these patients. The lower hemoglobin level also points out the higher percentage of patients with LVH in the survived group.[19]

UF may be associated with worsening renal function in patients with HF.[20-22] A study by Dev et al.[23] evaluated 70 ultrafiltrated patients with diagnosis of diuretic resistant acute decompensated HF. The percentage of dialysis dependent patients was 10% after UF. In another study, 11 diuretic resistant HF patients with a mean baseline eGFR of 38 ml/min were evaluated. The percentage of dialysis dependent patients was 45% after UF.[24] In our study, the percentage of dialysis dependent

patients in group 3 was %31. There was, however, no statistically significant result for dialysis dependency after hospital discharge when the survived and non-survived groups were compared.

Another finding of this study was the data regarding UF volume. Despite the total UF volume during hospitalization did not differ between 3 groups; the UF/weight at hospitalization was significantly higher in group 3. Again, the 24-urine volume was lower in group 1 and 3 which is most commonly encountered in patients with right sided HF because of increased central and renal vein pressures. These data can demonstrate that patients with HF are more prone to hypervolemia. The fluid retention in these patients makes the diuretic usage necessary. There should be vigorous volume control with diuretics during their follow-up. Unfortunately, the percentage of patients using diuretics were significantly lower in the non-survived group.

Hypervolemia may be a marker for poor prognosis. In a study, a relationship was found between fluid overload and length of stay in the intensive care unit in patients undergoing surgery.[25] In a different study, Stein et al.[26] similarly found a significant relationship between fluid overload and length of stay in the intensive care unit in patients undergoing cardiac surgery. Hypervolemia may worsen the prognosis in patients by causing myocyte damage and malignant ventricular tachyarrhythmia.[27] In our study, we found that the mortality rate was lower in patients with high creatinine levels compared to patients in group 3. The reason for this may be that patients with high creatinine are taken to ultrafiltration in a shorter time, preventing complications that may occur as a result of hypervolemia.

Study Limitations

The limitations of our study included retrospective nature and small number of patients. There was also not a specific UF protocol and UF was done based on the decision of patients' own doctors. However, UF volume was evaluated for the first time which is the main strength of our study.

CONCLUSION

Patients with HF were more prone to hypervolemia and mortality. The ultrafiltration volume/weight at hospitalization and serum uric acid levels were also significantly higher in these patients. Patients with chronic kidney disease had significantly higher proteinuria, creatinine and lower hemoglobin levels. The rate of loop diuretic usage at hospitalization was significantly higher in the survived group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Haydarpaşa Numune Training and Research Hospital Ethic Committee (Date: 28.05.2019, Decision No: 771).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Dosimetric evaluation of inclusion of proximal seminal vesicle in target volume in low-risk prostate cancer treated with stereotactic body radiotherapy

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ABSTRACT

Aims: Ultra hypofractionation using stereotactic body radiotherapy (SBRT) for low-risk PCa is considered a viable treatment option. The target volume for ultra hypofractionated RT was determined as prostate and/or proximal seminal vesicles; however, there are no clear guidelines on when to add a proximal seminal vesicle to the target volume. We aimed to dosimetrically assess the effect of inclusion of the proximal seminal vesicle in the planning target volume (PTV) on the dose distribution of organ at risk (OAR) when SBRT is administered to patients with low-risk PCa.

Methods: Low-risk PCa cases who underwent SBRT with CyberKnife were retrospectively screened, and 20 random cases were included. The contours of OARs and target volumes were checked as recommended in international contouring atlases by the same radiation oncologist. Two treatment plans by determining two different PTV (prostate alone in plan 1 and prostate with proximal seminal vesicles in plan 2) were made by the same specialist physicist. 5×7.25 Gy was chosen as the dose schedule defined for both plans.

Results: Regarding coverage, homogeneity index, and new conformity index (nCI), there was no significant difference between the two plans (p=0.397, p=0.452, p=0.225). The plan 2 had a greater PTV Dmax (p<0.001). There was better conformity index at plan 1, as well as lower monitor unit and beam on time (p<0.05). The plan 1 had statistically lower values for each treatment parameter assessed for bladder (p<0.05). The treatment parameters evaluated for the rectum were statistically lower in the plan 1, except for V32.625 (p<0.05). The plan 1 was statistically better in terms of V29.5 for the penile bulb and V37.5 and V38 for neurovascular bundles (p<0.05). There was no significant difference between the two plans in terms of femoral heads and bowel (p=0.180, p=0.209, p=0.398, p=0.726, p=0.053, p=0.068). In addition, regardless of plan type, a majority of treatment parameters for bladder were statistically significantly affected in plans with a PTV volume greater than 100 cc (p<0.05).

Conclusion: In low-risk PCa, inclusion of the proximal seminal vesicle in the target volume may be overlooked as quantitatively insignificant increases in high-dose OAR volumes as they do not exceed dose constraints in routine clinical practice, and these high-dose OAR volumes are likely to be important in the development of toxicity. We recommend that special attention be paid to the high doses exposed in OARs in low-risk PCa. In addition, it should be kept in mind that bladder toxicity may increase with increasing PTV volume, especially above 100 cc.

Keywords: Low-risk, prostate cancer, prostate, seminal vesicle, stereotactic body radiotherapy, target volume

INTRODUCTION

Since radiotherapy (RT) has comparable results with surgical treatment in prostate cancer (PCa), it is an accepted treatment method in both low-, medium-, and high-risk groups.[1] RT techniques have changed considerably over the years with the development of RT devices, and these innovations have significantly affected the management of PCa. The effectiveness of conventional RT schemes, whose daily treatment dose varies between 1.8-2 Gy and the total number of fractions varies between 37-45, is still valid, and their use continues today.[2,3] The fact that PCa has a radiobiologically lower alpha-beta ratio than adjacent healthy organs has led to the hypothesis that treatment-related toxicity may be lower than conventional methods, which has been the main reason to evaluate the potential of hypofractionated RT schemes in PCa management.[3] In addition, since the total duration of treatment is reduced with hypofractionated treatments, it both increases the patient's compliance and provides economic gain.

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Hypofractionated RT refers to applications where the daily treatment dose is larger and the number of fractions is lower than with traditional techniques. Moderate hypofractionation (2.35-3.4 Gy daily doses, 20-28 fractions) and extreme hypofractionation (>6Gy daily doses, 4-7 fractions) are the hypofractionation schemes adopted worldwide.[4,5] Ultra hypofractionation using stereotactic body radiotherapy (SBRT) for low-risk PCa is considered a viable treatment option with promising oncologic outcomes.[5-7]

Regardless of the RT scheme, target volumes are defined for the prostate, seminal vesicle, and pelvic lymph nodes according to the risk group. The target volume for ultra hypofractionated RT was determined as prostate and/or proximal seminal vesicles; however, there are no clear guidelines on when to add a proximal seminal vesicle to the target volume.[6,7] The entire prostate is always included in the clinical target volume (CTV). Regarding the inclusion of the seminal vesicles in the CTV, different practice patterns exist. To avoid underdosing at the base of the prostate, some clinicians include the proximal seminal vesicles, regardless of risk group or magnetic resonance imaging findings. Others prefer to include seminal vesicles when involved or in higher risk patients. With the expansion of the irradiated volume, there may be an increase in undesirable doses in neighboring critical organs such as the bladder, rectum, penile bulb, and bowel. Despite the benefits of SBRT already described, steep dose gradients require careful evaluation of nearby normal tissues. Therefore, during the SBRT treatment planning process, it is crucial for clinicians to have proper information of the dose limitations about normal tissues.

Although SBRT studies for late toxicity data are still under development, we aimed to dosimetrically assess the effect of inclusion of the proximal seminal vesicle in the target volume on the dose distribution of surrounding organs when SBRT is administered to patients with low-risk PCa. In this context, we intend to compare the dosimetric variations between the two treatment plans by determining two different targets (prostate alone or prostate with proximal seminal vesicles) that include both scenarios by using planning computed tomography (pCT) taken during the treatment of patients receiving SBRT.

METHODS

Ethics

The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective design, individual consent was not required. The study was initiated with the approval of the Samsun University Clinical Researches Ethics Committee (Date: 2023, Decision No: 6/10).

Patient population

Low-risk PCa cases who underwent SBRT with CyberKnife between March 2017 and March 2023 in the Radiation Oncology Clinic of Samsun Training and Research Hospital were retrospectively screened, and 20 random cases were included in the study.

Treatment

Four fiducial markers were implanted for image guidance in patients 1 week prior to simulation. All patients underwent pCT with a 1 mm slice thickness. During the simulation, they were instructed to have a comfortably full bladder and an empty rectum in the supine position with a knee wedge. Magnetic resonance imaging was performed and used for image fusion to contour target volumes and organ at risk (OAR). The planning target volume (PTV) was defined for the prostate in 11 patients and for the prostate and the proximal seminal vesicle in 9 patients. All patients recieved 35 Gy over five fractions.

Re-contouring and re-planning

Our study was carried out on the pCT for SBRT of these patients whose treatment had been completed previously. For the dosimetric study, the patients were evaluated by the same radiation oncologist, and the contours of OARs (bladder, rectum, penile bulb, femoral heads, neurovascular bundles, and bowel) and target volumes were checked as recommended in international contouring atlases.[8-10] It has been re-contoured for those who do not comply with the definitions specified in the guidelines in order to meet the same standards. The bladder and rectum were delineated as the entire organ. The rectum was contoured from anal verge to recto-sigmoid flexure. PTV was determined by giving a margin of 5 mm from all directions and 2 mm from the posterior to the CTV created by defining the prostate alone in plan 1 and the prostate plus 1 cm of the proximal seminal vesicle in plan 2. For each patient, two different plans were made by the same specialist physicist (**Figure 1**). Since the most commonly used dose for PCa SBRT is 5×7.25 Gy, it was chosen as the dose schedule defined for both plans in our study.[11]

The normal tissue dose constraints in our institution were shown in **Table 1**.[12] For the dosimetric evaluation, in addition to the dose constraints used in our clinic, the following treatment parameters were examined for PTV and OARs. For PTV: Dmax, coverage, conformity index (CI), homogeneity index (HI), new conformity index (nCI), monitor unit (MU), beam on time; for bladder: Dmax, V37.5, V37, V18.125, D0.1 cc, D1 cc, D5 cc, D10 cc, and D15 cc; for rectum: Dmax, V36.25, V32.625, V29, V29, V18.125, V5, V10, and V20; for penile bulb: V29.5, V30; for femoral heads: V14.5 and Dmax; for neurovascular bundles: V37.5 and V38; for bowel: Dmax and V29.

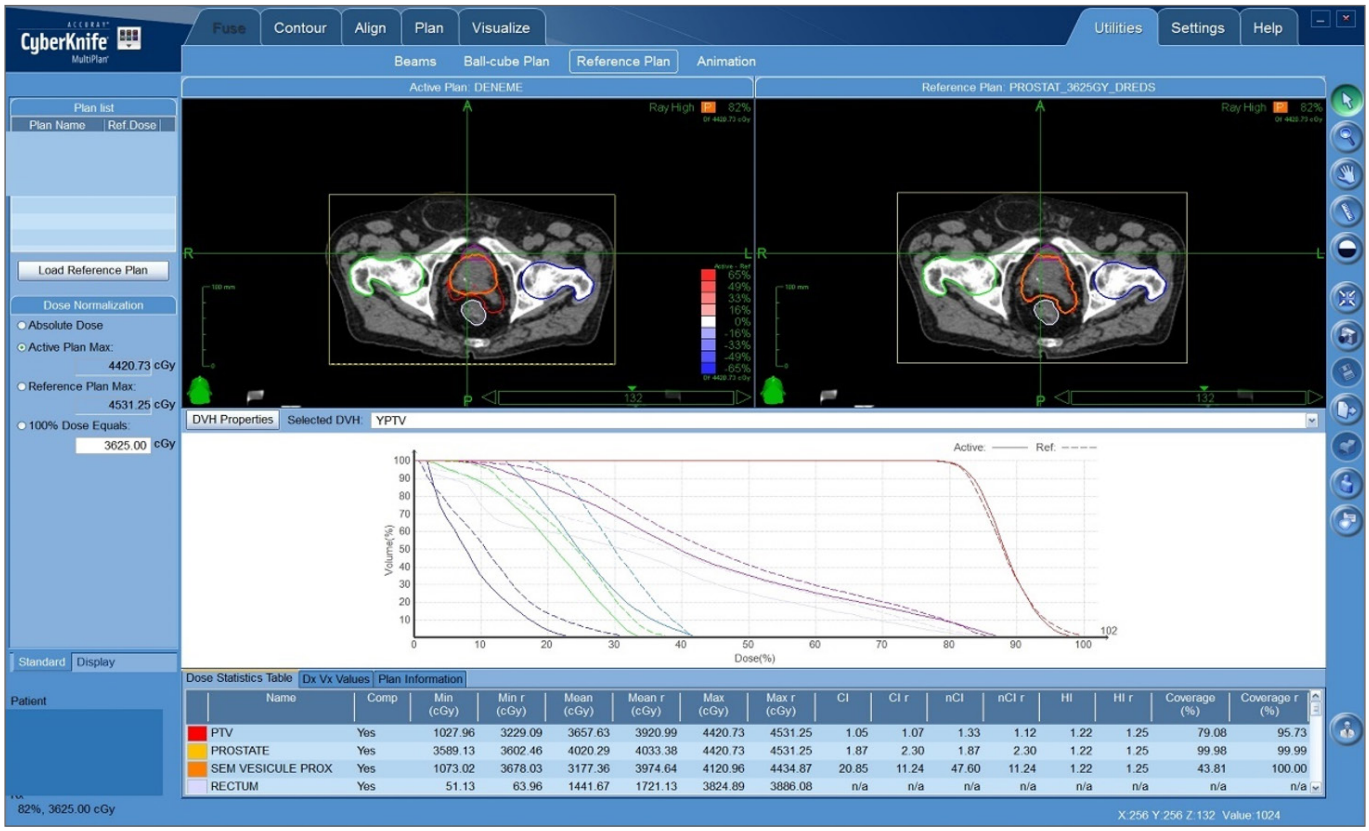

Figure 1. The dose distributions and dose-volume histograms of Plan 1 and Plan 2 for the same patient.

Table 1. Target volume and organs at risk dose constraints for treatment plans (36.25 Gy/5 fx)

Structure	Dosimetric index	Acceptance criteria
CTV	Coverage	100 %
PTV	Coverage CI HI	95 % ≤1.2 ≤1.2
Bladder	Dmax V37.5 V37	38 Gy < 5 cm3 < 10 cm3
Rectum	Dmax V36.25 V32.625 V29 V18.125	38 Gy < 5 % < 10 % < 20 % < 50 %
Penile Bulb	V29.5 V30	< 50 % < 3 cc
LFH	Dmax V14.5	< 30 Gy < 5 %
RFH	Dmax V14.5	< 30 Gy < 5 %
Neurovascular bundles	V37.5 V38	< 20 % < 50 %
Bowel	Dmax V24	25 Gy < 1 cc

CI: Conformity index; CTV: Clinical target volume; HI: Homogeneity index; LFH: Left femoral head; PTV: Planning target volume; RFH: Right femoral head

Statistical Analysis

All parameters were expressed as mean and/or standard deviation. The two-sided paired t-test was used for normally distributed data and Wilcoxon Cox test for non-normally distributed data. SPSS v25 statistical program was used, p<0.05 was considered significant.

RESULTS

A comparison of treatment parameters for PTV and each OAR for the two plans is shown in **Table 2**. Regarding coverage, HI and nCI, there was no significant difference between the two plans (p=0.397, p=0.452, p=0.225). The second plan had a greater PTV Dmax (p<0.001). There was better CI (p=0.007) at first plan, as well as lower MU (p=0.019) and beam on time (p=0.022).

The first plan had statistically lower values for each treatment parameter assessed for bladder (p<0.05). The treatment parameters evaluated for the rectum were statistically considerably lower in the first plan, except for V32.625 (p<0.05). The first plan was statistically better in terms of treatment parameters of V29.5 for the penile bulb (p=0.037) and V37.5 and V38 for neurovascular bundles (p<0.001, p=0.047). There was no significant difference between the two plans in terms of femoral heads and bowel (p=0.180, p=0.209, p=0.398, p=0.726, p=0.053, p=0.068).

In addition, regardless of plan type, a majority of treatment parameters for bladder and femoral head Dmax values were statistically significantly affected in plans with a PTV volume greater than 100 cc (p<0.05, **Table 3**). There was no difference for target and other OARs parameters with increasing target volume.

Table 2. Dosimetric comparisons of target volume and organs at risk doses for Plan 1 and 2

Structure	Dosimetric index	Acceptance criteria	Plan 1 (Prostate)		Plan 2 (Prostate+Proximal Seminal Vesicle)		p
			mean	SD	mean	SD	
PTV							
	Dmax	Gy	43.72	0.55	44.40	0.58	<0.001
	Coverage	> 95 %	96.73	0.94	96.50	0.92	0.397
	CI	≤ 1.2	1.19	0.004	1.20	0.004	0.007
	HI	≤ 1.2	1.09	0.03	1.09	0.03	0.452
	nCI	≤ 1.2	1.12	0.03	1.13	0.04	0.225
	MU	-	33187.65	3127.09	35507.60	2250.67	0.019
	Time	Minute	29.40	1.32	30.55	0.55	0.022
Bladder							
	Dmax	39 Gy	38.39	0.68	39.21	0.56	<0.001
	V37.5	< 5 cm3	1.38	1.32	3.03	1.60	<0.001
	V37	< 10 cm3	2.82	1.78	4.59	2.28	<0.001
	V18.125	< 40 %	28.78	15.13	35.25	20.85	0.007
	D0.1cc	Gy	38.12	0.61	38.71	0.75	0.004
	D1cc	Gy	37.40	0.61	38.03	0.66	<0.001
	D5cc	Gy	35.94	1.28	36.56	0.99	0.001
	D10cc	Gy	31.84	6.63	33.12	5.90	0.001
	D15cc	Gy	30.10	4.11	31.82	3.05	0.003
Rectum							
	Dmax	39 Gy	38.27	0.56	38.69	0.51	<0.001
	V36.25	< 5 %	0.88	0.55	2.35	2.91	0.042
	V32.625	< 10 %	5.47	2.01	5.93	2.54	0.198
	V29	< 20 %	10.78	2.99	12.26	3.41	0.001
	V18.125	< 50 %	28.43	8.70	34.37	9.34	<0.001
	V5	%	68.59	17.61	74.69	16.34	0.001
	V10	%	49.51	14.28	60.21	17.32	<0.001
	V20	%	25.61	5.97	29.81	8.32	0.010
Penile Bulb							
	V29.5	< 50 %	16.30	23.67	18.64	22.93	0.037
	V30	< 3 cc	1.41	3.33	1.48	3.34	0.131
LFH							
	V14.5	< 5 %	0.09	0.22	0.12	0.31	0.180
	Dmax	< 30 Gy	13.50	1.79	13.89	1.68	0.209
RFH							
	V14.5	< 5 %	1.06	1.66	0.63	1.32	0.398
	Dmax	< 30 Gy	15.12	1.66	15.25	1.58	0.746
Neurovascular bundles							
	V37.5	< 20 %	2.11	2.83	4.18	3.20	<0.001
	V38	< 50 %	0.86	1.77	1.18	1.85	0.047
Bowel							
	Dmax	25 Gy	15.25	7.55	16.45	8.00	0.053
	V24	< 1 cc	0.05	0.13	0.75	2.23	0.068

CI: Conformity index; CTV: Clinical target volume; HI: Homogeneity index; LFH: Left femoral head; MU: Monitor unit; nCI: New conformity index; PTV: Planning target volume; RFH: Right femoral head; SD: Standard deviation

Table 3. Dosimetric comparisons of target volume and organs at risk doses for volume of PTV

Structure	Dosimetric index	Plan 1 (Prostate)					Plan 2 (Prostate+Proximal Seminal Vesicle)				
		PTV volume <100 cc		PTV volume ≥100 cc		p	PTV volume <100 cc		PTV volume ≥100 cc		p
		mean	SD	mean	SD		mean	SD	mean	SD	
PTV											
	Dmax	43.44	0.45	44.13	0.42	0.003	44.14	0.70	44.53	0.47	0.149
	Coverage	97.07	0.95	96.20	0.67	0.039	96.62	1.13	96.43	0.83	0.659
	CI	1.19	0	1.19	0	0.165	1.2	0.01	1.2	0.00	0.180
	HI	1.08	0.01	1.08	0.04	0.094	1.1	0.04	1.08	0.03	0.393
	nCI	1.12	0.03	1.12	0.03	1.000	1.13	0.04	1.12	0.03	0.538
	MU	33127.58	3279.58	33277.75	3102.42	0.920	34206.85	2434.52	36208.23	1881.09	0.055
	Time	29.06	1.37	30	1.3	0.594	30.12	0.98	30.52	0.76	0.224
Bladder											
	Dmax	37.93	0.47	39.07	0.11	<0.001	38.81	0.39	39.41	0.53	0.017
	V37.5	0.56	0.71	2.45	1.18	<0.001	1.69	1.42	3.57	1.37	0.001
	V37	1.9	1.02	4.17	1.84	0.002	2.95	1.98	5.46	1.98	0.014
	V18.125	24.6	15.06	35.05	13.77	0.134	22.17	4.87	42.28	22.87	0.036
	D0.1cc	37.70	0.39	38.72	0.23	<0.001	38.32	0.42	38.91	0.82	0.095
	D1cc	37.06	0.58	37.88	0.13	0.001	37.54	0.48	38.29	0.61	0.012
	D5cc	35.54	1.37	36.57	0.87	0.087	35.82	1.23	36.94	0.57	0.001
	D10cc	32.65	3.07	31.61	10.08	0.514	32.88	2.39	33.23	7.23	0.011
	D15cc	28.62	4.11	32.31	3.15	0.046	29.72	3.25	32.94	2.36	0.020
Rectum											
	Dmax	38.26	0.59	38.27	0.55	0.975	38.57	0.64	38.74	0.44	0.479
	V36.25	0.82	0.52	0.97	0.61	0.567	2.95	4.92	2.02	1.00	0.509
	V32.625	5.02	2.21	6.12	1.56	0.241	5.24	2.79	6.3	2.43	0.390
	V29	10.02	3.49	11.9	1.61	0.176	10.25	3.74	13.33	2.79	0.051
	V18.125	26.66	10.26	31.07	5.19	0.279	29.21	10.81	37.13	7.48	0.069
	V5	63.41	19.15	76.35	12.27	0.109	67.35	22.30	78.63	11.22	0.145
	V10	45.86	15.58	54.97	10.74	0.168	54.14	22.79	63.46	13.50	0.252
	V20	25	7.20	26.43	4.05	0.621	25.21	8.99	31.34	7.80	0.129
Penile Bulb											
	V29.5	13.65	20.95	20.25	28.32	0.556	7.18	10.89	24.8	25.60	0.102
	V30	1.03	2.43	1.96	4.49	0.555	1.54	3.20	1.44	3.55	0.953
LFH											
	V14.5	0	0.00	0.21	0.32	0.031	0	0.00	0.17	0.37	0.233
	Dmax	13.16	1.47	14	2.20	0.321	12.5	1.12	14.63	1.46	0.003
RFH											
	V14.5	0.21	0.58	2.32	1.97	0.002	0.04	0.11	0.94	1.56	0.149
	Dmax	14.45	1.47	16.12	1.46	0.022	14.1	0.64	15.86	1.61	0.013
Neurovascular bundles											
	V37.5	2.85	3.44	0.98	0.89	0.153	4.21	2.70	4.16	3.55	0.973
	V38	1.37	2.15	0.08	0.25	0.112	1.61	1.97	0.94	1.82	0.457
Bowel											
	Dmax	14.33	8.23	16.61	6.68	0.523	14.71	8.48	17.38	7.92	0.492
	V24	0.05	0.12	0.05	0.14	0.891	0.67	1.78	0.79	2.53	0.913

CI: Conformity index; CTV: Clinical target volume; HI: Homogeneity index; LFH: Left femoral head; MU: Monitor unit; nCI: New conformity index; PTV: Planning target volume; RFH: Right femoral head; SD: Standard deviation

DISCUSSION

Prostate SBRT for low-risk PCa is an evolving treatment modality with promising oncologic outcomes.[5-7] The safety and feasibility of SBRT has been demonstrated in the light of data accumulated over the years.[11,13,14] Unlike conventional RT, data on dosimetric constraints for SBRT to guide treatment planning for OARs are still insufficient. While SBRT studies determining long-term late toxicity data are still under investigation, clinicians should consider the doses delivered to OARs exposed during the SBRT treatment planning process.

In this dosimetric investigation, we evaluated the effect of inclusion of the proximal seminal vesicle in the target volume on the dose distribution of adjacent organs in low-risk PCa patients undergoing SBRT. It was determined that Dmax value and CI increased in terms of target parameters with the inclusion of the proximal seminal vesicle. In addition, due to the expansion of the target volume, a prolongation of the beam on time and an increase in MU were detected. There was an increase in the doses to which OAR was exposed, especially in the bladder and rectum. However, it was observed that these increases did not exceed the acceptable values according to the dose constraints used in our clinic, except for bladder and rectum Dmax values. Another important point to be emphasized is that in patients with a PTV volume above 100 cc, doses to which only the bladder was exposed were found to be significantly increased.

First of all, due to the near proximity of OARs to the target, the use of steep dose gradients, and organ mobility, the definition of the target and OARs volumes for prostate SBRT is crucial. The rectum and bladder are stretchable organs with significant intra- and inter-fraction variation potential. In order to prevent these situations, before the simulation, applications such as Foley catheterization into the bladder, filling the bladder, and bowel preparation with rectal enema, or the use of rectal balloon have been tried so far. Also, placement of hydrogel spacers between the rectum and the prostate to reduce rectal toxicity has also been investigated. In some studies, it is seen that hollow organs such as the bladder and rectum are contoured as a whole organ, while in others, the wall is contoured separately. In some SBRT studies, this information is not explicitly stated. Taking into account all of this information, each clinic establishes its own protocol and accepts patients. In our clinic, patients are simulated a comfortably full bladder and an empty rectum, in order to give SBRT safely and accurately. Fiducial markers are implanted 1 week prior to simulation for target tracking. During SBRT, 4 fiducial markers are also monitored. When the bladder is not full or the rectum is not empty as in simulation CT, it causes a decrease in the number of fiducial markers that can be monitored during treatment, and the treatment is interrupted until these conditions are corrected. Thus, accurate reproducibility of the treatment is ensured and the doses calculated in the planning for the OARs are not exceeded.

In general, both acute and late genitourinary (GU) toxicity are known to occur more frequently than gastrointestinal (GI) toxicity.[15-17] King et al.[18] evaluated both early and late expanded prostate cancer index composite-26 (EPIC-26) quality of life (QOL) outcomes based on various prospective SBRT trials including 864 patients. Within the first three months following SBRT, there was a brief deterioration in the urine and bowel domains, which improved or returned to baseline level within six months, and remained that way for at least five years. They reported that up to a 5-y observation period, prostate SBRT was well tolerated.

Various dosimetric parameters, including high doses delivered to even small volumes or low/moderate doses delivered to large volumes, and GU toxicity have also been linked in several studies.[19-22] Gomez et al.[19] reported the results of comparison of the EPIC-26 QOL changes and dosimetric parameters for 75 patients. They claimed that a high bladder V100% value and high PTV V100% higher than 120 cc were linked to decreased GU QOL. Similarly, in their study published in 2016, Qi et al.[20] found that these parameters correlate with GU toxicity. Seymour et al.[21] reported the toxicity assessment according to the International Prostate Symptom Scores (IPSS) in 56 patients who underwent SBRT. Baseline IPSS >7, prostate volume >50 cc, urethra V44, and bladder V19 values all increased the likelihood of any grade 2+ GU toxicity. Iarrobino et al.[22] evaluated the EPIC-26 scores of a total of 95 patients. Both late urinary incontinence and obstructive/irritative decreases were linked with higher bladder V37 (≥3.35 cc) values. In our study, bladder Dmax and V37 value increased from 38.39 Gy and 2.82 cc in the first plan to 39.21 Gy and 4.59 cc in the second plan. At the same time, we found a significant increase in the second plan with the expansion of the target volume in all the dosimetric variables we examined. As in the above-mentioned studies, since high doses to which the bladder is exposed are important in the development of GU toxicity, expansion of the target volume may cause an increase in GU toxicity. In addition, in our study, it was observed that the increased volume of PTV affected bladder doses, which was consistent with the literature. Regardless of the plan type, it was determined that the bladder received dosimetrically higher doses in the plans with a PTV volume above 100 cc.

Regarding GI toxicity, several studies have shown that various dosimetric parameters are associated with GI side effects.[19,22-24] According to Gomez et al.[19] patients with rectal V90 and V100 values >4.2 and >1.5 cc, respectively, had considerably lower bowel QOL. Iarrobino et al.[22] reported higher rectum V36 values (>0.58 cc) and D5% (33 Gy) that were correlated with EPIC declines at 6 months. In the study in which 259 patients from 18 centers were evaluated, a rectum Dmax value above 37.4 Gy was associated with a decrease in the EPIC-26 score.[23] The recently published analysis highlighted moderate doses delivered in large volumes into the rectum in 103 patients. In terms of patient-reported bowel QOL and physician-scored grade 2+ GI toxicity, respectively, rectum D19% and V20 values were linked to an increased likelihood of a clinically significant decline.[24] In our study, statistically significant differences were found in all dosimetric variables examined for the rectum as well as for the bladder. The mean rectum Dmax value increased from 38.27 Gy in the first plan to 38.69 Gy in the second plan. We could not make a comparison because we evaluated rectum V36 as % instead of cc.

Another OAR that we evaluated dosimetrically was the penile bulb. Evaluation with the EPIC-26 score can be confusing, since sexual function depends on many factors such as age, co-morbidity, and use of hormone therapy. This is why, unlike bladder and rectum EPIC-26 scores, worsening rather than improvement is encountered.[18,25] Penile bulb V29.5 <50% and V30 <3 cc were evaluated dosimetric parameters, however, no significant relationship could be demonstrated between erectile dysfunction and these values.[25,26] In our study, lower dosimetric values were found in both plans, but only the mean value of penile bulb V29.5 was significant in terms of exposure doses, with 16.30 in plan 1 and 18.64 in plan 2.

In addition, femoral heads, neurovascular bundles, and bowel were also evaluated dosimetrically. While there was no dosimetric difference for the femoral heads and bowel with the enlargement of the target volume, the neurovascular bundles V37.5 and V38 values increased.

This study had several potential limitations. Although our study was a relatively small number with low heterogeneity, the results were statistically significant. Since the study was a retrospective comparison study, the possibility of toxicity and its reflection on the clinic could not be evaluated.

CONCLUSION

We evaluated the dosimetric differences that may occur in OARs by giving the same dose to two different target volumes. We chose the 5x7.25=36.25 Gy treatment scheme because it is now more safely preferred and its long results are better known. Numerous studies have demonstrated that the likelihood of developing GU and GI toxicity after prostate SBRT is associated with exposure of OARs to high doses delivered to small volumes. Therefore, increases in high dose volumes that may be considered quantitatively insignificant in routine clinical practice may be overlooked as they do not exceed dose restrictions and may possibly be important in the development of toxicity. As there are no clear guidelines on when to include the proximal seminal vesicle to the target volume in low-risk PCa, we recommend that special attention be paid to the high doses exposed in OARs in this patient group. In addition, it should be kept in mind that bladder toxicity may increase with increasing PTV volume, especially above 100 cc.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 2023, Decision No:06/10)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The effect of long-term use of pioglitazone on bone mineral density in patients with diabetes mellitus

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ABSTRACT

Aims: This study aimed to explore the incidence of osteoporosis in patients with diabetes mellitus (DM) who have been on a long-term pioglitazone regimen, and to ascertain the link between pioglitazone usage and the onset of osteoporosis.

Methods: We enrolled patients prospectively and conducted a comparative analysis between two groups of DM patients: those who had been using pioglitazone for a period exceeding two years, and those with no history of pioglitazone use. Bone Mineral Density (BMD) was assessed using dual energy X-ray absorptiometry (DEXA).

Results: There were no significant differences in age, gender, disease duration, fasting plasma glucose levels, and HbA1c levels between pioglitazone users and non-users. However, a significant variation was found in the BMD measurements. Patients on pioglitazone had an L1-L4 vertebra BMD T-score of -1.3, compared to -0.9 in non-users ($p<0.05$), signifying a substantial divergence in BMD between both cohorts. Furthermore, it was observed that patients with a disease duration of less than 10 years had higher BMD T-scores compared to those with disease durations exceeding 10 years, suggesting a decrease in BMD with increased disease longevity. Moreover, a higher BMD was observed in patients aged less than 50 years in comparison to those aged over 60 years.

Conclusion: Despite the clinical preference for pioglitazone in the management of DM and insulin resistance, our findings suggest that it may affect bone metabolism adversely in the long run. Hence, careful monitoring is advised during extended periods of pioglitazone use. To investigate the incidence of osteoporosis in patients with DM who use pioglitazone for a long time and to determine the relationship between pioglitazone and the cause of this osteoporosis.

Keywords: Pioglitazone, bone mineral density, diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a diverse metabolic disorder that is predominantly prevalent among adults, causing disruptions in carbohydrate, fat, and protein metabolism due to the absolute or relative deficiency of insulin secretion and/or insulin action.[1,2] There is established knowledge that bone and skeletal metabolism are affected in DM patients, hence positioning DM as a potential risk factor for osteoporosis.

In addition to DM itself being a risk factor for osteoporosis, pioglitazone, an oral antidiabetic agent used in treating Type 2 DM, has been associated with potential deleterious effects on bone health. These effects are presumably brought about by pioglitazone's role in decreasing osteoblast differentiation and promoting adipocyte differentiation.[3] Especially in women, pioglitazone has been linked to an increase in bone loss, and it has been associated with an augmented risk of fractures.[3,4] Moreover, the use of pioglitazone has been related to alterations in markers of bone turnover and a reduction in bone mineral density (BMD).[5] There are a number of possible explanations for this association, with some in vitro data suggesting that activation of the peroxisome proliferator-activated receptor (PPAR)-g increases adipogenesis at the cost of osteoblastogenesis, with the potential to prevent bone formation and lead to bone loss.

Pioglitazone functions as a ligand for nuclear receptors, specifically peroxisome proliferator-activated receptors (PPAR). When pioglitazone binds to the PPAR-gamma receptor, it either activates or inhibits numerous gene transcriptions, thereby impacting lipid metabolism, insulin action, and the regulation of adipose tissue differentiation.[6] Pioglitazone's primary pharmacological effects involve the enhancement of insulin-mediated glucose uptake (thereby reducing insulin resistance) and the promotion of adipogenesis in muscle tissue in vivo.

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It reduces insulin resistance by decreasing proteins such as TNF-alpha, resistin, and leptin in adipose tissue, and concurrently increasing adiponectin, which heightens hepatic insulin sensitivity. Besides improving glycemic control, it also ameliorates several components of insulin resistance syndrome. For instance, pioglitazone reduces the levels of plasminogen activator inhibitor type 1 (PAI-1), thereby minimizing the inhibition of fibrinolysis, a characteristic feature of insulin resistance.[7] It also leads to an increase in subcutaneous adipose tissue and a slight reduction in visceral adipose tissue.[8,9]

Studies have indicated that pioglitazone increases bone marrow adipose tissue, diminishes osteoblastic activity, and is associated with a decrease in BMD in women by reducing the activity of the aromatase enzyme. However, more extensive research is needed for pioglitazone to be firmly classified among the risk factors for osteoporosis.[10,11]

The primary objective of this study is to investigate the incidence of osteoporosis in DM patients with long-term pioglitazone use and to establish the relationship between pioglitazone usage and the development of osteoporosis.

METHODS

Ethics

The study was approved by the Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.12.2012, Decision No: 20149/2012). This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study Population

We conducted a retrospective analysis of data collected from our cohort of type 2 DM patients. Patients younger than 18 years of age, those with diseases predisposing them to osteoporosis (such as hyperthyroidism, hyperparathyroidism, chronic renal failure, long-term steroid use, etc.), and nondiabetic individuals were excluded from the study.

Data Collection

The study employed data retrospectively obtained from electronic medical records and outpatient clinics. The collected data included demographics, past medical histories, and bone mineral density (BMD). A comparative analysis was performed between patients who had been using pioglitazone for more than two years and those who had never used pioglitazone. Dual Energy X-ray Absorptiometry (DEXA), recognized as the gold standard for BMD measurement, was used on all patients.[12]

Patient management

The age, gender, and disease duration of patients who had been using pioglitazone for over two years, as well as those who had no experience with pioglitazone, were noted. All patients were on a daily dosage of 30mg of pioglitazone. Patients were questioned about their use of steroids and heparin. Blood samples were collected from all patients to test for fasting blood glucose, HbA1c, kidney function, thyroid function, serum parathormone level, and serum fasting cortisol level. DEXA was used to measure BMD in each patient, with BMD calculated based on the L1-L4 vertebral T-score. T-scores ranging between -1 and -2.5 SD were classified as osteopenia, while T-scores lower than -2.5 SD were considered indicative of osteoporosis.

Statistical Analysis

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). The study data was evaluated using descriptive statistical methods (Mean, Standard Deviation, Minimum, Maximum, Median, Frequency, Ratio). For comparisons of quantitative data, the Mann Whitney U test was used for two-group comparisons when parameters did not conform to normal distribution. The Kruskal Wallis test was employed for the comparison of groups of three or more that did not conform to normal distribution, while the Mann Whitney U test was used to ascertain the group causing the difference. The Yates Continuity Correction Test (Chi-square with Yates correction) was utilized for comparing qualitative data. Finally, Spearman's Correlation Analysis was used to assess the relationships between parameters.

RESULTS

Our study involved a total of 102 patients, out of which 67 (65.7%) were female. The patient cohort was divided into two groups: 52 (51%) were using pioglitazone (pioglitazone group), while the remaining 50 comprised the control group (without pioglitazone experience). There were no statistically significant differences in fasting blood glucose and hemoglobin A1c measurements between the two groups in relation to pioglitazone use ($p>0.05$) (**Table 1**). Similarly, gender distribution was not statistically different with regard to pioglitazone use. The female gender ratio was 61.5% in the pioglitazone group versus 70% in the control group, with no statistically significant difference observed ($p>0.05$) (**Table 2**).

Table 1. Evaluation of related parameters according to study groups

	Pioglitazone (+)		Pioglitazone (-)		p
	Range	Mean±sd	Range	Mean±sd	
Fasting blood glucose	92-302 (150.0)	157.96±47.10	86-423 (151.5)	168.08±61.12	0.529
HbA1c	5.7-11.3 (7.1)	7.38±1.18	5.6-14.9 (7.4)	7.82±1.69	0.161
Disease duration (years)	4-20	9.37±3.72	3-25	9.60±4.80	0.890

Mann-Whitney U Test

Table 2. Relationship between gender distribution and pioglitazone use

		Pioglitazone Use		p
		(+)	(-)	
		N (%)	N (%)	
Gender	Male	20 (38.5%)	15 (30.0%)	0,489
	Female	32 (61.5%)	35 (70.0%)	

Yates Continuity Correction Test

A comparison between the pioglitazone and control groups revealed a statistically significant difference in DEXA measurements (-1.37±1.29 vs -0.82±1.16, p=0.032, respectively). The DEXA measurements of patients who used pioglitazone for more than two years were significantly lower than those who had never used it (**Figure 1**).

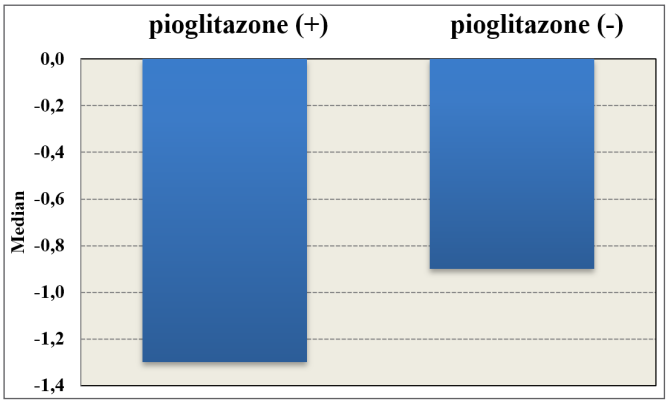

Figure 1: L1-L4 vertebral T-score measurement distribution by pioglitazone usage.

Within the pioglitazone group, a comparison of DEXA measurements between patients with a disease duration of <10 years and >10 years revealed no statistical difference. However, the DEXA values of patients with diabetes for over 10 years were lower (-1.9 vs -1.1, respectively, p=0.054). The DEXA measurements varied significantly according to age (p=0.011). The pairwise comparisons indicated that although DEXA measurements were lower in subjects under 50 years compared to those aged between 50 and 60, the difference was not statistically significant (p=0.054). DEXA measurements were significantly lower in subjects aged <50 years than in those aged over 60 years (p=0.004). No significant difference was observed in DEXA measurements between subjects aged 50-60 years and those aged >60 years (p>0.05) (**Table 3**).

Table 3. Osteoporosis evaluation based on disease duration and age in pioglitazone users.

Pioglitazone (+) (n=52)		DEXA			p
		Mean±sd	Median	Range	
Disease duration	<10 years	1.17±1.21	-1.1	-4.2-1.5	[a]0.054
	>10 years	-1.79±1.39	-1.9	-3.8-1.8	
Age range	<50 years	-0.67±0.99	-0.4	-3.0-0.5	[b]0.011
	50-60 years	-1.33±1.28	-1.2	-4.2-1.5	
	>60 years	-1.83±1.32	-1.9	-3.8-1.8	

[a]Mann-Whitney U Test, [b]Kruskal-Wallis Test

A statistically significant negative correlation was observed between age and DEXA measurements (DEXA level decreases with increasing age) (r=-0.450; p=0.001). Furthermore, a statistically significant negative correlation was observed between disease duration and DEXA measurements (the DEXA level decreases as the duration of diabetes increases) (r=-0.364; p=0.008) (**Table 4**).

Table 4. Evaluation of the relationship between age, diabetes year and osteoporosis in pioglitazone users.

	DEXA	
	r	p
Age	-0.450	0.001
Disease duration	-0.364	0.008

r=Spearman's correlation coefficient

DISCUSSION

In the present study, we did not find any difference in age, gender, disease duration, fasting plasma glucose, and HbA1c levels when comparing patients using pioglitazone for >2 years to patients without pioglitazone experience. However, a statistically significant difference was found in bone mineral density (BMD) between both groups, with a T-score of -1.3 in pioglitazone users versus -0.9 in non-users (p<0.05). This observation suggests that pioglitazone use may be associated with lower BMD. Furthermore, we found that BMD was higher in patients with a disease duration of <10 years compared to those with >10 years, supporting the notion that BMD decreases with the progression of the disease. A statistically significant higher BMD level was found in patients aged <50 years compared to those aged >60 years.

An interesting meta-analysis of 19 pioglitazone-related studies conducted at the University of Ottawa,[13] reviewed 8157 patients retrospectively. This analysis found no

increased fracture risk in men, while an increased risk of forearm fractures was observed in women, increased by 2.6%. Unlike our study, BMD was normal in this meta-analysis. Interestingly, the fractures in these cases were not associated with osteoporosis or trauma. The reason for the increase in forearm fractures in this study is unclear. However, we considered the use of pioglitazone over 2 years in our study. Therefore, the resorptive effects of possible pioglitazones on bone may have become more pronounced during this time. In a study supporting this possibility, it was determined that after 1 year of use of pioglitazone in patients with type 2 DM, serum osteocalcin level decreased in the pioglitazone group, however, while the bone mineral density of the femoral and radial bones decreased, the vertebral bone mineral density did not change.[14]

Our findings align with another study which also showed that pioglitazone use decreased bone mineral density in women.[15] The increased risk of fracture has been attributed to increased adipocyte activity in the bone marrow, decreased osteoblastic activity, and increased bone resorption associated with decreased estrogen levels due to decreased aromatase activity. The reason why pioglitazone has less resorptive effects on bone tissue in men has been attributed to the fact that postmenopausal women have more estrogen than estrogen levels.[16] Similarly, some studies have shown an increased risk of vertebral fractures in both sexes due to the use of pioglitazone.[17,18] However, it was not clear whether the increased risk of fracture was with pioglitazones or due to DM.

Studies have clearly shown that bone turnover is increased in patients with type 2 DM, and it has been determined that the use of high-dose insulin increases osteoblastic activity in the bone and decreases osteoclastic activity.[19,20] Again, in the same study, it was suggested that advanced glycosylated products create a more fragile bone tissue by disrupting the crosslinks between collagen fibrils, and this causes osteoporosis, especially in poorly controlled diabetics. In our study, it is clear that the use of pioglitazone, in parallel with previous studies, reduces bone mineral density and triggers osteoporosis.

The strengths of the study were the clear demonstration of the effect of pioglitazone on bone tissue based on long-term use of pioglitazone, the inclusion of patients using standard dose pioglitazone (30 mg/day), and the design of the study to include both genders. The weaknesses of the study were that it was retrospective design and we could not specify the fracture risk. Based on the L1-L4 vertebral T-score, the effect of pioglitazone on bone tissue was assessed in the current study. As well as with bone mineral density, evaluating the risk of fracture as a clinical outcome may be beneficial.

Pioglitazone, especially together with metformin, are antidiabetic agents that have valuable effects in reducing insulin resistance in the treatment of DM. However, in the decision-making process of pioglitazone use and in the follow-up of pioglitazone use, measurement of bone mineral density may be useful, especially in patients using pioglitazone for >2 years, and may be a clinical laboratory parameter that warns against the risk of fractures that may occur in the future.

CONCLUSION

Although pioglitazone remains a valuable choice for managing DM and insulin resistance, its potential effects on bone metabolism warrant careful monitoring during long-term use. Regular measurement of bone mineral density, particularly in patients using pioglitazone for >2 years, may help to identify increased fracture risks.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.12.2012, Decision No: 20149/2012).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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The effect of mask use on allergic rhinitis symptoms during COVID-19 pandemic

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ABSTRACT

Aims: Inspiratory particle load including the allergens in the inhaled air is decreased by the use of the mask, which is one of the methods for COVID-19 protection. The aim of the study is to investigate the effect of masks used by seasonal allergic rhinitis patients with pollen allergy on the control of rhinitis symptoms.

Methods: Mask usage characteristics of patients (mask type used, average number of days per week for mask usage, daily usage time),whether there was a change in the time spent outdoors during the pandemic compared to the pre-pandemic period, and rhinitis complaints and frequency of rhinitis-related drug use before the pandemic compared to the pandemic period were investigated.

Results:The frequency of nasal discharge (6.62±1.69; 6.00±1.89: p<0.001), obstruction (4.56±1.64; 4.28±1.86: p=0.099), itching(7.49±1.55; 7.16±1.83: p=0.038), sneezing (5.54±1.60; 5.21±1.89: p=0.046), and frequency of drug use (5.52±1.62; 5.17±1.91: p=0.037) decreased statistically significantly after the pandemic according to the visual analog scoring. However, an increase was found in ocular symptoms.

Conclusion:Although studies with larger patient and control groups are needed, we think that the use of face masks during the COVID-19 pandemic is an effective protective measure for protection from pollen in patients with allergic rhinitis,who have pollen sensitivity.

Keywords: Mask usage, allergic rhinitis, COVID-19, rhinitis symptoms, pandemic

INTRODUCTION

At the end of December 2019, a series of reports of upper respiratory tract infections were noticed from Wuhan city of China.[1] In a short time, the coronavirus disease 2019 (COVID-19) has affected the whole world and by the date June 13, 2023 the number of cases reached 767,750,853 worldwide.[2] COVID-19 is mainly transmitted via droplets from the nose and mouth mucosa that include viruses.[3] Exposure of eyes, mouth, or nose to droplets or inhalation of airborne viruses after coughing or sneezing are considered as common transmission mechanisms.[4] Washing hands with soap and water, using hand disinfectant, not touching face and eyes, avoiding social contact with people who have flu symptoms, and using personal protective equipment (face masks, eye protection) are among the COVID-19 protective measures.[4,5] Inspiratory particle load including the allergens in the inhaled air is decreased by the use of the mask, which is one of the protective measures for COVID-19 protection.[6] While standard surgical masks filter particles larger than 3 µm, N95 respirator masks can filter as small as 0,04 µm.[7,8]

Rhinitis can be classified by pathogenic mechanisms, as allergic or non-allergic. Allergic rhinitis is viewed as either seasonal or perennial, and it is the classification system that the United States Food and Drug Administration uses when approving new medications for allergic rhinitis.[9] Allergic rhinitis is characterized by one or more symptoms including sneezing, nasal itching, nasal obstruction and discharge,[10] if ocular symptoms are also present it is identifies as allergic rhinoconjunctivitis.[11] Allergic rhinitis is an inflammatory state caused by an IgE-mediated response to a variety of environmental aeroallergens, including pollen (10-100 µm), house dust mites (10-40 µm), and fungal spores (2-50 µm).[9] The key to diagnosis of allergic rhinitis is awareness of

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symptoms of the patient. Allergic rhinitis has negative economic, clinical and social consequences. It can cause work day loss in adults, school day loss and learning difficulties in children.[12] There are not enough studies on its prevalence. Studies have shown that the prevalence of allergic rhinitis varies between 10% and 58,5% according to the geographical regions.[13] A 2020 study revealed a 15,9% allergic rhinitis prevalence in Turkey.[14]

Allergen avoidance and control of environmental exposure are the most important steps in the treatment of allergic rhinitis. Complete avoidance of allergen is usually not feasible or practical. The use of masks is also among the methods of protection in pollen-sensitive allergic rhinitis patients.[13] In the pandemic, with the introduction of regular mask use into our lives, investigating the effect of mask use on many diseases has become possible. Since the pandemic, controversial results regarding mask use and rhinitis symptoms have been reported in the literature. Although there are publications that report a decrease in the severity of rhinitis symptoms with mask use,[15] there are also publications reporting an increase in rhinitis symptoms with mask use.[4]

The aim of the study is to investigate the effect of masks used by seasonal allergic rhinitis patients with pollen (10-100 µm) sensitivity on the control of rhinitis symptoms.

METHODS

Ethics

The ethical approval of the study was obtained from the Keçiören Training and Research Hospital Clinical Researches Ethics Committee. (Date: 11/05/2021, Decision No: 15/2301). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

Patients with allergic rhinitis who were admitted to the Health Sciences University Ankara Atatürk Sanatoryum Training and Research Hospital Immunology and Allergy Diseases Outpatient Clinic between May-November 2021, who were over 18 years of age and had only pollen allergy in the skin prick test, had no change in their place they live in the last 3 years and had seasonal complaints for at least 2 years were included in the survey study after an informed consent form was obtained. Patients had complaints before the pandemic and the complaints patients before using the mask were compared with the 2020 season retrospectively.

Data Collection

Demographic features and mask usage characteristics of patients (mask type used, average number of days per week for mask usage, daily usage time), whether there was a change in the time spent outdoors during the pandemic compared to the pre-pandemic period, and rhinitis complaints and frequency of rhinitis-related drug use before the pandemic compared to the pandemic period were investigated. Patients were asked to rate their rhinitis symptoms according to the visual analog scoring (grading from 0 to 10 and scoring, 0: no complaints, 10: the most intense complaint) and score their complaints (nasal sneezing, nasal itching, nasal obstruction, nasal discharge, watering eye, swollen eyes, eye itching) considering both pre-pandemic period and during the pandemic period while using a mask. Sneezing, nasal itching, nasal obstruction, and rhinorrhea and watering eye, swollen eyes, eye itching) scoring was requested. In addition, patients were asked to score the frequency of drug use, both for pre-pandemic and pandemic periods, using visual analog scoring.

Statistical Analysis

SPSS (statistical package for social sciences) for Windows 25 program was used for statistical analyses performed for the evaluation of the study data. For the evaluation of the normally distributed data, mean and standard deviation, for data that does not show normal distribution, median and interquartile range and percentages for rates were calculated as descriptive statistical methods. Chi-square, Fisher, Student's t-test, and Mann-Whitney U tests were used for the univariate analyses where appropriate. The results were evaluated with a 95% confidence interval and the significance value was accepted as $p<0.05$.

RESULTS

A total of 171 patients, 87 females and 84 males were included in the study. Demographic characteristics of the patients are given in **Table 1**. All of the patients had a history of seasonal allergic rhinitis confirmed by the skin prick test and had only pollen sensitivity in the skin prick test.

Table1. Demographic characteristics of the patients.

	n=171
Female, n (%)	87 (50.8)
Age,years, mean±SD	28.9±7.01
Allergic rhinitis duration, years, mean±SD	5.4±2.49

The type of mask that all patients preferred to use during 2020 in the COVID-19 pandemic was the surgical mask (n=171, 100%). The frequency of mask usage by patients is given in **Table 2**.

Table 2. Frequency of mask usage

Frequency within a week, n (%)	1 day - 51 (29.8) 2-3 day - 44 (25.7) 4.5.6 day - 64 (37.4) Everyday - 12 (7.0)
Frequency within a day, n (%)	Less than 1 hour- 49 (28.6) 1-5 hours - 36 (21) >5- 8 hours - 76 (44.4) More than 8 hours - 10 (5.8)

The frequency of nasal discharge, itching, sneezing, and frequency of drug use decreased statistically significantly after the pandemic according to the visual analog scoring. There was also decrease in nasal obstruction but it was not statistically significant. However, an increase was found in ocular symptoms (watering eyes, swollen eyes, itching eyes) (**Table 3**). When compared to the pre-pandemic period, there was no change in the time spent outdoors in 59.06% (n=101) of the patients, while there was a decrease in the time spent outdoors of 22.80% (n=39) patients, and there was an increase in the time spent outdoors in 18.12% (n=31) of the patients.

Table 3. Comparison of rhinitis complaints and frequency of drug use before and during the pandemic period by Visual Analog Scoring.

Variable	Before Pandemic	During Pandemic	p value
Nasal symptoms			
Discharge, mean ±SD	6.62±1.69	6.00±1.89	<0.001
Obstruction, mean±SD	4.56±1.64	4.28±1.86	0.099
Sneezing, mean±SD	5.54±1.60	5.21±1.89	0.046
Itching, mean±SD	7.49±1.55	7.16±1.83	0.038
Ocular symptoms			
Watering eye, mean±SD	2.25±1.86	2.447±2.18	0.003
Swollen eyes, mean±SD	2.18±1.84	2.42±2.21	0.002
Itching eyes, mean±SD	3.00±2.10	3.24±2.57	0.008
Drug use			
Frequency of drug use(daily)±mean SD	5.52±1.62	5.17±1.91	0.037

DISCUSSION

In the current study, we showed that using masks reduced the symptoms of allergic rhinitis and decreased the patients need for use of medication of the 171 patients included in the study.

Treatment of allergic rhinitis includes control of environmental exposure by allergen avoidance, pharmacotherapy, and immunotherapy. One of the most important steps in the treatment is explaining the recommendations for allergen avoidance to the patients and compliance of the patient.[13] Avoiding pollen is more difficult than avoiding other allergens. Pollen avoidance is only relevant during the time that the offending pollen is airborne. Using the face masks in the pollen period, which is among the protective measures of pollen protection, was not a method commonly preferred by patients before the pandemic, however, face masks are being used quite commonly during the pandemic.[13,15] Considering that standard surgical masks filter particles larger than 3 µm, theoretically, it is thought that they can easily filter pollen between 10-100 µm in size. In our study, it is also thought that this may be the mechanism in patients with statistically significant regression was detected in nasal symptoms. During the use of a mask, exhaling into the mask increases the temperature and humidity of the inhaled air between the mouth and the mask.[16] There are publications showing that the nasal response to the allergen may decrease with increased temperature and humidity.[15] In other words, the symptoms of allergic rhinitis can be reduced by the mask, by both physical filtration and suppression of the nasal response, while the response to allergens that cannot be filtered by the mask is also decreased.

There was no significant decrease in the ocular symptoms of the patients, as in the nasal symptoms, and even a statistically significant increase was detected. We think that this may be related to the fact that while the face masks protect the airways from inspiratory particles, the conjunctiva of the eye is still exposed to allergens. Similar to our study, Drorr et al.[15] also detected that nasal symptoms of patients with allergic rhinitis decreased, while ocular symptoms were not decreased. We think that the increase in the ocular symptoms of the patients may be due to the decrease in the frequency of drug use because of the decrease in nasal symptoms, compared to the previous year.

Although there was no change in the time spent outdoors in a large percentage of the patients (59.06%), the decrease in the nasal symptoms of the patients suggests that this condition is related to the decrease in allergen exposure by wearing a mask, not by not going out. In addition, while there was a decrease in nasal symptoms of the patients, the absence of the same decrease in ocular symptoms suggests that this decrease is due to using masks rather than lockdown.

CONCLUSION

although studies with larger patient and control groups are needed, we think that the use of face masks during the COVID-19 pandemic is an effective protective measure for protection from pollen in patients with allergic rhinitis, who have pollen sensitivity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Keçiören Training and Research Hospital Clinical Research Ethics Committee. (Date: 11/05/2021, Decision No: 15/2301)

Informed Consent: Written consent was obtained from the patient participating in this study

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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Tau protein hyperphosphorylation in children with cerebral palsy with sleep disorders

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ABSTRACT

Aims: In this study, we aimed to evaluate the relationship between sleep disorder and serum tau protein levels in children with cerebral palsy.

Methods: The sample was selected among children aged 6-10 years who applied to our physical medicine and rehabilitation outpatient clinic. In order to evaluate sleep quality, the Pittsburgh Sleep Quality Index (PSQI) questionnaire was recorded by asking parents of all participants. Children with CP who had a Pittsburgh Sleep Quality Index value above 5 were determined as the sleep disorder group. We recruited 27 children with CP and sleep disorders in the first patient group (Group 1), 27 children with CP but without sleep disorders in the second group (Group 2). The third group (Group 3), which was the healthy group, included 27 children without any disease. We also recorded the age of children at diagnosis, risk factors for CP (premature, prolonged birth, etc.), CP type, gross motor function classification system (GMFCS), botox application, orthoses usage, maternal age at birth, and additional problems. We measured total tau protein (T-tau) and phosphorylated tau protein (P-tau) levels in blood samples through a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). The correlation between tau protein and PSQI values was examined.

Results: Maternal age (p=0.001), gross motor function classification system (GMFCS) (p=0.001), and pittsburgh sleep quality index (PSQI) (p=0.001) were significantly higher in the group with sleep disorders. There was a statistically significant difference between the groups in terms of serum T-Tau and P-tau protein levels (T-tau p=0.003, P-tau p=0.004). In the group sleep disorders, PSQI was significantly correlated with T-tau (r=0.499) and P-tau (r=0.473).

Conclusion: This study shows that tau protein levels are higher in CP patients with sleep disorders than in participants without sleep disorders. In the correlation analyzes, a positive and significant correlation was observed between PSQI values and T-tau and P-tau in sleep disorders groups, and no correlation was found in without sleep disorders.

Keywords: Cerebral palsy, Tau protein, phosphorylated tau protein, sleep disorders

INTRODUCTION

Cerebral palsy (CP) is defined as a group of persistent disorders characterized by non-progressive impairments in movement and posture development occurring in the developing fetal or infant brain.[1] It is shown to occur between 1.5-3 per 1000 live births worldwide and 4.4 in Turkey.[2] The etiology of CP bears multiple risk factors; the prevalent causes are intraventricular bleeding, periventricular leukomalacia, bronchopulmonary dysplasia, intrauterine growth retardation, intrauterine infections, antepartum bleeding, severe placental pathologies, and multiple pregnancies. Ultimately, such factors directly or indirectly trigger hypoxic brain damage, leading to neuronal losses in the pathogenesis of CP.[3,4] Besides, many comorbidities (vision, hearing, or cognitive impairment and epilepsy) often accompany motor disorders in CP.[5] Sleep problems are also a common phenomenon in this population at 23-50% and are probably triggered by the above comorbidities.[6-9] Long-term sleep disorders in children may lead to neuronal losses. Additional neuronal losses due to sleep disorders to the already existing upper motor neuron damage are likely to bring unprecedented negativities to a child with CP.

Tau protein forms polymers of the cytoskeleton mainly in the axons of the central nervous system. Its major functions may be listed as ensuring the formation and coupling of microtubules, maintaining the structure and stability of neurons, and mediating the transport of intracellular microvesicles.[10] It is also a neuronal skeletal protein joining actin filaments made up of neurons. In general, tau protein is released in the case of any neuronal damage; therefore, the degree of neuronal damage is

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measured by identifying serum or CSF levels of tau protein.[11] Tau protein appears in two forms: dephosphorylated and phosphorylated. In the progression of hypoxia, tau protein becomes excessively phosphorylated, affecting regular physiological functions. Tau protein accumulates in neurons, altering normal microtubule formation. In addition, it separates normal microtubule-linked proteins from the microtubule, causing microtubule collapse and generating large amounts of accumulated neuron-damaging matter.[12,13]

Tau protein hyperphosphorylation is often demonstrated in Alzheimer's disease, traumatic brain injury, and acute ischemic stroke.[14] We believe that Tau and phosphorylated Tau protein molecules have a significant role in elaborating on the etiology of sleep problems, a common condition among those with CP at 23-50%. In this study, we aimed to measure serum tau protein levels in relation to existing brain damage in CP patients with sleep disorders.

METHODS

The study was carried out with the permission of Hitit University Medical Faculty Clinical Researches Ethics Committee (Date: 19.08.2020, Decision No: 2020/171). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, 54 children with CP and 27 healthy children were included, which was carried out at Hitit University Faculty of Medicine, Department of Physical Medicine and Rehabilitation. The sample was selected among children aged 6-10 years. Children with CP who had a Pittsburgh Sleep Quality Index value above 5 were determined as the sleep disorder group. Accordingly, we recruited 27 children with CP and sleep disorders in the first patient group (Group 1), 27 children with CP but without sleep disorders in the second group (Group 2). The third group (Group 3), which was the healthy group, included 27 children without any disease. We also recorded the age of children at diagnosis, risk factors for CP (premature, prolonged birth, etc.), CP type, gross motor function classification system (GMFCS), botox application, orthoses usage, maternal age at birth, and additional problems. We obtained informed consent from the parents and children for voluntary participation in the study. Patients between the ages of 6 and 10 who were diagnosed with CP and who did not have a history of genetic, epilepsy, metabolic disease or mental retardation were included in this study. A nurse took the blood samples of the patient and control groups into 8 mL clot activator tubes in our polyclinic between 08.00 and 10.00 after 12 hours of fasting. After keeping the samples in the tubes at room temperature for half an hour, they were centrifuged at 4,000 g for 10 minutes, and then 4 mL of serum was obtained from each. The serum samples separated into eppendorfs were stored at -70°C until the analysis.

Tau and phosphorylated tau protein levels: We measured tau protein and phosphorylated tau protein levels in blood samples through a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). In this method, we added the samples to plate wells coated with monoclonal antibodies and incubated them. Following incubation, an immune complex was formed with a biotin-labeled antibody and streptavidin-HRP solution. Unbound protein and enzymes were washed from the medium. Then, chromogenic reagent A and B solutions were added and incubated at 37°C for about 10 minutes in an environment away from light. Finally, the stop solution was added, and the optical density was determined at a wavelength of 450 nm within 10 minutes.

Pittsburgh Sleep Quality Index (PSQI): The PSQI was developed in 1989 to evaluate sleep quality and adapted into Turkish by Agargün et al.[15] The instrument includes 24 questions within 10 components and measures sleep quality over a 1-month time interval. One may obtain a maximum score of 21 points, and a score greater than 5 indicates poor sleep quality.

Statistical Analysis

While nominal and ordinal data were presented as frequencies and percentage, we showed the continuous data as means and standard deviations. The categorical variables were compared between the groups using Chi-Square, Likelihood Ratio, and Fischer's Exact tests. Besides, we tested the normality of distribution using the Kolmogorov-Smirnov test. Accordingly, while non-normally distributed variables were subjected to Kruskal Wallis-H and Mann-Whitney U tests, we performed independent samples t-test and one-way analysis of variance (ANOVA) to test the variables showing a normal distribution. Moreover, we tested the association between our main variables using Spearman's rho correlation analysis. We performed all statistical analyses on SPSS 17.0 at a 95% confidence interval, and a p-value < 0.05 was considered significant.

RESULTS

Our study included 27 CP patients with sleep disorders, 27 CP patients without sleep disorders, and 27 healthy volunteers. The mean age of the participants was 7.89±1.42. There were 24 (29.6%) female and 57 (70.4%) male participants. There was no difference between the groups in terms of gender and age (p=0.072, p=0.110). The findings revealed that the groups significantly differed by CP type. Accordingly, spastic CP was significantly more common in the group 1 (p=0.001). Speech disorder (p=0.033), hearing disorder(p=0.041) and vision defect (p=0.007) were significantly more common in the group 1. Moreover, we found maternal age (p=0.001) and GMFCS (p=0.001) were significantly higher in the group 1. No statistically significant difference was found between the SP groups in

terms of orthosis use (**Table 1**). Mean serum T-tau protein level was 11.19±7.12 ng/ml (min-max: 5.41-36.56) ng/ml in group 1, 8.79±3.59 ng/ml (min-max: 4.78-14.9) in Group 2 and 7.04±2.62 ng/ml (min-max: 0.47-14.7) in group 3. Mean serum P-tau protein level was 136.85±88.7 pg/ml (min-max: 71.9-495) in group 1, 105.79±29.20 pg/ml (min-max: 74.11-151.5) in Group 2 and 88.51±12.27 pg/ml (min-max: 67.9-112.5) in group 3. There was a statistically significant difference between the groups in terms of serum T-Tau and P-tau protein levels (T-tau p=0.003, P-tau p=0.004), and this difference was found between Group 1 between Group 2 (T-tau and P-tau p=0.001) and Group 1 between Group 3(T-tau and P-tau p=0.001). No statistically significant difference was found between Group 2 and Group 3 in terms of serum T-tau and P-tau protein levels (T-tau p=0.06, P-tau p=0.062) (**Table 2**). T-tau and P-tau levels are shown in **Figures 1** and **2**. In the correlation analyzes, a positive and significant correlation was observed between PSQI values and T-tau (r=0.499; p < 0.05) and P-tau (r=0.473; p < 0.05) in Group 1, and no correlation was found in Group 2 and Group 3 (**Table 3**).

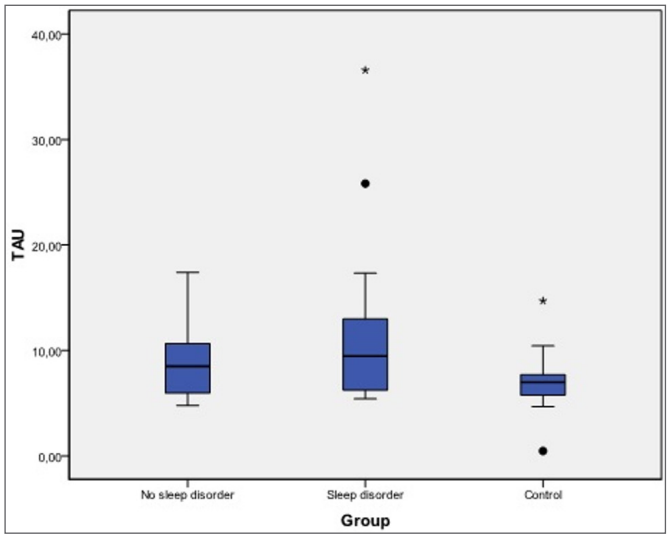

Figure 1: Tau protein levels by groups

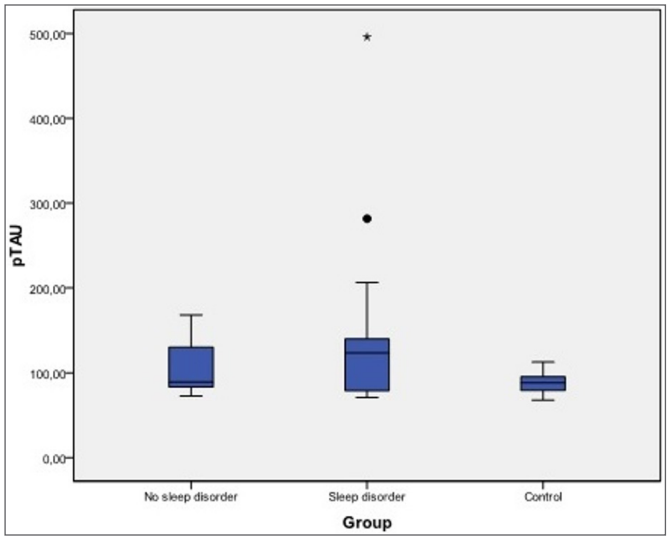

Figure 2: Phosphorylated tau protein levels by groups

Table 1. Comparison of demographic and clinical data of groups

	Group 1 (n=27)	Group 2 disorder (n=27)	Group 3 (n=27)	p
Age, mean±SD	7.48±1.42	8.00±1.66	8.32±1.36	0.110[a]
Sex, n (%)				
Female	5 (18.5)	9 (33.3)	10 (35.7)	0.072[b]
Male	22 (81.5)	18 (66.7)	18 (64.3)	
CP type, n (%)				
Spastic	20 (74.1)	9 (33.3)		0.001[b]
Hypotonic	5 (18.5)	9 (33.3)		0.005[b]
Dyskinetic	2 (7.4)	4 (14.8)		
Ataxic	-	5 (18.5)		
Risk factor, n (%)				
Premature	18 (66.7)	18 (66.7)		0.486[c]
Prolonged birth	9 (33.3)	8 (29.6)		
Postnatal thyroid	-	1 (3.7)		
Speech disorder, n (%)	23 (85.2)	16 (59.3)		0.033[d]
Hearing disorder, n (%)	18 (66.7)	9 (33.3)		0.014[d]
Vision defect, n (%)	19 (70.4)	9 (33.3)		0.007[d]
Orthosis usage, n (%)				
None	7 (25.9)	6 (22.2)		
SOLID AFO	12 (44.4)	14 (51.9)		
KAFO	5 (18.5)	4 (14.8)		0.952[c]
PAFO	3 (11.1)	3 (11.1)		
Botox, n (%)	17 (63.0)	13 (48.1)		0.206[d]
Maternal age	35.00±1.82	29.78±4.20	26.54±4.39	0.001[e]
GMFCS				
1		1 (3.7)		
2	1 (3.7)	6 (22.2)		
3	7 (25.9)	15 (55.6)		0.001[c]
4	12 (44.4)	4 (14.8)		
5	7 (25.9)	1 (3.7)		
PSQI	13.48±3.27	2.59±0.97	2.21±0.83	0.001[a]

a. Kruskal Wallis-H Test, b. Chi-Square Test, c. Likelihood Ratio Test, d. Fischer's Exact Test, e. One Way ANOVA, f. Independent Samples t-test, SD: Standard Deviation, AFO: Ankle foot orthosis, KAFO: Knee foot orthosis, PAFO: powered ankle-foot orthoses, GMFCS: Gross motor function classification system, T-tau: Total tau protein, P-tau: phosphorylated tau protein, PSQI: Pittsburgh Sleep Quality Index

Table 2. Comparison of T-tau and P-tau levels between groups

Groups	T-tau***	p value		P-tau***	p value	
Group 1	11.19±7.12	0.001**		136.85±88.70	0.001**	
Group 2	8.79±3.59	0.001**	0.003*	105.79±29.20	0.001**	0.004*
Group 3	7.04±2.62	0.061**		88.51±12.27	0.062**	

*: Kruskal Wallis analysis of variance; **: Mann Whitney U test, ***: Mean and standard deviation (minimum-maximum), Group 1 was compared with Groups 2 and 3, it was statistically significant at the p=0.001 level; Group 2 and Group 3 were compared, not statistically significant, T-tau: Total tau protein, P-tau: phosphorylated tau protein

Table 3. Spearman's rho correlation analysis between PSQI between T-tau and P-tau for groups

PSQI	Group 1 (n=27)	Group 2 (n=27)	Group 3 (n=27)
T-tau	0.499*	-0.177	0.153
P-Tau	0.473*	-0.058	-0.189

* p< 0.05, T-tau: Total tau protein, P-tau: phosphorylated tau protein, PSQI: Pittsburgh Sleep Quality Index

DISCUSSION

CP represents one of the most common physical childhood disabilities worldwide.[16] Children with CP are a population at risk of developing sleep problems. While the prevalence rates reported by parents range from 23% to 46%, it ranges from 20% to 30% in healthy developing children.[17,18] The previous research showed that children with CP with more severe functional motor limitation, stiffness, and contractures, often characterized by bilateral spasticity, have more severe sleep disorders.[19] In this study, spasticity was found to be significantly higher in the group with sleep disorders. The studies by Romeo et al.[20] (with children with GMFCS level V) and Sandella et al.[21] revealed that GMFCS predicts sleep problems. Overlapping the findings in the literature, we found that the sleep disorders group had significantly higher GMFCS values than the without sleep disorders group.

Many comorbidities, such as vision, hearing or cognitive impairment often accompany motor disorders in CP.[5] Sleep problems are a common phenomenon in this population at 23-50% and are probably triggered by the mentioned CP comorbidities.[6-9] In our study, speech, vision and hearing disorders were significantly higher in the sleep disorders group than in the without sleep disorders group.

Tau is among the essential microtubule-associated proteins in neurons. Balanced phosphorylation binds it to microtubules, maintaining the coupling of microtubules and the structures and stability of neurons. Tau protein brings stability and plastic properties to the neuronal cytoskeleton, facilitating the formation of synaptic networks that underlie essential neurobiological functions.[22] On the other hand, hyperphosphorylation of tau protein leads it to aggregate and form paired helical filamentous structures known as neurofibrillary tangles.[23] The emergence of increased expression of its gene following brain ischemia raises hopes for a better understanding of the roles of tau protein, whose functions are not fully understood in the effects of ischemic diseases.[24] Besides, despite significant progress in recent research on the pathogenicity of tau protein following ischemia, the problems caused by impaired mechanisms resulting from tau protein after ischemia are unclear in children with CP.[7]

Sleep and rest refer to global states of control at all levels of biological organization, including genes, neural circuits, and brain systems.[25] The insomnia loop may be one of the best examples of self-organized operations in neuronal circuits and brain systems, requiring perfect synaptic coordination in multiple cerebral organizations. In mammals, sleep-wake sequencing and timing are regulated by circadian and homeostatic processes that contribute to one's sleep pattern.[26,27] Both processes require coordinated interaction between the suprachiasmatic nucleus and diencephalic structures, basal forebrain, and brainstem.[25] Thus, the emergence of such a complex circuitry requires both stable and plastic properties of the neuronal cytoskeleton promoted by tau protein in the early postnatal period. In addition, it was concluded that microtubules affect circadian activity patterns by modulating the sensitivity of different melatonin receptors.[28] There are many studies related to tau protein in sleep disorders. Evidence from animal models in the study by Di Meco et al.[29] suggested that changes in the sleep-wake cycle may increase levels of hyperphosphorylated tau protein in the brain. Winer and colleagues,[30] assessed associations of tau levels with sleep in older adults, comparing objective (wristwatch actigraphy) and subjective (PSQI) sleep measures over 1 week. Objective and subjective (PSQI) sleep disturbance was associated with higher tau levels. Benedict and et al.[31] study on 15 healthy men observed that serum tau protein levels increased from evening to morning in sleep loss. Work from Holth[32] and Lucey[33] and colleagues, demonstrated > 50% increased cerebral spinal fluid tau in healthy adults (30-60 years old) with one-night of sleep deprivation. As far as we know, our study will be the first study to examine the tau protein level measurement in CP and its relationship with sleep disturbance. In our study, T-tau and P-tau levels were found to be significantly increased in CP patients with sleep disorders. A significant relationship was observed between PSQI values and tau proteins, and taupatology was found to be important in sleep disorder.

There are some limitations to this study. First, we did not consider cerebrospinal fluid tau and phosphor-tau protein levels and neuroimaging in this study. In addition, since the literature does not host a similar study with patients with CP, we could not compare our results fully with what was previously found in the literature. We think that tau protein can be used as a marker as an indicator of sleep dysfunction in patients with CP. But, our findings need to be confirmed by further research.

CONCLUSION

This study shows that tau protein levels are higher in CP patients with sleep disorders than in participants without sleep disorders. In the correlation analyzes, a positive and significant correlation was observed between PSQI values and T-tau and P-tau in sleep disorders groups, and no correlation was found in without sleep disorders.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Medical Faculty Clinical Researchs Ethics Committee (Date: 19.08.2020, Decision No: 2020/171).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Comparison of infraclavicular block and axillary block activities performed in ultrasonography coexisting in upper extremity surgery

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ABSTRACT

Aims: Infraclavicular and axillary block performed with ultrasound guidance are effective peripheral anesthesia methods applied in upper extremity surgery. We aimed to compare these methods in terms of duration of the block and action, first analgesic requirement and side effects.

Methods: This prospective, randomized study was conducted for upper extremity surgery. 100 patients were included to perform infraclavicular block (Group 1, n=51) and axillary block (Group 2, n=49) USG guided. Patients are between 19 and 85 years old. Both groups were premedicated with 0.3 mg/kg midazolam or 0.5-1 µg/kg fentanyl. Both groups were treated with a mixture of local anesthetics in a total volume of 30 mL [7.5 mL 0.5% bupivacaine (Bustesin®, 56.25 mg), 7.5 mL 2% prilocaine (Priloc®, 225 mg) and 5 mL saline] was injected. Block placement time, motor and sensory tests, postoperative 2nd, 4th, 8th, 12th. and analgesic requirement at the 24th hour, Bromage scale, Verbal Rating scale, nausea vomiting, patient satisfaction, and block adequacy data were recorded.

Results: In this study, 60% of the participants included were male and 40% were female. The systolic, diastolic and mean arterial pressures were higher in group of axillary blockade than those with blockade of infraclavicular blocks. Radial, median, ulnar and musculocutaneous nerve pin-prick test loss and loss of touch test was more frequent in infraclavicular block patients. According to the Bromage scale, the partial block was seen more frequently in patients who had a close block and a full block infraclavicular block. In patients with the axillary blockade, sedoanalgesia and general anesthesia needs after postoperative intraoperative 20 min and postoperative sedoanalgesia was needed. According to the postoperative Bromage scale; complete and close to the thumb and more frequent in infraclavicular block patients. In Postop VRS, it was observed that the patients with the axillary block group had mild, moderate, and severe pain complaints. Patient satisfaction in the postoperative period was similar in both groups.

Conclusion: There is no significant difference between these techniques regarding surgical adequacy and subjective postoperative analgesia and dysesthesia. Complete and near-complete block rates in the infraclavicular block approach are minimally higher than in the axillary block approach.

Keywords: Upper extremity surgery, infraclavicular block, axillary block, USG

INTRODUCTION

The use of regional anesthesia techniques in orthopedic surgical operations continues to develop and become more popular. Regional anesthesia techniques can be used to provide effective and reliable analgesia in the postoperative period. Especially in the postoperative period, to be less costly, to shorten the length of stay in the hospital, to cause less physiological damage to all organs, to provide faster postoperative nausea, vomiting, aspiration, because of the many advantages of extubating strength. In addition, possible anesthesia complications such as malignant hyperthermia and long-term exposure to harmful effects of general anesthetic agents are reduced.[1-4]

The technique of needle nerve stimulation has been the standard method for about 30 years. However, in recent years, peripheral nerve block applications have become more popular with the use of ultrasound (USG) technology. Ultrasonics is a very high-frequency sound wave. These are divided into infrasound, audible sound, and ultrasonic according to the frequency. The use of envy began in the 1950s. Its first use in anesthesia was in

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1978 with the application of supraclavicular block. Since anesthetic agents can be safely applied in peripheral blocks performed under ultrasound guidance, these techniques are now widely used in extremity surgeries. The preference for peripheral nerve blocks has increased due to the relatively more invasive and traumatic nature of central blocks, the use of anticoagulants, and related contraindications and complications. Especially in extremity surgery, perioperative analgesia and anesthesia is another important factor.[5,6]

According to the patient, the plexus nerves can be blocked from any of the 5 anatomical regions such as interscalene, supraclavicular, infraclavicular, axillary and terminal nerves.[7-9] The brachial plexus, located in the infraclavicular region, provides the anatomical innervation of the region from the upper part of the axilla to the region covering the musculocutaneous nerve from the shoulder to the hand.[10] Therefore, the brachial plexus can be formed from the fingers to the shoulder on the upper extremity thanks to injections performed in the infraclavicular region.[11]

The perivascular approach is the easiest and most used technique in brachial plexus block (BPB) application. So, with an axillary approach, the radial, ulnar and median nerves are blocked at the same time in forearm, wrist, and hand surgery. For this reason, the axillary block provides the opportunity to perform surgery on the hand, forearm, and 1/3 distal part of the arm in the upper extremity.[12] The lack of complications such as central neural block and pneumothorax is one of the biggest advantages of being able to easily apply the other blocks to large patients who are difficult to carry out. In the axillary approach, the arm is abducted. This position complicates the application of the method. However, it provides a suitable anesthesia area for operations to be performed under the elbow. The presence of infection or tumoral structure at the injection site, factors that prevent abduction of the arm, and a history of mastectomy reduce the chance of success of the procedure.[13]

In this study, we aimed to compare the duration of block, onset time, duration of action, first analgesic requirement after surgery, onset time of motor block and side effects. USG guided infraclavicular and axillary block control in patients undergoing upper extremity surgery.

METHODS

The study was approved by the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.02.2014, Decision No: 498). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Between the ages of 19-85 and undergoing hand surgery, wrist and forearm surgery, totally 100 patients were included in the study. They were treated with USG guided infraclavicular block (Group I n=51) and axillary block (Group II n=49). The patients were randomly divided into two groups by the closed envelope technique. The two groups were compared in terms of application time, the block onset time, duration of action, time to first postoperative analgesic requirement, time to motor block removal and side effects. Patients who did not cooperate, were outside the specified age range, pregnant, infection at the injection area, had coagulation disorders, had any neurological deficit or have an allergy to local anesthesia were excluded from the study.

The patients were monitorised with electrocardiogram, SpO_2 and noninvasive blood pressure in the block application room and peripheral vascular catheter was inserted. Before the procedure, both groups received 0,3 mg/kg midazolam or 0,5-1 μg/kg fentanyl as premedication. All blocks were performed by two experienced anesthesiologists in USG-guided block exercises. Patients' blood pressures (systolic, diastolic, and mean arterial pressures), heart rate (HR) and peripheral oxygen saturation (SpO_2) values, block placement time, motor and sensory tests, postoperative 2^{nd}, 4^{th}, 8^{th}, 12^{th} and analgesic requirement at the 24^{th} hour, Bromage Scale (BS), Verbal Rating Scale (VRS), nausea and vomiting, patient satisfaction and block adequacy data were recorded.

Group I (Infraclavicular Block): This method was made according to the lateral sagittal infraclavicular block (LSIB) technique proposed by Klaastad et al.[10] Electrocardiography, SpO_2 and noninvasive blood pressure monitoring of the patient admitted to the supine position were performed. After the disinfection with povidone-iodine, the injection point was loosened at a 90° angle from the limb to the limb to be surgically loosened, as suggested by the LSIB technique. The patient's head was slightly inverted on the opposite side of the block.[10] The local anesthetic (LA) mixture was prepared with 7,5 mL of 0,5% bupivacaine (Bustesin®, 56,25 mg), 7,5 mL of 2% prilocaine (Priloc®, 225 mg), and 5 mL of saline and applied to the block area. During the process, Siemens® Sonoline (Germany) G20 USG machine and 10-18 MHz linear probe were used. Immediately after the axillary artery was visualized, the stimulation needle was directed to the posterior part of the artery in the same plane with the probe (in-plane technique).[10] The position of needle was confirmed by observing the rhythmic contraction movements of the hand and wrist with the neurostimulator. In order to avoid intravenous injection, 2 mL of LA mixture was injected to check whether there was an increase in heart rate. The rest of the drug mixture was injected with the intermittent aspiration to give a total of 20 mL. During LA application, "U" distribution was observed between 3 and 11 hours around the axillary artery with USG.

Group II (Axillary Block): Electrocardiography, SpO_2 and noninvasive blood pressure monitoring of the patient admitted to the supine position were performed. The patient's head is slightly turned to the opposite side. The stimulation needle to be used for the block was concurrently connected to the nerve stimulator (Stimuplex HNS 11, Braun Medical, Melsungen, Germany). The arm was abducted on the side to be operated at an angle of at least 90° with the body. The arm and forearm were flexed to 90° and the area to be blocked was sterilized. The injection site was determined with the nerve stimulator. After the blood was aspirated and no blood was seen, 20 mL volume of LA mixture [7,5 mL of 0,5% bupivacaine (Bustesin®, 56,25 mg), 7,5 mL of 2% prilocaine (Priloc®, 225 mg) and 5 mL of saline] was injected. During the process, 20 Gauge (G), 50 mm USG compliant needle, Siemens® Sonoline (Germany) G20 USG machine and a 10-18 MHz linear probe was used again. The high frequency linear probe was inserted transversely into the humerus. Radial, median, ulnar and musculocutaneous nerves around the axillary artery and vein were determined. Then, the stimulation needle was directed to the upper and posterior side of the axillary artery with the in-plane technique. Later, LA mixture was injected around median, ulnar or radial nerve. The distribution around the cord and axillary arteries were observed with USG during LA application.

Pin-prick Test: A scale that assesses the development of sensory loss in patients after block application.

0: No sensory loss,
1: Pin-prick test (loss of sensation)
2: Loss of touch test

Motor Block Start Time (Modified Bromage Scale): A scale that evaluates the development of the motor block after the patient has a value between 0-3.

0: No motor block (arm, forearm flexion complete)
1: Partial block (partial flexion at the heart, full flexion at the front)
2: Tama-close block (no arm flexion, reduced flexion in the forearm, moving fingers)
3: Full block (no fingers in arm and forearm, fingers in motion).

Verbal Rating Scale (VRS): A scale on that patients express their pain with a value between 0-4.

0: No pain,
1: Slight pain,
2: Moderate pain,
3: Severe pain,
4: Irritable pain.

The datas obtained from the research were analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0 statistics program. Descriptive statistics were summarized as mean±SD deviation, median, the minimum, maximum value for numerical variables, and numbers and percentages for categorical data. The Kolmogorov-Smirnow test checked normal dissociation suitability. Variance analysis was used in repeated measures to examine the difference between repeated measures in continuous variables. Chi-square and Fisher's exact test was used to assess the differences between the categorical variables. Statistical significance in the study was accepted as $p < 0.05$.

RESULTS

There were no statistically significant differences in terms of mean age, height, weight, ASA classifications, mean duration of application, and gender distribution in the groups during the study period. In addition, there was no statistically significant difference when we compared groups in terms of the duration of block application in our study.

Demographic characteristics and duration of administration were similar in both groups (**Table 1**). The duration of operation was significantly higher in Group I ($p=0.02$). When the mean arterial pressures were compared, it was found that Group II was generally higher than Group I. This difference was statistically significant ($F=3.63$, $p=0.006$). While the mean heart rate was analyzed, at Group II, it was observed that the measurements were generally higher than Group I ($F=7.885$, $p<0.001$). As the oxygen saturation was evaluated, it was found that at Group II, the measurements were similar ($F=2,961$, $p=0.14$) (**Table 1**).

Table 1. Demographic data of the groups and duration of application and operation (Mean±SD, %)

	Group1 (n:51)	Group 2 (n:49)	p
Age	42.70±14.80	41.30±17.34	0.66
Length (cm)	168.74±10.45	170.0±11.03	0.53
Weight (kg)	74.94±12.53	77.73±11.57	0.25
ASA	1.86±0.56	1.77±0.62	0.46
Application time (min)	4.21±1.87	4.85±2.23	0.12
Operation time (min)	71.73±36.79	56.93 ±23.38	0.02
Sex (K / E) (%)	45.1/54.9	34.7/65.3	0.28

According to the radial "pin-prick test" results of the groups; statistically significant difference was found between the percentage of sensory loss and the percentage of loss of touch between the groups at the 5^{th}, 20^{th}, 25^{th}, 30^{th}, 35^{th}, 40^{th} and 45^{th} minutes of the application. Corresponding to the results of the median "pin-prick test", a statistically significant difference was found between the percentage of sensory loss and the

percentage of loss of touch between the groups at the 5th and 10th minutes of the application. According to the results of the "pin-prick test" of ulnar, there was no statistically significant difference between the two groups in terms of the percentage of sensory loss and the percentage of loss of touch at the 0th, 15th, 20th, 25th, 30th, and 35th min. Based on the musculocutaneous "pin-prick test" was lost in 56.9% of patients in Group I and 24.5% of patients in Group II in the 5th minute of the procedure. So, this difference was significant (**Table 2**).

Table 2. Evaluation of radial, median and ulnar nerve pin-prick test results according to groups (%)

	Group 1 (n:51)		Group 2 (n:49)		p
	n	%	n	%	
Radial 20. min					<0.001
No sensory loss	5	9.8	26	53.1	
Pin-prick test loss	37	72.5	22	44.9	
Loss of touch test	9	17.6	1	2.0	
Median 5. min					<0.001
No sensory loss	19	37.3	37	75.5	
Pin-prick test loss	31	60.8	12	24.5	
Loss of touch test	1	2.0	0	0.0	
Ulnar 20. min					0.450
No sensory loss	8	15.7	12	24.4	
Pin-prick test loss	35	68.6	36	73.5	
Loss of touch test	8	15.7	1	2.0	
Musculoc utaneous 5. min					<0.001
No sensory loss	22	43.1	37	75.5	
Pin-prick test loss	29	56.9	12	24.5	
Loss of touch test	-	-	-	-	

Intraoperative analgesic requirements of the patients were evaluated at the beginning of the treatment, at 5th and 10th minutes. None of the patients in the groups needed analgesia. At the 15th, 20th, and 25th minutes of the procedure, sedoanalgesia didn't required both of groups. However, despite sedoanalgesia, general anesthesia was administered at 30th, 35th, 40th and 45th minutes in both groups. While BS results of the groups were examined; at the beginning of the procedure, the partial block was observed in 7,8% of patients in Group I. In Group II, partial block was observed in 4.1% of the patients and this difference was not statistically significant. Additionally, at 5th, 10th, 15th, 20th, 25th, 30th, 35th, 40th minutes, BS differed in percentages of partial block, the close-to-the-thumb block between and complete block percentages. However, this was not statistically significant in both groups. At the postoperative 2nd hour, 49.0% partial block, 19.6% the close-to-the-thumb block, and 9.8% complete block were seen in Group I. In Group, II 40.8% partial block, 16.3% close-to- the-thumb block were observed and this difference was significant (**Table 3**).

Table 3. Evaluation of preoperative and postoperative Bromage Scale results according to patients (%)

	Group 1 (n:51)		Group 2 (n:49)		p
	n	%	n	%	
0. min					0.67
No block	47	92.2	47	95.9	
Partial Block	4	7.8	2	4.1	
20. min					0.69
No block	1	2.0	1	2.0	
Partial Block	18	35.3	23	46.9	
Preoperative Period					
Tama-close block	23	45.1	18	36.7	
Full block	9	17.6	7	14.3	
45. min					0.29
No block	1	2.0	2	4.1	
Partial Block	12	23.5	19	38.8	
Tama-close block	26	51.0	21	42.9	
Full block	12	23.5	7	14.3	
2. hour					0.03
No block	11	21.6	21	42.9	
Partial Block	25	49.0	20	40.8	
Tama-close block	10	19.6	8	16.3	
Full block	5	9.8	0	0.0	
4. hour					0.09
No block	25	49.0	35	71.4	
Postoperative Period					
Partial Block	20	39.2	11	22.4	
Tama-close block	4	7.8	3	6.1	
Full block	2	3.9	0	0.0	
8. hour					0.35
No block	43	84.3	44	89.8	
Partial Block	6	11.8	5	10.2	
Tama-close block	2	3.9	0	0.0	
Full block	-	-	-		

There was no significant difference in postoperative analgesia requirements between the groups at the postoperative 2nd and 12th hours. But, at the 4th and 8th hours, analgesic requirements were significantly higher in Group II than Group I (p=0.01 and p <0.001) (**Table 4**).

Table 4. Evaluation of postoperative analgesia needs of the groups (%)

	Group 1(n:51)		Group 2 (n:49)		p
	n	%	n	%	
2. hour					0.53
No	50	98.0	47	95.9	
Yes	1	2.0	2	4.1	
4. hour					0.01
No	46	90.2	35	71.4	
Yes	5	9.8	14	28.6	
8. hour					<0.001
No	41	80.4	23	46.9	
Yes	10	19.6	26	53.1	
12. hour					0.95
No	47	92.2	45	91.8	
Yes	4	7.8	4	8.2	

When the groups were evaluated in terms of postoperative VRS results; there was a statistically significant difference between mild pain, moderate pain, and severe pain frequency between the groups at the 8th hour (p= 0.01). These complaints were seen more frequently in Group II (**Table 5**).

Table 5. Evaluation of postoperative Verbal Rating Scale results of patients according to groups (%)

VRS	Group1 (n:51)		Group 2 (n:49)		p
	n	%	n	%	
2. hour					0.35
No pain	49	96.1	46	93.9	
Mild Pain	1	2.0	3	6.1	
Severe Pain	1	2.0	0	0.0	0.06
No pain	45	88.2	34	69.4	
4. hour					
Mild Pain	5	9.8	10	20.4	
Severe Pain	1	2.0	5	10.2	
8. hour					0.01
No pain	37	72.5	20	40.8	
Mild Pain	11	21.6	20	40.8	
Middle-Grade Pain	3	5.9	8	16.3	
Severe Pain	0	0.0	1	2.0	
12. hour					0.07
No pain	45	88.2	44	89.8	
Mild Pain	2	3.9	5	10.2	
Middle-Grade Pain	4	7.8	0	0.0	

In addition, there were complaints of nausea and vomiting in the patients at postoperative 2nd, 4th and 8th hours. Postoperative nausea and vomiting complaints were seen in one patient (2,0%) in Group II at 12th hour and this difference was not statistically significant (chi-square=1,051 p=,89). No statistically significant difference was found between the groups when postoperative patient satisfaction was assessed at 2nd, 4th, 8th, and 12th hours.

When the satisfaction of the surgeons was examined, 78.4% of the infraclavicular block was very satisfied according to 65.3% of the axillary block application. But this difference was not statistically significant (Chi-square=2,350 p=0,30).

DISCUSSION

Peripheral nerve blocks are a procedure performed to allow surgical interventions and provide analgesia by administering LA to the peripheral nerve or ganglion. Peripheral nerve blocks are used in a wide area for anesthesia, medical treatment, postoperative analgesia and pain therapy purposes.1 In addition, the trend towards less invasive techniques in anesthesia practice has led to an increased interest in peripheral nerve blocks.[12]

Nowadays, it is accepted that BPB is an effective method that can be used safely for anesthesia or analgesia in upper extremity surgeries. This method is widely used with the axillary approach because the neurovascular envelope in which the local anesthetic drug is distributed is far from the vital organs, the risk of complications is low, and it can be applied easily. In this study, infraclavicular block and axillary block methods, which are regional anesthesia techniques used in upper extremity surgery, were used.[13,14]

With the use of USG in peripheral nerve block approaches, imaging of the needle tip, nerve localization and local anesthetic injected area distribution can be observed. In addition to this, patient comfort is increased by decreasing the number of needle passes. When the complication rate is reduced in USG-guided blocks, the success rate is increased.[15-17] However, the USG guideline shortens the block performance period, the number of trial and the block starts time. Also, the block can be performed using lower LA doses.[18,19]

In our study, peripheral nerve block applications were performed in the presence of USG and neurostimulator. In this regard, the literature does not show any superiority between the groups using USG and neurostimulators for infraclavicular block.[20] However, the duration of administration was shorter in the USG group.[21-23] In a study, Sauter et al.[21] randomly divided 80 patients into USG and neurostimulation groups for lateral sagittal infraclavicular block (LSIB) application. They found no statistically significant difference in the comparison of success rates, application times, sensory block formation times and patient satisfaction related to the block procedure in their studies (p>0.05). In addition to this, it is the most important advantage of the USG-guided blocks to display not only target tissues but also neighboring anatomical organ at risk.[24]

Sandhu et al.[25] in their study in 2006, retrospectively evaluated 1146 adult patients who underwent USG-guided infraclavicular block. They found a success rate of approximately 100% when USG was used alone and applied around all three cores.[20] Ootaki et al.[26] in their study with 60 patients, they provided 100% complete block in the musculocutaneous nerve with USG-guided infraclavicular block. On another study, Sauter et al.[21] found that the success rate of LSIB application was 85% in neurostimulation technique and 95% in USG use. In the studies evaluating supraclavicular block, USG has also been found to be more successful, safety and shorter application time compared to the neurostimulator. It has been concluded that not only the technique, but also the experience of the practitioner, the type and amount of LA, anatomical differences and obesity in the patient are effective for successful block.[26,27]

However, in a study, there was a statistically significant difference between the administration times of infraclavicular block (n=11, duration=622±139 sec) and axillary block (n=11, duration=789±131 sec).28 In addition, in the study of Tran et al.[29] 70 patients were randomized to receive USG guided infraclavicular block using double bubble sign or axillary block with triple-stimulation. The axillary block method was significantly longer than in the infraclavicular block method (p <0.001).

Heid et al.[15] compared vertical blocks of infraclavicular plexus (n=30) and blocks of high axillary plexus (n=30) in their study. The patient underwent sensory testing at intervals of 15 minutes, and analgesia and development of anesthesia were investigated for the radial nerve, 80% of the vertical infraclavicular plexus group achieved anesthesia after 30 minutes, whereas 36.7% of the high axillary plexus group achieved anesthesia and a statistically significant difference was found (p <0.005). There was no significant difference between the groups when compared for ulnar sensory loss. Similarly, in the study of Heid et al.[15] no difference was found in the sensory test for the ulnar nerve. However, in the study of Heid et al.[15] a significant difference was found between the vertical infraclavicular plexus (70%) and the high axillary plexus (34%) blocks only at the 15th minute of the sensory test for the musculocutaneous nerve (p <0.05).

There was no statistically significant difference for BS in all measurements between the groups in terms of the partial block, proximal block, and complete block percentage. In addition, both block formation and block administration durations were found to be similar between the infraclavicular block and supraclavicular block approach in Gurkan[24] and colleagues studying 110 patients in two groups. In the study of Song et al.[28] patients with axillary and infraclavicular block were examined for motor loss rates of 1 to 5 days (5=normal, 1=full paralysis) during the interval of 0 to 30 minutes. Only the motor loss ratios of the musculocutaneous nerve at the 0 and 5 min were significantly higher than the axillary blunt infraclavicular block.

The sensation of pain, nausea, and vomiting in patients with regional anesthesia is undesirable to anesthesiologists.[30] In our study, no statistically significant difference was found in the complaints of nausea and vomiting in the groups. However, patients who underwent infraclavicular block had faster recovery times, lower pain scores, quadruple nausea, and fewer hospital discharge than patients receiving general anesthesia.[31]

When postoperative analgesic requirements of the groups were compared, it was significantly higher in group II than group I at the 4th and 8th hours. Tran et al.[29] randomized 70 patients to receive USG guided infraclavicular block using double bubble sign or axillary block with triple stimulation. They found that the need for analgesia was 5 (14%) and 8 (23%) patients, respectively.

There was no statistically significant difference in VRS between the groups at postoperative 2nd, 4th, and 12th hours in our study. However, in the infraclavicular block group at the 8th hour postoperatively, 21.6% of the patients had mild pain, 5.9% had moderate pain. The group applied axillary block, 40.8% of the patients had mild pain, 16.3%, and severe pain at 2.0% was observed and this difference was statistically significant. In a study comparing the lateral vertical infraclavicular plexus block with the axillary plexus block in 40 children between 1 and 10 years of age, Fleischmann et al.[14] used the Visual Analogue Scale (VAS) (1-5 points corresponding to the face expression) for pain recipe and between two treatment groups no significant difference was observed between VAS values before pneumonectomy, during pneumonectomy, and after 30 minutes after pneumonia.

The first general anesthesia was applied in Group II at the 30th minutes (4 patients, 8,16%) and in Group I at the 40th minutes (2 patients, 3.92%). Sandu et al.[32] also reported that 114 patients underwent general anesthesia in 3 patients (2.4%) in their study of infraclavicular block administration in the presence of USG.

CONCLUSIONS

In our study, there was no significant difference in terms of duration and block characteristics of the USG-guided infraclavicular block method and the axillary block method. However, the infraclavicular block method is more advantageous in terms of analgesia requirements during and after the operation. When the satisfaction of the surgeon was examined, there was no statistically significant difference between the groups. In addition, complete and near-complete block ratios in the infraclavicular block method are minimally higher than in the axillary block method. As a result, interest in the use of USG in regional anesthesia applications is increasing rapidly. The reason for this is that the success rate is higher and the complication rate is lower in USG-guided blocks.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.02.2014, Decision No: 498).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Adnexal torsion: a single-center retrospective study of diagnosis and treatment

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ABSTRACT

Aims: This study was conducted to review the clinical, laboratory, and ultrasound findings of patients with a confirmed post-operative adnexal torsion diagnosis in a tertiary university hospital and to reflect the management of adnexal torsion.

Methods: 44 patients (ages [15,44] with a median of 30 yr) who had an operation at Ankara University Hospital Gynecology and Obstetrics Clinics between October 2013 and February 2021 and in whom the preoperative diagnosis of adnexal torsion was confirmed intraoperatively were included in this retrospective study. Patients' complaints, existing risk factors, physical examination, laboratory, and radiological findings were evaluated.

Results: 26 (65%) of the patients complained about acute abdominal pain isolated on one side. Torsion was observed on the right side in 29 (66%) patients. Risk factors: History of ovarian torsion in 1 patient (2%), in vitro fertilization treatment in 5 (11%) patients, 4 (9%) of which also had ovarian hyperstimulation syndrome and 2 (5%) of them had polycystic ovary syndrome, and finally, 28 (65%) patients had increased ovarian size on ultrasound. Ovarian blood flow was not observed in 25 (81%) of 31 patients who underwent transvaginal Doppler ultrasound. Preoperative blood examination showed anemia (Hb<12 g/dL) in 14 (32%), leukocytosis (>10000/mm^3) in 26 (59%), and an increase of neutrophil-lymphocyte ratio (NLR) (>3) in 36 (82%). Laparoscopy was performed in 37 (84%) patients and laparotomy in 7 (16%).

Conclusion: There is no objective diagnostic tool that can definitively lead to the diagnosis of adnexal torsion. It may be recommended to use ultrasound, Doppler, and NLR in addition to clinical findings and anamnesis. Considering the consequences of delay in the treatment, the most appropriate approach would be to perform a laparoscopy if torsion is suspected. Additionally, the patient's age, menopausal status, ovarian pathology, and desire for fertility are factors that should be considered in the treatment decision, and ovarian protection should be the primary goal.

Keywords: Adnexal torsion, laparoscopy, ovary, ultrasound, neutrophil-lymphocyte ratio

INTRODUCTION

Adnexal torsion is caused by complete or partial rotation of the ovary and fallopian tube in the axis between the infundibulopelvic ligament and the utero-ovarian ligament, which can occur in women at any age but most often occurs in reproductive ages. It is one of the few gynecological surgical emergencies, and misdiagnosis or delays in treatment can result in peritonitis, ovarian loss, and even death. Since the diagnosis is made definitively only during surgery, the true incidence is unknown, and some patients may be misdiagnosed because they are not operated. However, the annual prevalence is about 2 to 6%,[1] and it is estimated that about 3% of patients admitted to the emergency department with acute abdominal pain have adnexal torsion.[2]

Common symptoms of adnexal torsion are pain, nausea, and vomiting with abdominal or pelvic pain, although symptoms may differ in premenarchic and pregnant patients. Imaging diagnostic tools, including Doppler analysis, magnetic resonance imaging, computed tomography, and laboratory findings, may be useful in diagnosis but should not overshadow clinical judgment. Normal Doppler flow can be seen in up to 60% of adnexal torsion cases.[3]

The main goal of treatment is to preserve ovarian function where detorsion is the recommended course of action to achieve this goal. Recent evidence indicates that normal ovarian function is restored after detorsion even in the presence of blue-black discoloration, so excision is only recommended when there is obvious gelatinous necrosis.[4,5]

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Despite extensive research, preoperative diagnosis of adnexal torsion is challenging. This study was conducted to review the clinical, laboratory, and ultrasound (US) findings of patients with a confirmed post-operative adnexal torsion diagnosis in a tertiary university hospital and to reflect the management of adnexal torsion.

METHODS

The study was initiated with the approval of the Ankara University Medical Faculty Clinical Researches Ethics Committee (Date: 10.05.2023, Decision No: İ04-274-23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, patients who were operated at Ankara University Hospital Gynecology and Obstetrics Clinics between October 2013 and February 2021 and diagnosed intraoperatively with adnexal torsion were included. Women with a suspected diagnosis of torsion on ultrasound that are not confirmed by surgery and asymptomatic patients who underwent surgery for other reasons and were diagnosed intraoperatively with torsion were excluded from the study. Preoperatively, the diagnosis of adnexal torsion was made with or without sonographic concordance with clinical suspicion.

Data regarding patient age, infertility treatment, previous torsion episodes, clinical features, laboratory findings, preoperative pelvic ultrasound findings, transvaginal Doppler US examinations, course of the operation, and histological findings were obtained from electronic medical records and case files. An ultrasonographic evaluation was performed by gynecologists (resident/specialist physicians). Data were entered into an MS Excel spreadsheet and frequency and median values were calculated.

RESULTS

Forty-four patients were included in the study who were operated and diagnosed with adnexal torsion. Nine of the cases (20%) occurred during pregnancy. The ages of the patients ranged from 15 to 44, with a median of 30 years.

While 26 (65%) patients presented with the complaint of acute abdominal pain isolated on one side, it was followed by widespread abdominal pain in four (13%) patients and inguinal pain in one (3%) patient. One of the patients complained of vomiting as well as abdominal pain.

As risk factors, history of ovarian torsion in 1 (2%) patient, in vitro fertilization (IVF) treatment in 5 (11%) patients, 4 (9%) of the patients with IVF treatment also had ovarian hyperstimulation syndrome (OHSS), in 2 (5%) patients polycystic ovary syndrome (PCOS), and in 28 (65%) patients an increase in ovarian size were observed on US. The median of cyst sizes ranging from 3.3 cm to 20 cm was calculated as 5.15 cm. Of the cysts seen, 10 (48%) were classified as simple, 8 (38%) hemorrhagic, 1 (5%) endometrioma, and 2 (10%) complex cysts. Two cysts, which were defined as complex cysts on ultrasound, were diagnosed as mature cystic teratoma after the pathological examination.

Free fluid was observed in 7 (16%) patients, hydrosalpinx was observed in 9 (20%) patients in the preoperative US, and the absence of ovarian blood flow was observed in 25 (81%) of 31 patients who underwent Doppler examination.

Anemia (Hb <12 g/dl) in 14 (32%) patients, leukocytosis (>10,000/mm^3) in 26 (59%) patients, and increased neutrophil-to-lymphocyte ratio (NLR) (>3) in 36 (82%) patients were observed in blood tests before surgery.

Laparoscopy (L/S) was performed in 37 (84%) patients and Laparotomy (L/T) was performed in 7 (16%) patients. L/T was preferred due to pregnancy in two of the 7 patients, one had a 20 cm cyst on ultrasound, and the remaining four had a history of laparotomy. Torsion was observed on the right side in 29 (66%) patients and on the left side in 15 (34%) patients. Detorsion was performed in 42 (95%) patients, and cyst extirpation and detorsion were performed in 2 (5%) patients. Salpingoopherectomy was not performed in any patient. The median value for the operation time was 40 minutes, and the median value for the postoperative observation time was 2 days. No postoperative complications, including pulmonary embolism, were observed in any of the patients. Of the 9 patients who were operated during pregnancy, two underwent L/T and seven had L/S. Four of the pregnant women were in the first trimester, four were in the second trimester and one was in the third trimester. The two pregnant women who underwent laparotomy were in the 32nd and 15th weeks of pregnancy.

Table 1. Laboratory and radiological findings in the study group

Preoperative Findings	Count (%)
Initial symptom	
Unilateral lower quadrant pain	26 (84)
Diffuse abdominal pain	4 (13)
Groin pain on the left	1 (3)
Anemia (Hb<12 gr/dL)	14 (32)
Leukocytosis (>10000/mm^3)	26 (59)
NLR (>3)	36 (82)
Free fluid on US	7 (16)
Hydrosalpinx on US	9 (20)
Pathological Doppler flow	25 (81)

NLR: Neutrophil-lymphocyte ratio; US: Ultrasound

Table 2: Risk factors in cases with adnexal torsion	
	Count (%)
Pregnancy	9 (20)
Infertility treatment	5 (11)
PCOS	2 (5)
Adnexal torsion history	1 (2)
OHSS	4 (9)
Increase in ovarian size on US	28 (65)
Accompanying cyst on US	21 (48)
Cyst Type	
Simple	10 (48)
Hemorrhagic	8 (38)
Endometrioma	1 (5)
Complex	2 (10)
Cyst Localization	
Unilateral	21 (100)
Contralateral	0
Bilateral	0

PCOS: Polycystic ovary syndrome; OHSS: Ovarian hyperstimulation syndrome; US: Ultrasound

Table 3. Surgical procedures	
	Count (%)
Operation Type	
Laparoscopy	37 (84)
Laparotomy	7 (16)
Torsion localization	
Right	29 (66)
Left	15 (34)
Operation	
Detorsion	42 (95)
Right/left salpingo-oophorectomy	0
Cyst extirpation and Detorsion	2 (5)

DISCUSSION

Torsion is usually associated with an ovarian cyst in women with moderately increased ovarian size. 46% of cases of torsion occur in normal-sized ovaries,[6,7] whereas it is less common in significantly enlarged ovaries. This is because enlarged ovaries tend to descend and prevent torsion. In our study, an increase in ovarian size was observed in 28 (65%) of 44 patients who underwent US. Three of the patients with an increase in ovarian size were treated with IVF and five were pregnant. Cysts associated with torsion commonly include corpus lutei, follicular cysts, cystadenomas, and benign cystic teratomas. Malignant lesions are relatively rare causes (approximately 2%) of torsion cases.[8] Our data also showed a similar picture, with 10 (48%) classified as simple, 8 (38%) as hemorrhagic, 1 (5%) as endometrioma, and 2 (10%) as complex cysts. Two cysts, defined on ultrasound as complex cysts, were diagnosed as mature cystic teratomas on pathologic examination.

Consistent with the literature,[2] our study showed a higher incidence of torsion cases in the right relative to the left ovary (66%-32%). An adnexal torsion on the right side was seen in seven out of nine pregnant patients (about 78%). This is probably due to the proximity of the left ovary to the relatively stable sigmoid colon compared to the hypermobility of the right cecum and ileum.

History of adnexal torsion and tubal ligation, polycystic ovary syndrome, ovulation induction, ovarian hyperstimulation syndrome, and pregnancy have been shown as risk factors for adnexal torsion.[9] In our study, pregnancy was reported in 9 (20%) patients, infertility treatment in 5 (11%), PCOS in 2 (5%), torsion history in 1 (2%), and OHSS in four of the five patients who received IVF treatment.

A comprehensive medical history and physical examination are the two most important components of the diagnosis. Isolated acute abdominal pain (90-100%) on one side is the most common symptom in women with adnexal torsion.[3] This pain, resulting from occlusion of the vascular pedicle followed by hypoxia, can be described as constant or intermittent, as the ovary can torsion and detorsion over time, which can begin with a sudden change in position or activity. The venous and lymphatic systems are usually affected first because they are low-pressure systems.[10] In our study, 84% of patients had isolated abdominal pain, 13% had diffuse abdominal pain, and 3% had groin pain. In addition, one of the patients complaining of abdominal pain also complained of vomiting. Nausea (70%), vomiting (45%), fever (20%), and flank pain are among the symptoms reported in the literature.[6,7] If the torsion is prolonged, the adnexa may become necrotic or even infected, while the patient may show signs of peritonitis.[10] Findings on physical examination include normal body temperature to low-grade fever (18%),[7] mild tachycardia, and high blood pressure accompanying severe pain. Lower abdominal tenderness is usually unilateral but may spread to the side. However, in a broad retrospective study, up to 30% of patients reported a lack of pain on examination although confirmed later to have intraoperative torsion.[11]

Laboratory and imaging examinations can be used as diagnostic aids, but clinical assessment should not be overshadowed. Numerous studies have demonstrated how difficult it is to accurately diagnose adnexal torsion preoperatively since the symptoms and signs can be similar to several other diagnoses, and the diagnosis is confirmed laparoscopically in approximately 10% to 44% of patients.[1,12-14]

Ectopic pregnancy should be ruled out. Most laboratory findings are normal, although mild leukocytosis can be seen in 27% to 50% of patients.[6,7] The C-reactive protein (CRP) value and white blood cell count are usually lower than in acute appendicitis.[15] However, in one of our cases, in the 28th week of pregnancy with a CRP level of 21.8 mg/l, appendicitis could not be ruled

out preoperatively. In case of doubt, general surgical consultation is recommended. Mild leukocytosis and anemia were observed in 59% of the patients in our study, and NLR was increased in 82% of the patients. In a retrospective study, it was shown that NLR is increased in torsion patients.[16] In this study where patients with surgically proven torsion were compared with patients who were operated for non-malignant ovarian masses, the sensitivity of NLR was calculated as 88.9% and the specificity as 100%.

Pelvic ultrasonography with or without Doppler analysis is the most frequently used imaging tool in adnexal torsion diagnosis. Common findings of pelvic ultrasonography include unilateral ovarian enlargement, ovarian mass, uniform peripheral cystic structures, and free fluid in the Douglas.[15] Consistent with the literature in our study, free fluid was observed in 16% of patients, hydrosalpinx in 20%, unilateral ovarian enlargement in 65%, and cystic structures in 48% of patients.

There are conflicting views in the literature on the use of color Doppler analysis. In a retrospective study of intraoperatively proven cases of adnexal torsion, it was shown that the absence of venous Doppler flow had a high positive predictive value of 94% for ovarian torsion.[7] However, it was shown that arterial Doppler flow was maintained in up to 60% of patients with torsion.[2,7,17] In our study, the pathological flow was observed in 81% of the patients who underwent Doppler, which might be used as a good diagnostic tool according to our results.

Adnexal torsion is a gynecologic emergency, and the most common treatment is laparoscopic detorsion of the adnexa. Most cases of torsion were managed by adnexectomy, as it was previously thought that detorsion in adnexal torsion could cause a vascular embolism.[10] However, this has proven to be untrue. In a review of more than 1000 cases of torsion, McGovern et al.[18] showed a 0.2% risk of pulmonary embolism in cases both with and without adnexal detorsion.[6] Even if the ovary appears macroscopically black-blue intraoperatively, most (90%) ovaries show normal appearance in second look operation with normal follicular development on ultrasound, and normal Doppler flow, after only 6 weeks.[3] In our study, L/S was performed in 37 (84%) patients and L/T was performed in 7 (16%) patients. Detorsion was performed in all patients, as recommended in the literature, and salpingo-oophorectomy was not performed in any of the patients. The median value for the operation time was 40 minutes, and the median value for the postoperative observation time was 2 days. No postoperative complications, including pulmonary embolism, were observed in any of the patients, supporting the laparoscopic detorsion as the best therapy option.

Maintaining ovarian protection as the primary goal, patient's age, menopausal status, ovarian pathology, and desire for fertility are factors that should be considered in the treatment decision. There are two options for treatment, conservative and definitive. Conservative treatment corresponds to detorsion of the adnexa and aspiration of associated cysts or opening and removing associated cysts. Since torsion causes edema, some authors recommend only detorsion of the adnexa and postoperative follow-up with ultrasonography to determine if cystectomy is necessary.[3] Due to the loss of tissue layers, a cystectomy can be challenging. On the other hand, if the cyst is not removed, there is a risk of retorsion and additional surgical intervention.

Definitive treatment includes salpingectomy and/or oophorectomy. In decision-making, the time from the onset of pain to surgery has been suggested as a marker of necrosis, rather than ovarian appearance, although this time varies across studies.[3] Although malignancy-related torsion is uncommon (2% of torsion cases), this possibility should also be considered in decision-making.[3]

It has been reported in the literature that up to 25% of cases of torsion occur during pregnancy.[3] In our study, 20% (9) of the patients were pregnant. Most cases of torsion were reported in the first or second trimester and only 5% were observed after 20 weeks of gestation. The most common pathological conditions are mature cystic teratomas, followed by corpus lutei and para tubal cysts, respectively.[3] In our study, mature cystic teratoma was diagnosed in two pregnant women. Ultrasound may not show the same findings as torsion in a non-pregnant patient. As the follicle-stroma ratio increases in multifollicular ovaries, the edematous appearance of the stroma may be absent, and the ovaries may be characterized as normal.[19] Also, as pregnancy progresses, the ovaries become harder to visualize. Torsion treatment for the pregnant is the same as for non-pregnant patients. In our study, L/S was applied to seven of nine pregnant women and no complications were observed in the postoperative follow-up. In the operating room, especially in the third trimester, the patient should be tilted to the left to avoid compression of the inferior vena cava. Laparoscopy can be performed in all trimesters,[20] and all access methods can be used. For optimal visualization, it is recommended to stay a few centimeters above the fundus. The pregnant woman should be informed about the risk of premature birth, miscarriage, and premature rupture of membranes. The benefits of laparoscopy is similar in pregnant and non-pregnant patients.[3] In the case of surgery in the first trimester, the administration of supplemental progesterone is recommended, so all our patients received progesterone in the first semester.

A patient with an early pregnancy (only gestational sac was visible on preoperative ultrasound) suffered from miscarriage after the surgery.

CONCLUSION

In summary, it may be recommended that in addition to clinical findings, medical history, transvaginal ultrasound and Doppler, the neutrophil-to-lymphocyte ratio can be used as an additional marker in the diagnosis. Considering the consequences of delay in the treatment of adnexal torsion, the most appropriate approach would be to perform a laparoscopy if torsion is suspected. A laparoscopy can be performed in all trimesters. Supplemental progesterone in the first trimester is recommended. Maintaining ovarian protection as the primary goal, patient's age, fertility desire, menopausal status, and ovarian pathologies are factors to be considered in the management decision.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Ankara University Medical Faculty Clinical Researches Ethics Committee (Date: 10.05.2023, Decision No: İ04-274-23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

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The relationship between the prognostic nutritional index and non-dipping blood pressure pattern in patients with newly diagnosed hypertension

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ABSTRACT

Aims: It has been suggested that immuno-nutritional status may play a role in blood pressure (BP) variations. This study aimed to investigate whether prognostic nutritional index (PNI) values differ between normotensive individuals and patients with newly diagnosed untreated hypertension (NDHT) and to clarify the relationship between the PNI and circadian BP patterns in NDHT patients.

Methods: This retrospective study included 328 adult participants, comprising 164 NDHT patients and 164 normotensive individuals. The non-dipper BP pattern (NDP) was defined as a nighttime decline in BP of less than 10%. The PNI was calculated using the following formula: PNI=([10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count]).

Results: The mean PNI value was lower in the NDHT group than the normotensive group (53.6±6.1 vs. 58.2±5.3, p<0.001). There was a positive correlation between the PNI and the decline in nighttime BP levels (r=0.517; p<0.001). NDP was identified in 45.1% (n=74) of the NDHT patients. The mean PNI value was lower in the NDP group compared to the dipper BP group (49.9±5.6 vs. 56.6±4.8, p<0.001). Decreased PNI was an independent predictor of NDP (OR=0.70, 95% CI=0.61-0.81, p<0.001). The cut-off value of the PNI in predicting NDP was established as ≤51.3 with 72.4% sensitivity and 69.8% specificity.

Conclusion: Patients with hypertension had poorer immuno-nutritional statuses and a low PNI value was an important predictor of NDP. The PNI may be a useful screening tool for circadian BP patterns in patients with NDP.

Keywords: Circadian rhythm, hypertension, nutritional status, prognostic nutritional index

INTRODUCTION

The circadian rhythm of metabolism causes differences in blood pressure (BP) levels throughout the day.[1] The non-dipper BP pattern (NDP) is defined by a reduction of less than 10% in BP levels during sleep relative to daytime BP levels,[2] and it is associated with an increased risk of cardiovascular events.[3] The precise factors contributing to the impairment of circadian BP variations are not yet fully understood. However, several mechanisms have been proposed, including autonomic nervous dysfunctions, systemic inflammation, and insulin resistance.[4,5]

Nutritional status is closely related to potential mechanisms involved in the pathogenesis of hypertension.[6-8] Experimental studies have shown that nutritional factors play a role in modulating peroxisome proliferator-activated receptor-gamma (PPARγ), which is involved in increasing insulin sensitivity, differentiating lipid metabolism, and activating the renin-angiotensin- aldosterone system (RAAS).[9-11] Additionally, it has been shown that inadequate nutrition is associated with the modulation of glycemic, hormonal, and cytokine parameters.[12] This can also lead to an inflammatory response, resulting in leukocyte activation.[13] The activation of T and B lymphocytes leads to the induction of reactive oxygen species and cytokines, which in turn contribute to elevated BP levels.[14,15] Many studies have shown that insulin resistance and inflammation, characterized by increased cytokine release and activation of RAAS, are associated with variations in BP levels.[16-20] Therefore, poor nutrition may be an important mechanism underlying the factors that contribute to variations in BP levels.[21] The prognostic nutritional index (PNI), a surrogate marker of immunological nutritional and systemic inflammation status, is a simple and cost-effective combined score calculated from serum albumin value

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and lymphocyte count.[22] Low PNI levels are indicative of malnutrition.[23] Previous studies have shown that low PNI is associated with resistant hypertension, cardiovascular diseases, and cardiovascular events.[24-27] However, the relationship between the PNI and circadian BP patterns in patients with newly diagnosed untreated primary hypertension (NDHT) has not yet been investigated.

Given the impact of the aforementioned mechanisms of nutritional status on BP variations, we hypothesized that the PNI could be an important indicator of NDP. This study aimed to investigate whether PNI values differ between normotensive individuals and NDHT patients and to investigate the relationship between the PNI and circadian BP patterns in NDHT patients.

METHODS

The study was initiated with the approval of the Bursa City Hospital Clinical Research Ethics Committee (Date: 04.01.2023, Decision No: 2023-1/9). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This research was planned as a single-center retrospective study between December 2020 and December 2022 in the Cardiology Clinic of Bursa City Hospital. Due to the retrospective design, the ethics committee that approved the study deemed it appropriate to waive the need for informed consent.

Study Population

A total of 1060 patients over the age of 18 years who were diagnosed with NDHT were retrospectively evaluated. The inclusion criteria were NDHT with complete ambulatory BP monitoring (ABPM) data and no comorbidities. The exclusion criteria were previously documented hypertension, history of diabetes mellitus, cardiovascular diseases such as coronary artery disease, coronary revascularization, myocardial infarction, angina pectoris, or heart failure, history of peripheral artery disease, history of any systemic inflammatory or autoimmune diseases, coronavirus disease 2019, inflammatory bowel diseases, rheumatic diseases, malignancy, liver or kidney disease, presence of nephrotic proteinuria, cerebrovascular disease, dementia, clinical depression, eating disorders, obesity, use of antioxidants or lipid-lowering agents, metabolic syndrome, thyroid disease, pregnancy or delivery in the last 90 days, lactation and missing clinical data. After the exclusion criteria were applied, 164 NDHT patients and 248 normotensive individuals who met the inclusion criteria were included in the study. The control group was selected from normotensive individuals. Considering the age, gender, and body mass index (BMI) of the patients included in the study, a normotensive control group was formed with propensity score matching using the 1:1 nearest-neighbour matching method. Finally, 164 NDHT patients and 164 normotensive individuals were included in the study.

The hospital's electronic information system and patient files were used to gather demographic and clinical data.

Laboratory Measurements

Blood samples were collected at the time of hospital admission and measured with a Beckman Coulter LH 780 device (Mervue, Galway, Ireland). Levels of hemoglobin (photometrically), platelets (impedance method), C-reactive protein (CRP) (immunoturbidimetric method), albumin (bromocresol green method), triglycerides and total cholesterol (enzymatic colorimetric method), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetric method) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C) (28). PNI values were calculated according to the following formula: PNI=([10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count]). Triglyceride-to-glucose (TyG) index values were calculated using the following formula: TyG=ln [fasting triglyceride (mg/dL) × fasting glucose (mg/dL)]/2.

In-office BP Measurements

All participants rested for 5 minutes after hospital admission before BP measurements were performed. Their BP levels were subsequently measured 3 times at 5-minute intervals using an Omron M3 sphygmomanometer (Omron Healthcare, Japan). All measurements were averaged.

Ambulatory BP Monitoring

A Tonoport V device (PAR Medizintechnik, Berlin, Germany) was used to perform 24-hour ABPM. Data from the first hour of monitoring were not included in the analysis. BP readings were automatically recorded at 15-minute intervals over 24 hours. Recordings were only included in the analysis if more than 85% of the raw recordings were valid. The pure reduction and percentage reduction in systolic BP for the nighttime-to-daytime period were assessed. Bedtime was determined from the patients' diaries, which documented the time of going to bed and getting up. Nighttime BP levels following bedtime were evaluated from the ABPM records. Average BP levels for the remainder of the 24-hour period were evaluated as daytime BP. Diastolic BP plus 1/3 of the pulse pressure was assessed as the mean BP. The decline in nighttime BP (%) was calculated using the following formula based on average values: (daytime BP-nighttime BP/daytime BP × 100). NDP was defined as a <10% decline in nighttime BP.

The definition of hypertension was based on the 2018 guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH).[29]

Statistical Analysis

IBM SPSS Statistics for Windows 20.0 (IBM Corp., USA) and Medcalc 11.4.2 (MedCalc Software, Belgium) programs were utilized in the analysis of all data obtained in this study. In light of the results of the Kolmogorov-Smirnov test, numerical data with normal distribution were identified and presented as mean±standard deviation, while data found to have non-normal distribution were presented as median values with interquartile ranges. For comparisons between groups, Student's t-test and Mann-Whitney U test were used based on the normal distribution of numerical data. Categorical variables were provided as numbers and percentages, and comparisons between groups were conducted using the Chi-square test and Fisher's exact test. Relationships between numerical variables were assessed with Pearson or Spearman correlation analysis. Multivariable logistic analysis was conducted to establish any possible independent predictors of NDP. Receiver operating characteristic curve analysis was performed to evaluate diagnostic performance. A two-sided P-value<0.05 were accepted as statistically significant.

RESULTS

The mean age of the NDHT patients was 50.5±13.7 years and the majority of them were male (66.5%). Mean age, gender distribution, mean BMI, and smoking rate did not differ significantly between the normotensive and NDHT groups. NDP was detected in 45.1% (n=74) of the NDHT patients. Baseline characteristics are presented in **Table 1**.

The mean PNI value was lower in the NDHT group than the normotensive group (53.6±6.1 vs. 58.2±5.3, p<0.001), while the mean TyG index value was higher (9.0±0.5 vs. 8.3±0.7, p<0.001) (**Table 1**).

The proportion of male patients was higher in the NDP group compared to patients with the dipper BP pattern, while other demographic characteristics did not differ significantly between the groups. The mean neutrophil count (5.6±1.6 vs. 5.0±1.8 × 103/μL, p=0.035), median triglyceride level (170 vs. 133 mg/dL, p=0.033), and mean LDL-C level (133.7±35.3 vs. 120.3±32.7, p=0.013) were higher in the NDP group compared to patients with the dipper BP pattern, while the mean lymphocyte count (2.1±0.5 vs. 2.6±0.6 × 103/μL, p<0.001) was lower. The mean PNI value was lower in the NDP group compared to patients with the dipper BP pattern (49.9±5.6 vs. 56.6±4.8, p<0.001), while the mean TyG index value was higher (9.2±0.5 vs. 8.9±0.5, p<0.001) (**Table 2**).

Table 1. Demographic characteristics and clinical parameters in study population

Variables	Hypertension group n=164	Normotensive group n=164	p
Demographic findings			
Age, years	50.5±13.7	49.8±16.4	0.675
Gender, n (%)			0.488
Male	109(66.5)	103(62.8)	
Female	55(33.5)	61(37.2)	
BMI, kg/m²	26.2±3.3	25.8±3.5	0.287
Smoking, n (%)	65(39.6)	70(42.6)	0.581
Baseline HR, bpm	80.4±11.4	78.8±10.6	0.189
In-office SBP, mmHg	143.8±12.0	112.2±6.8	<0.001*
In-office DBP, mmHg	84.1±9.2	71.6±3.6	<0.001*
Laboratory findings			
Hemoglobin, g/dL	14.0±1.7	14.2±1.8	0.302
FBG, mg/dL	91.0±8.5	84.0±12.0	<0.001*
WBC, ×10³/μL	7.5±2.2	7.1±2.1	0.093
Neutrophil count, ×10³/μL	5.3±1.9	4.7±1.9	0.013*
Platelet count, ×10³/μL	264.8±59.2	260.5±67.4	0.531
Monocyte count, ×10³/μL	0.7±0.3	0.6±0.3	0.017*
Lymphocyte count, ×10³/μL	2.4±0.6	2.8±0.8	<0.001*
Cholesterol, mg/dL	204.1±53.5	177.1±47.6	<0.001*
Triglyceride, mg/dL	150(115-241)	113(83-185.5)	<0.001*
HDL-C, mg/dL	46.2±13.1	51.1±14.7	0.002*
LDL-C, mg/dL	126.5±35.7	116.1±37.7	0.020*
Creatinine, mg/dL	0.9±0.3	0.8±0.2	0.003*
Albumin, g/dL	4.3±0.5	4.5±0.3	<0.001*
CRP, mg/L	3.5(1.6-5.9)	1.4(1.1-3.2)	<0.001*
PNI	53.6±6.1	58.2±5.3	<0.001*
TyG index	9.0±0.5	8.3±0.7	<0.001*
ABPM findings			
24- hours			
SBP, mmHg	141.6±10.5	123.2±7.0	<0.001*
DBP, mmHg	87.6±17.9	75.7±8.1	<0.001*
Day-time			
SBP, mmHg	144.4±24.1	127±6.6	<0.001*
DBP, mmHg	93.0±9.9	77.6±6.1	<0.001*
Night-time			
SBP, mmHg	127.1±15.3	107.6±6.0	<0.001*
DBP, mmHg	79.4±9.7	66.0±10.2	<0.001*
Decline in night-time BP, %	11.0±4.5	15.2±3.5	<0.001*

Data shown as mean±standard deviation or median (IQR) or number (percentage). * p<0.05 indicates statistical significance. Abbreviations: ABPM, ambulatory blood pressure monitoring; BMI, body mass index; CRP, C- reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, high-density lipoprotein cholesterol; PNI, prognostic nutrition index; SBP, systolic blood pressure; TyG, triglyceride-glucose index; WBC, white blood cell.

A negative correlation was found between the PNI and 24-hour systolic BP (r=-0.418; p<0.001) and diastolic BP (r=-0.412; p<0.001). A negative correlation was also found between the PNI and TyG index (r=-0.332; p<0.001), while a positive correlation was found between the PNI and the decline in nighttime BP levels (r=0.517; p<0.001) (**Figure 1**). Parameters associated with the decline in nighttime BP (%) and the PNI in patients with hypertension are presented in **Table 3**.

Table 2. Distribution of demographic characteristics and clinical parameters according to dipper and non-dipper blood pressure patterns in hypertensive patients.

Variables	Non-dipper pattern group n=74	Dipper pattern group n=90	p
Demographic findings			
Age, years	50.2±14.4	50.8±13.1	0.792
Gender, n (%)			**0.031***
Male	56(75.7)	53(58.9)	
Female	18(24.3)	37(41.1)	
BMI, kg/m²	26.0±2.9	26.3±3.5	0.556
Smoking, n (%)	30(40.5)	35(38.9)	0.830
Baseline HR, bpm	80.7±10.9	80.2±11.8	0.788
In-office SBP, mmHg	144.3±11.8	143.4±12.2	0.634
In-office DBP, mmHg	85.5±9.0	83.6±9.3	0.189
Laboratory findings			
Hemoglobin, g/dL	13.9±1.8	14.1±1.6	0.438
FBG, mg/dL	92.7±9.4	89.6±7.4	0.023*
WBC, $\times 10^3/\mu L$	7.8±2.3	7.3±2.1	0.148
Neutrophil count, $\times 10^3/\mu L$	5.6±1.6	5.0±1.8	0.035*
Platelet count, $\times 10^3/\mu L$	271.6±57.1	260.5±60.9	0.234
Monocyte count, $\times 10^3/\mu L$	0.7±0.2	0.7±0.3	0.569
Lymphocyte count, $\times 10^3/\mu L$	2.1±0.5	2.6±0.6	<0.001*
Cholesterol, mg/dL	210.5±67.9	198.2±38.1	0.146
Triglyceride, mg/dL	170(123-250)	133(113-210)	0.033*
HDL-C, mg/dL	44.9±13.3	47.4±12.9	0.224
LDL-C, mg/dL	133.7±35.3	120.3±32.7	0.013*
Creatinine, mg/dL	0.9±0.3	0.9±0.2	0.558
Albumin, g/dL	3.9±0.5	4.4±0.3	<0.001*
CRP, mg/L	4.6(2.0-7.8)	2.3(1.8-4.7)	0.012*
PNI	49.9±5.6	56.6±4.8	<0.001*
TyG index	9.2±0.5	8.9±0.5	<0.001*
ABPM findings			
24- hours			
SBP, mmHg	142.9±11.9	140.5±9.2	0.163
DBP, mmHg	88.9±9.2	86.5±22.7	0.362
Day-time			
SBP, mmHg	146.7±12.1	142.5±30.6	0.234
DBP, mmHg	92.5±9.3	93.5±10.4	0.512
Night-time			
SBP, mmHg	134.9±11.4	120.7±15.2	<0.001*
DBP, mmHg	83.4±9.8	76.1±8.4	<0.001*
Decline in night-time BP, %	6.2±2.1	14.0±3.6	<0.001*

Data shown as mean±standard deviation or median (IQR) or number (percentage). * P<0.05 indicates statistical significance. Abbreviations: ABPM, ambulatory blood pressure monitoring; BMI, body mass index; CRP, C- reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, high-density lipoprotein cholesterol; PNI, prognostic nutrition index; SBP, systolic blood pressure; TyG, triglyceride-glucose index,; WBC, white blood cell.

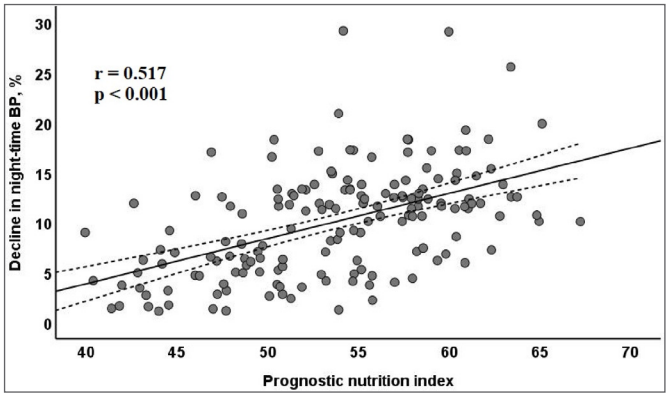

Figure 1. Relationship between prognostic nutritional index and decline in nighttime BP (%) in patients with hypertension.

Table 3. Parameters associated with the decline in nighttime BP (%) and prognostic nutrition index in patients with hypertension

Variables	Decline in nighttime BP (%)		PNI	
	r	p	r	p
Age	-0.115	0.328	-0.105	0.379
BMI	-0.029	0.713	-0.033	0.675
Baseline HR	0.033	0.673	-0.027	0.730
Hemoglobin	-0.105	0.180	-0.106	0.177
FBG	-0.245	0.048*	-0.257	0.040*
WBC	-0.115	0.342	-0.108	0.359
Neutrophil count	-0.297	0.026*	-0.289	0.031*
Platelet count	-0.202	0.383	-0.211	0.334
Monocyte count	-0.149	0.406	-0.123	0.645
Lymphocyte count	0.341	<0.001*	0.679	<0.001*
Cholesterol	-0.124	0.462	-0.178	0.320
Triglyceride	-0.283	0.019*	-0.298	0.011*
HDL-C	0.155	0.483	0.277	0.032*
LDL-C	-0.273	0.046*	-0.267	0.039*
Creatinine	0.018	0.822	-0.043	0.584
Albumin	0.302	0.009*	0.859	<0.001*
CRP	-0.268	0.042*	-0.341	<0.001*
TyG	-0.412	<0.001*	-0.332	<0.001*
PNI	0.517	<0.001*	-	-

* p<0.05 indicates statistical significance. Abbreviations: BMI, body mass index; CRP, C- reactive protein; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, high-density lipoprotein cholesterol; PNI, prognostic nutrition index; TyG, triglyceride-glucose index, WBC, white blood cell.

Variables associated with NDP (**Table 2**) were considered as potential confounding factors. Among these factors, due to their multicollinearity with their respective indices, neither the components of the PNI nor the components of the TyG index were included in the multivariable regression analysis. Multivariable regression analysis showed that decreased PNI (OR=0.70, 95% CI=0.61-0.81, p<0.001) and increased TyG index (OR=7.16, 95% CI=2.30-22.26, p<0.001) values, as well as increased LDL-C levels, were independent predictors of NDP (**Table 4**).

Table 4. Independent predictors of non-dipper pattern in patients with hypertension.

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
Gender						
Male	2.17	1.10-4.27	0.031*	-	-	-
Female	ref			ref		
FBG	1.05	1.01-1.09	0.023*		not included	
Neutrophil count	1.20	1.01-1.43	0.035*	-	-	-
Lymphocyte count	0.20	0.10-0.38	< 0.001*		not included	
Triglyceride	1.08	1.05-1.11	0.033*		not included	
Albumin	0.80	0.73-0.87	< 0.001*		not included	
LDL-C	1.09	1.02-1.18	0.013*	1.10	1.03-1.35	0.021*
CRP	1.05	1.01-1.14	0.012*	-	-	-
PNI	0.78	0.73-0.85	< 0.001*	0.70	0.61-0.81	< 0.001*
TyG index	6.62	2.33-13.14	0.004*	7.16	2.30-22.26	< 0.001*
					Adjusted R2=0.592; p<0.001	

Due to their multicollinearity with their respective indices, neither the components of the PNI nor the components of the TyG index were included in the multivariable regression analysis. Abbreviations: CI, confidence interval; CRP, C- reactive protein; FBG, fasting blood glucose; LDL-C, high-density lipoprotein cholesterol; OR, odds ratio; PNI, prognostic nutrition index; SE, standard error; TyG, triglyceride-glucose index.

The diagnostic performance of the independent predictors in predicting NDP is shown in **Figure 2**. The cut-off value of the PNI in predicting NDP was ≤51.3 with 72.4% sensitivity and 69.8% specificity. The diagnostic performance of the PNI in predicting NDP did not differ significantly compared to the TyG index (difference between areas under the curves=0.014, p=0.218) (**Figure 1A**). However, both indices had superior diagnostic performance compared to LDL-C.

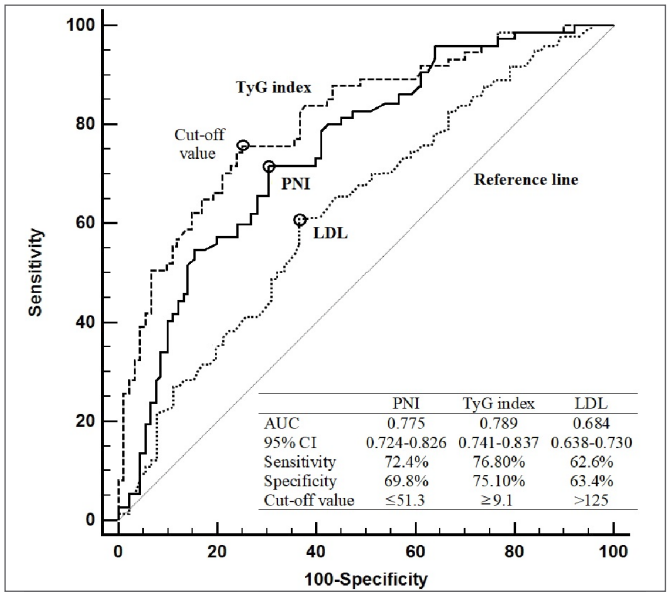

Figure 2. The receiver operating characteristic (ROC) curve analysis of prognostic nutritional index in predicting non-dipper pattern among hypertension patients.

DISCUSSION

This study of NDHT patients has demonstrated that a low PNI value was positively associated with BP level and the decline in nighttime BP (%). The PNI was lower in hypertensive patients compared to normotensive individuals. Low PNI values independently predicted NDP in hypertensive patients. To our knowledge, this is the first study to examine the relationships between the PNI and the decline in nighttime BP (%) and the presence of NDP in NDHT patients.

Epidemiological studies have reported that poor nutrition is common in hypertensive patients.[30-32] Circulating levels of albumin as a negative acute phase reactant and lymphocyte counts as reflectors of immunological status are usually reduced in cases of malnutrition.[33] Therefore, the PNI derived from these parameters is an important indicator of nutritional status beyond the context of inflammation.[34] To the best of our knowledge, there is only one study in the existing literature that compares the PNI between hypertensive patients and normotensive individuals.[27] Consistent with the findings of this study, hypertensive patients exhibited lower PNI levels. Nutritional status is closely associated with insulin resistance and impaired lipid metabolism, both of which contribute to the pathogenesis of hypertension.[12,13,21] This is consistent with the negative correlations between the PNI and atherogenic lipid profile and the TyG index, a surrogate marker of insulin resistance, in patients with hypertension. Experimental studies have shown that PPAR-γ and zinc-alpha-2-glycoprotein (ZAG) may be responsible for this relationship.[9] It has been suggested that PPAR-γ exerts pleiotropic effects on the vascular system, and these effects of PPAR-γ may specifically be due to inhibition of angiotensin-II type 1 receptor expression, which involves suppression of the RAAS and leads to lower BP levels.[10] Besides, ZAG, which plays a role in insulin resistance and lipid modulation, may be suppressed by PPAR-γ.[11] On the other hand, changes in nutritional status can affect the metabolism and function of immune cells,[35] leading to elevated BP levels.[36]

The above-mentioned mechanisms support the previously reported findings that malnutrition can contribute to variations in BP, as well as the development of hypertension and atherosclerosis.[21,37] Although approximately half of all genes expressed in the body have circadian regulatory mechanisms, components of the circadian clock play a role in every cell type and tissue.[38] These mechanisms are likely responsible for diurnal variations in physiological functions such as body temperature, sleeping and waking patterns, metabolism, and BP. The BP levels of healthy individuals repeat throughout the circadian rhythm and there is usually a decrease of more than 10% in nighttime BP levels compared to daytime BP levels.[3] Additional diseases ruled out with the exclusion criteria of this study, such as diabetes mellitus, rheumatic diseases, coronary artery disease, eating disorders, metabolic syndrome, and cancer, may also increase the susceptibility to NDP and affect the variations in BP levels, which play a role in the pathophysiology of hypertension.[39-44] Therefore, we excluded patients with potential additional diseases to more objectively evaluate the relationship between immunological nutritional status and NDP in NDHT patients.

PNI values were lower among NDHT patients with NDP. To the best of our knowledge, this is the first study investigating the relationship between PNI and NPD. In a previous study conducted in hypertensive patients, nutritional status was evaluated using the Control Nutritional Status and the Nutritional Risk Index.[45] It was found that these indices were lower in the NDP group compared to the dipper BP group. Additionally, it was reported that NRI is an independent predictor of NDP.[45] A previous study examining the effects of nutritional parameters on nocturnal BP in Turkish hemodialysis patients revealed an association between malnutrition and a disruption in the circadian BP rhythm.[46] The malnutrition score showed a positive correlation with nighttime and 24-hour BP levels, while it exhibited a negative correlation with serum albumin and anthropometric indices.[46] Therefore, it has been suggested that low serum albumin levels and hypervolemia contribute to the association between impaired nutritional status and elevated nighttime BP.[46] Serum albumin has been identified as a significant predictor of the decline in nocturnal BP, even in patients without albuminuria, proteinuria or diabetes.[47] On the other hand, there is increasing evidence to indicate that nutritional status can play a role in modulating insulin resistance, lipid metabolism, and inflammation, thus contributing to the disruption of the circadian BP rhythm.[35,48,49] This is consistent with the correlations between PNI levels and high triglycerides, low HDL-C, high BP, and high fasting blood glucose, which are important components of metabolic syndrome.

Malnutrition may also exacerbate the effects of sympathetic and parasympathetic nervous system dysfunction in addition to insulin resistance or inflammation.[6] Low serum albumin levels have been shown to be important predictors of autonomic nervous system dysfunction.[8] Some previous studies reported that levels of heart rate recovery at 1 min (HRR1), as an indicator of sympathetic and parasympathetic nervous system activation, were lower in patients with hypertensive NDP.[50,51] Moreover, the negative correlation between the TyG index and HRR1 in NDHT patients was associated with a decline in nighttime BP (%).[51] The negative correlation between the TyG index and PNI detected in the present study may indicate a possible underlying mechanism of malnutrition for both insulin resistance and autonomic function. Furthermore, the PNI was found to be an independent predictor of NDP. The diagnostic performance of the TyG index in predicting NDP was consistent with the results of a previous study with sensitivity and specificity exceeding 70%.[52] However, no significant difference was found in diagnostic performance between the PNI and TyG index in predicting NDP. The cut-off value for the PNI in predicting NDP was ≤51.3, and at this cut-off value, 72.4% of patients were classified as true positive cases. This study shows that the PNI may be an important screening tool for NDP and an important marker for potential mechanisms underlying NDP.

This study has some important limitations. First, it was retrospective in design and the sample size was relatively small. Due to the retrospective nature of the study design, it was not possible to include participants' dietary records. Incorporating dietary records could have provided more insights into the relationship between the PNI and NDP. Finally, the relationship among the PNI index, heart rate recovery, and target organ damage resulting from hypertension could not be evaluated because of the study's retrospective design.

CONCLUSION

Hypertensive patients had worse immuno-nutritional statuses than normotensive individuals. Decreased PNI values correlated positively with declines in nighttime BP and the PNI was found to be an independent predictor of NDP. The negative correlation between the PNI and the TyG index as a surrogate marker of insulin resistance suggests that hypertensive patients may be at risk of insulin resistance. Since these patients may be predisposed to NDP, the PNI may be an important screening tool for circadian BP patterns.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Bursa City Hospital Clinical Research Ethics Committee (Date: 04.01.2023, Decision No: 2023-1/9).

Informed Consent: Because the study was designed prospectively, informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Thymoma radiotherapy: a retrospective multicentre study

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ABSTRACT

Aims: In this study, we aimed to evaluate the outcomes of thymoma patients who underwent radiotherapy (RT).

Methods: Data from thymoma patients who underwent RT at Ankara Bilkent City Hospital, Ankara Atatürk Education and Research Hospital and Ankara Numune Education and Research Hospital were analysed retrospectively. The primary endpoints of this study were acute and late side effects and the secondary endpoints were overall survival(OS) and disease-free survival (DFS).

Results: Data from 22 patients who received RT between 10.03.2008 and 05.10.2022 were analysed.The median follow-up time was 33 months (range: 1–76). RT-related acute toxicity was observed in 6 patients(27.3%). Late RT-related toxicity was noted in 4 patients (18%). As a late toxicity one patient (4.5%) had a secondary malignancy five years after RT.Patients younger than 40 years of age had significantly higher acute (p=0.039) and late (p=0.01) toxicity. Recurrence was observed in 7 patients (31.8%). The median DFS was 13 months (range: 1–176),the 1-year DFS was 58%, the 5-year DFS was 23%. Lower DFS was observed in patients with myasthenia gravis (MG) (p=0.018). Six patients(27.3%) died, the median OS was 33 months (range: 1–176),the 1-year OS was 84.4%, the 5-year OS was 76.7%. There was a significant correlation between performans status and OS (p=0.047).

Conclusion: Side effects were more frequently observed in patients younger than 40 years of age. Poor prognostic factors were identified as MG for DFS and poor performance status for OS. Thymoma patients have high OS, studies are needed to identify subgroups that do not require RT.

Keywords: Thymic epithelial tumours, radiotherapy, thymic carcinoma, thymoma

INTRODUCTION

Thymic epithelial tumours (TETs) are rare tumours with an incidence of 0.15 cases per 100,000 individualy.[1] They are observed at higher rates in men than women and their incidence increases with age. The World Health Organization (WHO) divides thymic malignancies into two groups: thymomas and thymic carcinomas (TCs). Thymomas are indolent tumours with a more benign course; they are usually detected incidentally and show local progression. Thymomas are divided into five subtypes (A, AB, B1, B2, and B3) and the prognosis worsens from A to B3. In addition to these classical subtypes, other subgroups such as thymoma-not otherwise specified, micronodular thymoma with lymphoid stroma, metaplastic thymoma, and lipofibroadenoma have also been documented. TCs constitute 10–12% of thymic malignancies, are more aggressive than thymomas, and have higher metastatic potential.[2-5]

Masaoka–Koga staging is commonly used for staging both thymomas and TCs.[1] This staging scheme was first described by Masaoka et al. in 1981 and later reinterpreted by Koga in 1994. Masaoka–Koga staging is based on surgical and pathological findings. The current widespread use of this staging is based on its power to predict OS.[1,3,6] Because it is a rare malignancy, multidisciplinary approaches should be at the forefront.[7] Surgery is usually the first-line treatment, but radiotherapy (RT) and less frequently chemotherapy (CT) are indicated as second-line treatments according to risk status and histology.[8] RT plays an important role in the treatment of thymoma and TC. RT is indicated for definitive purposes when surgery cannot be performed, adjuvant purposes in high-risk patients such as those with positive surgical margins, and palliative purposes in patients with recurrent or advanced-stage disease.[4,9,10] Indications for

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RT are based on non-randomized retrospective data with a limited number of patients.[7] Long-term side effects in thymoma patients are also important to consider, as long survival periods are achieved. For this reason, ongoing studies are working to identify subgroups of patients that do not require RT. In this study, we aimed to analyse the acute and late toxicities and survival of thymoma patients who received RT.

METHODS

Data from thymoma patients who received RT at Ankara Bilkent City Hospital, Ankara Atatürk Education and Research Hospital and Ankara Numune Education and Research Hospital were analysed retrospectively. Patient files, patient interviews, electronic system data, and RT dose-volume histograms were used in this study. Patient demographic data, pathology results, CT data, surgical details, RT information, acute side effects, late side effects, recurrence, and final status were noted. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.[11]

Patient Selection

Patients at least 18 years of age with a diagnosis of pathological thymoma were included in this study. Other inclusion criteria for these patients included an (Eastern Cooperative Oncology Group) ECOG performance status of 0–4, receipt of RT, and availability of complete file data. Patients with missing files and follow-up data, as well as those with a diagnosis of TC or without a pathological diagnosis, were excluded.

Primary and Secondary Endpoints

The primary endpoints of this study were acute and late side effects, whereas the secondary endpoints were overall survival (OS) and disease free survival (DFS). DFS was defined as the time after the end of RT that a patient had no evidence of cancer. The end date for DFS was the relapse date for patients with relapse and the last control date for those without relapse. OS was defined as the time from diagnosis until death, independent of recurrence. The starting point for OS was the date of diagnosis. The OS end date was the date of death for patients who succumbed to their disease or the date of last control for patients who were alive.

Statistical Analysis

Data were analysed using SPSS version 26. The conformity of the data to a normal distribution was evaluated with the Shapiro–Wilk test; as the data were not normally distributed, parametric tests were used. The Chi-squared test and Fisher's exact test were used to analyse categorical variables. The Mann–Whitney U test was used for independent two-group analyses. The Kruskal–Wallis test was used for the analysis of 3 or more independent groups and Tukey's post hoc test was performed in cases of significance. For survival analyses, the Kaplan–Meier test was used for univariate analyses and the Cox regression test was used for multivariate analyses. The hazard ratios (HR) and 95% confidence intervals (CI) of results that were significant in our survival analyses were calculated. A HR > 1 denotes an increased relative risk compared to the reference category. The significance limit of this study was set to 0.05.

RESULTS

Data from 22 patients who received curative RT at Ankara Bilkent City Hospital, Ankara Atatürk Education and Research Hospital and Ankara Numune Education and Research Hospital Hospitals between 10.03.2008 and 05.10.2022 were analysed retrospectively. The median follow-up period was 33 months (range: 1–76 months). The median patient age was 47.5 years (range: 26–69 years). Six patients (27.3%) were female and 10 patients (45.5%) did not have comorbidities. With respect to patients' performance status, no patients were ECOG 4 and only 2 patients (9.1%) were ECOG 3. The median size of the largest tumour from each patient was 63 mm (range: 13–180 mm). Eight of the patients (36.4%) were diagnosed with myasthenia gravis (MG). Main vessel, pulmonary, and pericardial invasion were reported in 9 patients (40.9%), 4 patients (18.4%), and 10 patients (45.5%), respectively. Neoadjuvant CT was administered to 4 patients (18.4%) and 5 patients (22.7%) were inoperable. Neoadjuvant CT protocols were as follows: doxorubicin, cisplatin, vincristine, and cyclophosphamide (ADOC; 2 patients); cisplatin plus etoposide (1 patient); and cisplatin plus cyclophosphamide (1 patient). Pathology reports were evaluated in terms of tumour resection; 8 patients (47.1%) were R0, 4 patients (23.5%) were R1, and 5 patients (29.4%) were R2. Fifty percent of the patients were B2. Staging was performed according to Masaoka–Koga guidelines; 1 patient (4.5%) was stage I; 9 patients (40.9%) were stage II, 3 patients (13.6%) were stage III, and 9 patients (40.9%) were stage IV. Of the 17 operated patients, 4 received adjuvant CT. Adjuvant CT protocols were as follows: ADOC (1 patient), cisplatin plus etoposide (1 patient), and cisplatin-cyclophosphamide (1 patient). The adjuvant CT regimen received by the remaining patient was unavailable. Patient and treatment details are summarized in **Table 1**.

Radiotherapy Details

Seventeen patients (77.3%) received adjuvant RT, 2 patients (9.1%) received definitive RT, and 3 patients (13.6%) received palliative RT. The median total RT dose was 50 Gy (range: 20–66 Gy) and the median fraction dose was 1.8 Gy (range: 1.8–4 Gy). Concurrent CT (cisplatin)

and RT were administered to 3 patients (13.6%). With respect to RT technique, 3 patients (13.6%) received two dimensional (2D) RT, 7 patients (31.8%) received three dimensional (3D) RT, 5 patients (22.7%) received intensity-modulated RT (IMRT), and 7 patients (31.8%) received volumetric modulated arc therapy (VMAT). All patients completed their RT treatment protocols. The median mean heart dose was 7.2 Gy (range: 1.1–21.3 Gy) and the median mean lung dose was 8.7 Gy (range: 3.8–15.7 Gy) (**Figure 1**) (**Table 2**).

Table 2. RT details

Parameters		N(%)
RT		
Adjuvant		17 (77.3%)
Definitive		2 (9.1%)
Palliative		3 (13.6%)
RT Total Dose	Median (range)	50 (20-66)Gy
RT Fraction dose	Median (range)	1.8 (1.8-4) Gy
Mean heart dose	Median (range)	7.2(1.1–21.3)Gy
Mean lung dose	Median (range)	8.7(3.8–15.7) Gy
Concurrent CT		
Yes		3 (13.6%)
No		19 (90.9%)
RT tecnique		
2D		3 (13.6%)
3D		7 (31.8%)
IMRT		5 (22.7)
VMAT		7 (31.8%)
Acute RT tox		
Yes		6 (27.3%)
Edema		1 (4.5%)
Esophagitis		2 (9.1%)
Pain		3 (13.6%)
No		16 (72.7%)
Late RT tox		
Yes		4 (18.2%)
Aspiration		1 (4.5%)
Lung fibrosis		1 (4.5%)
Pain		1 (4.5%)
Secondary malignancy		1 (4.5%)
No		4 (18.2%)
Missing		14 (63.6%)

Abbreviations: RT=Radiotherapy; Tox=Toxicity; CT=Chemotherapy; 2D=Two Dimensional; 3D= Three Dimensional; IMRT =Intensity Modulated Radiotherapy; VMAT=Volmetric Arc Therapy

RT-related acute toxicity was observed in 6 patients (27.3%) as follows: oedema (1 patient; 4.5%), oesophagitis (2 patients; 9.1%), and pain (3 patients; 13.6%). There were no significant relationships between acute toxicity and a diagnosis of MG (p=0.510), neoadjuvant CT (p=0.477), concurrent CT (p=0.378), total RT dose (p=0.972), RT fraction dose (p=0.056), or RT technique (p=0.713). There was a significant relationship between acute side effects and age (p=0.039; Z score: -2081). Specifically, there was a higher incidence of acute toxicity among patients less than 40 years of age (**Figure 2**).

Table 1. Patients and Treatment Details

Parameters	N(%)
Gender	
Female	6 (27.3%)
Male	16 (72.7%)
Age	
Median (range)	47.5 (26-69)
Comorbidity	
Yes	7 (31.8%)
No	15 (68.2%)
ECOG	
0	5 (22.7%)
1	8 (36.4%)
2	7 (31.8%)
3	2(9.1%)
MG	
Yes	8 (36.4%)
No	14 (63.6%)
Great Vessel Invasion	
Yes	9 (40.9%)
No	13 (59.1%)
Lung Invasion	
Yes	4 (18.4%)
No	18 (81.8%)
Pericard Invasion	
Yes	10 (45.5%)
No	12 (54.5%)
Neoadjuvant CT	
Yes	4 (18.4%)
No	18 (81.8%)
Surgery	
Yes	17 (77.3%)
No	5 (22.7%)
Resection	
R0	8(47.1%)
R1	4 (23.5%)
R2	5 (29.4%)
Thymoma Subtype	
A	2 (9.1%)
AB	2 (9.1%)
B1	3 (13.6%)
B2	11 (50%)
B3	4 (18.2%)
Masaoka Koga	
1	1 (4.5%)
2	9(40.9%)
3	3 (13.6%)
4	9(40.9%)
Adjuvant CT	
Yes	4 (18.2%)
No	13 (59.1%)
Recurrrence	
Yes	7 (31.8%)
No	15 (68.2%)
Recurrrence Site	
Local	3 (13.6%)
Regional	1 (4.5%)
Distance	2 (9.1%)
Local + Distance	1 (4.5%)
Last Status	
Ex	6 (27.3%)
Alive	16 (72.7%)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; MG=myastenia gravis; CT= Chemotherapy

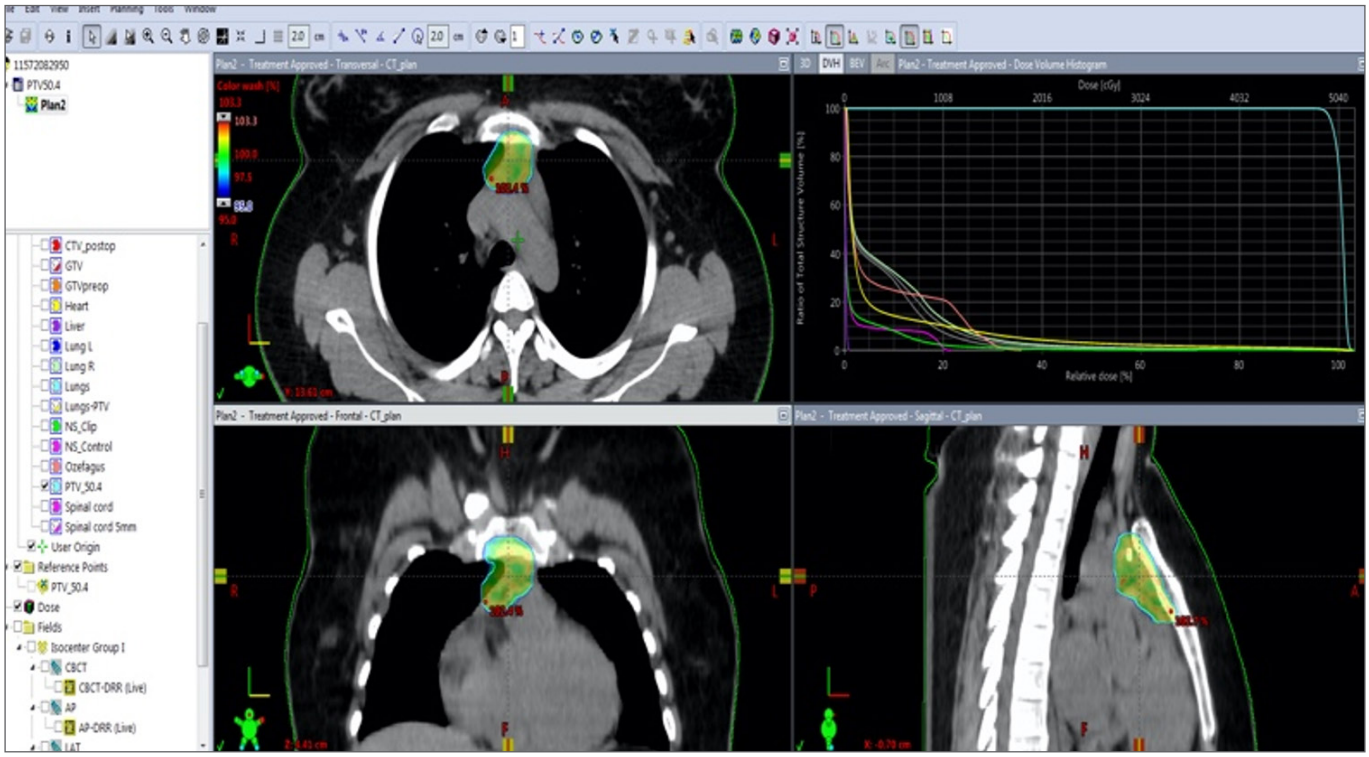

Figure 1. RT- planning image of a thymoma patient

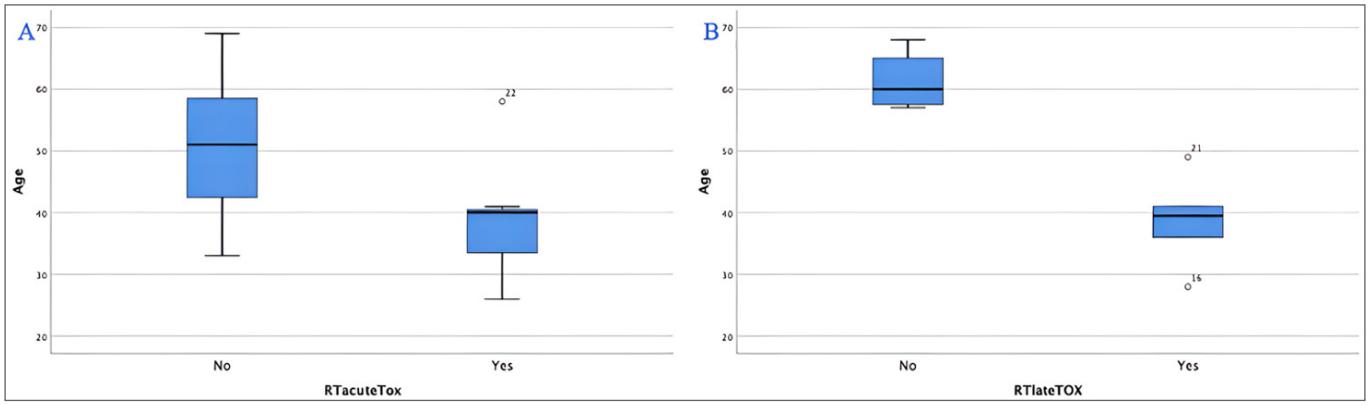

Figure 2. Patients younger than 40 years of age had significantly higher acute (A) and late toxicity (B).

Information on late toxicity associated with RT is available in only 8 (36.4%) patients, of which 4 reported late toxicity. However information on late toxicity associated with RT were not available for 14 patients (63.6%). The following late side effects were observed: chronic aspiration and dysphagia (1 patient; 4.5%), lung fibrosis (1 patient; 4.5%), chronic pain (1 patient; 4.5%), and secondary malignancy (1 patient; 4.5%). As a secondary malignancy, breast cancer was observed in our 36-year-old female patient 5 years after the treatment. There were no significant relationships between late toxicity and a diagnosis of MG (p=0.667), neoadjuvant CT (p=0.333), concurrent CT (p=0.610), total RT dose (p=0.380), RT fraction dose (p=0.516), or RT technique (p=0.383). There was a significant relationship between late side effects and age (p=0.011; Z score: -2558). Specifically, late toxicity was more prevalent among patients less than 40 years of age (**Figure 2**).

Details of DFS Analysis

Recurrence was observed in 7 patients (31.8%) (**Table 3**). The median DFS was 13 months (range: 1–176 months), the 1-year DFS was 58%, and the 5-year DFS was 23%. Lower DFS was observed among patients with MG (p=0.018; HR: 6.7; 95% CI: 1.2–36.7). There were no significant relationships between DFS and age (p=0.954), comorbidity status (p=0.426), ECOG performance status (p=0.717), great vessel invasion (p=0.326), pulmonary invasion (p=0.136), pericardial invasion (p=0.740), tumour size (p=0.742), neoadjuvant CT (p=0.837), surgery status (p=0.643), resection status (R0, R1, R2) (p=0.374), pathological subtype (A–B3) (p=0.964), stage (p=0.171), adjuvant CT (p=0.058), concurrent CT (p=0.651), RT technique (p=0.894), total RT dose (p=0.367), mean heart dose (p=0.383), or mean lung dose (p=0.625) (**Figure 3**).

Table 3. Patient's Details

Patients	Age Gender ECOG	Co.	MG	Surgery	Stage	CT	RT	RT tox	Recurrence DFS	Last Status OS
1	57, M ECOG 1	DM, HT, BPH	No	Operated R0 TS: 30 mm	Stage 1 , B2 (no total thymectomy)	None	50 / 2Gy IMRT	None	Rec: No DFS: 11.5 mo	Alive OS: 11.5 mo
2	44, M ECOG 0	None	Yes	Operated, R0 TS: 36 mm	Stage 2 , B2 GV invasion : +	None	50 / 2Gy IMRT	Acute: none Late: NS	Rec: No DFS: 2.5 mo	Ex OS: 11.5 mo
3	46, F ECOG 1	None	No	Operated R1 TS: 67 mm	Stage 2 , B2 Pericard inv: +	CCT Cisp	54/2 Gy VMAT	Acute : none Late: none	Rec: No DFS: 5.45 mo	Alive OS: 5.45 mo
4	39, M ECOG 1	None	No	Operated R2 TS: 23 mm	Stage 2 , B1	CCT Cisp	45/1.8 Gy IMRT	Acute : Upper Ext Edema Late: none	Rec: No DFS: 7.16 mo	Alive OS: 7.16 mo
5	62, M ECOG 2	HT BPH	No	Operated R0 TS: 143 mm	Stage 2 , A	None	50 / 2Gy VMAT	Acute: None Late: None	Rec: No DFS: 19.0 mo	Alive OS: 19.0 mo
6	68, M ECOG 2	HT, DM	No	Operated R0 TS: 41 mm	Stage 2 , B3	None	45 / 3 Gy VMAT	Acute: None Late: None	Rec: No DFS: 24.6 mo	Alive OS: 24.6 mo
7	28, M ECOG 0	None	No	Operated R1 TS: 67 mm	Stage 2 , B3	None	54/ 2 Gy 3D	Acute: Pain Late: Lung Fibrosis	Rec: No DFS: 104 mo	Alive OS: 104 mo
8	60, M ECOG 1	None	No	Operated R0 TS: 65 mm	Stage 2 , AB GV inv: +	None	50 Gy /2 Gy 3D	Acute: None Late: None	Rec: No DFS: 131.9 mo	Alive OS: 131.9 mo
9	26, F ECOG 0	None	Yes	Operated R0 TS: 25 mm	Stage 2 , B2	None	50.4/1.8 VMAT	Acute: Pain Late: NS	Rec: yes (local) DFS: 5.72 mo	Alive OS: 7.70 mo
10	33, M ECOG 1	None	No	Operated R0 TS: 62 mm	Stage 2 , B3	None	50.4/1.8 3D	Acute: None Late: None	Rec: yes (local + distant) DFS: 9.95 mo	Alive OS: 11.04 mo
11	53, M ECOG 2	None	No	Operated R2 TS: 122 mm	Stage 3 , AB GV inv: + Pericard inv: +	Neoadj: ADOC	66/2 Gy IMRT	Acute: None Late: None	Rec: No DFS: 45.04 mo	Alive OS: 45.04 mo
12	53, F ECOG 1	None	Yes	Inoperable TS: 80 mm	Stage 3 , B1 GV inv: +	None	50 / 2 Gy 2D	Acute: Pain Late: NS	Rec: Yes (distant) DFS: 39.0 mo	Ex OS: 42.0 mo
13	40, F ECOG 3	None	Yes	Operated R1 TS: 35 mm	Stage 3 , B2 GV inv: + Pericard inv: +	None	50.4/1.8 3D	Acute: Esophagitis Late: Chronic aspiration	Rec: Yes (local) DFS: 12.25 mo	Ex OS: 12.42 mo
14	69, M ECOG 3	None	No	Inoperable TS: 180 mm	Stage 4, GV inv: +	None	36 / 3 Gy VMAT	Acute: None Late: None	Progression DFS: 1 mo	Ex OS: 1 mo
15	40, M ECOG 2	None	No	Inoperable TS: 100 mm	Stage 4,B2 GV inv: + Pericard inv: +	Neoadj: Cisp + Cyclo	60 /2 Gy 3D	Acute: Esophagitis Late: NS	Rec: No DFS: 9.59 mo	Alive OS: 9.59 mo
16	69, F ECOG 2	HT	No	Operated R0 TS: 170 mm	Stage 4, A Lung inv: +	None	30/3 Gy VMAT	Acute: None Late: NS	Rec: No DFS: 48.33 mo	Alive OS: 48.33 mo
17	51, M ECOG 0	No	Yes	Operated R1 TS: 110 mm	Stage 4, B3 Pericard inv: +	CCT Cisp	54/2 Gy VMAT	Acute: None Late: NS	Rec: No DFS: 71.7 mo	Alive OS: 71.7 mo
18	41, M ECOG 2	No	Yes	Inoperable TS: 110 mm	Stage 4, B2 Pericard inv: +	Neoadj: Cisp + etoposide	20/4 Gy 3D	Acute: None Late: NS	Rec: No DFS: 128.1 mo	Alive OS: 128.1 mo
19	46, M ECOG 1	None	No	Operated TS: 45 mm	Stage 4, B2 Lung inv: +	None	50/2 Gy 2D	Acute: None Late: NS	Rec: No DFS: 166.6 mo	Alive OS: 166.6 mo
20	49, M ECOG 1	None	No	Operated R2 TS: 45 mm	Stage 4, Lung inv: + Pericard inv: +	Neoadj: ADOC Adj: Carbo +pacli	30/3 Gy 2D	Acute: None Late: Pain	Rec: Yes (distant) DFS: 93.3 mo	Alive OS: 114.2 mo
21	54, M ECOG 2	None	Yes	Operated R2 TS: 60 mm	Stage 4, B1 GV inv: +	Adj CT	66 /2 Gy IMRT	Acute: None Late: NS	Rec: Yes (local) DFS: 176.4 mo	Ex OS: 177.1 mo
22	36, F ECOG 0	None	Yes	Operated R2 TS: 65 mm	Lung inv: + Pericard inv: +	Adj CT: ADOC	60 /2 Gy 3D	Acute: None Late: Secondary Malignancy, Breast Cancer, 5 years after RT	Rec: Yes (local) DFS: 6.4 mo	Alive OS: 126,36 mo

Abbreviations: ECOG=Eastern Cooperative Oncology Group; F=Female; M= Male; Co=Comorbidity; MG= myastenia gravis; CT=Chemotherapy, RT=Radiotherapy; CCT=Concurrent Chemotherapy; mo=months; DFS=Disease free survey; OS=Overall Survey; Tox=Toxicity; DM=Diabetes Mellitus; HT=Hypertension; BPH=Benign Prostatic Hyperplasia; IMRT= Intensity Modulated Radiotherapy; VMAT=Volmetric Arc Therapy, TS= Tumor Size; ADOC=doxorubicin, cisplatin, vincristine , cyclophosphamide; NS=Not Specified;

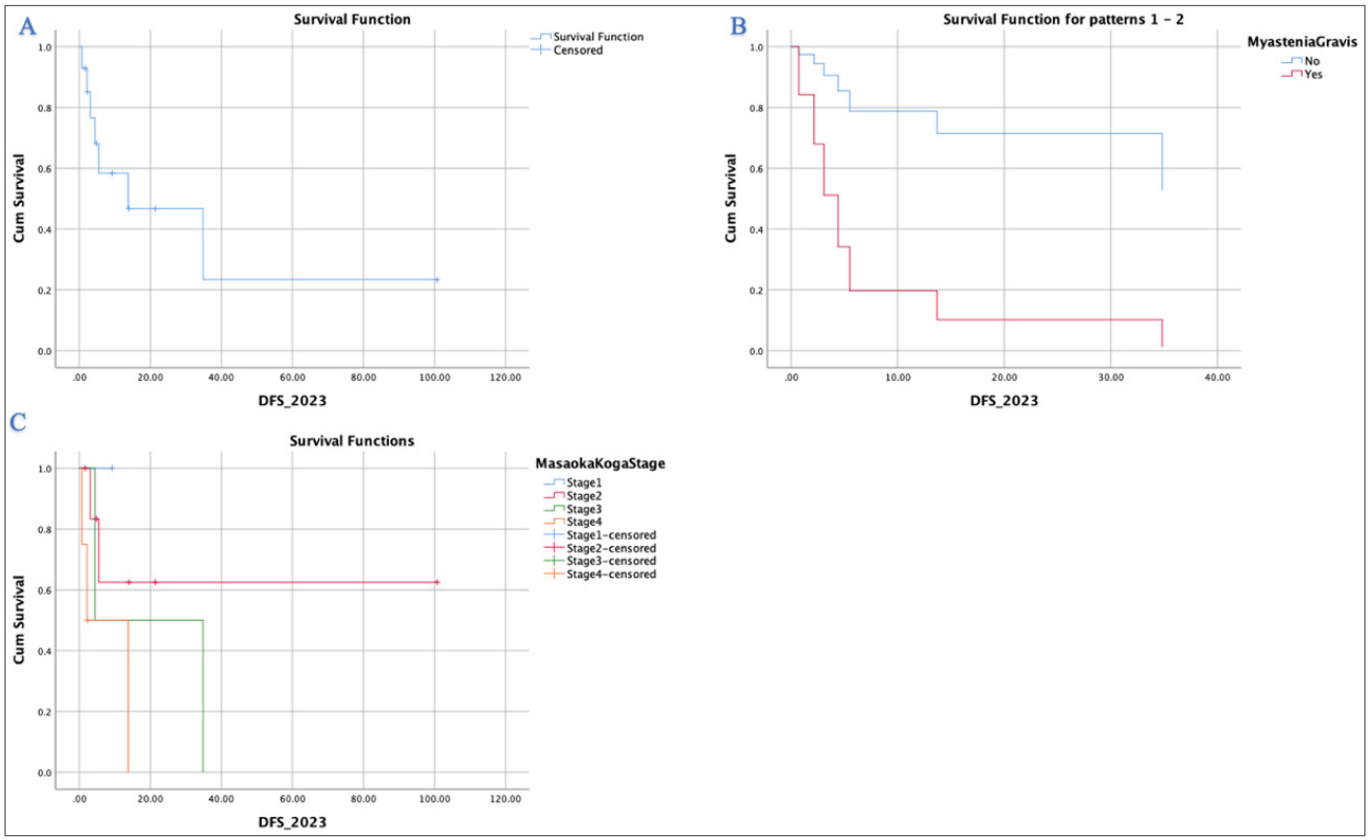

Figure 3. A. Image of DFS's Kaplan Meier Analysis; B. Lower DFS was observed in patients with MG (p=0.018); C. The relationship between Masaoka Koga Stage and DFS was not statistically significant.

Details of OS Analysis

During the follow-up period, 6 patients (27.3%) died (**Table 3**). The median OS was 33 months (range: 1–176 months). The 1-year OS was 84.4% and the 5-year OS was 76.7%. There were no significant relationships between OS and sex (p=0.482), age (p=0.633), comorbidity status (p=0.860), MG diagnosis (p=0.428), great vessel invasion (p =0.098), pulmonary invasion (p=0.711), pericardial invasion (p=0.462), tumour size (p=0.551), neoadjuvant CT (p=0.838), surgery status (p=0.427), resection status (R0, R1, R2) (p=0.703), pathological subtype (A–B3) (p=0.514), stage (p=0.363), adjuvant CT (p=0.327), concurrent CT (p=0.649); RT technique (p=0.763), total RT dose (p=0.765), mean heart dose (p=0.837), or mean lung dose (p=0.580).

There was a significant correlation between ECOG performance status and OS, in that patients with good general condition had better OS (p=0.047; HR: 18.2; 95% CI: 1.02–32.2). Significantly higher OS was achieved in patients without complaints (ECOG 0). Specifically, the median OS was 71 months (range: 2–126 months), 26 months (range: 5–166 months), and 44 months (range: 9–177 months) among patients with ECOG performance statuses of 0, 1, and 2, respectively (**Figure 4**).

DISCUSSION

Consistent with the literature, we observed high RT compliance and long survival periods among thymoma patients in our study. One patient (4.5%) in our series presented with secondary malignancy as a late side effect. Another remarkable result is that both acute and late side effects were significantly higher in patients under 40 years of age. However, OS and DFS values were not significantly different in patients younger than 40 years of age vs. those older than 40 years of age. Poor prognostic factors were identified as MG and poor performance status for DFS and OS, respectively.

Thymomas typically affect men and women equally but a higher incidence has been observed in males in some case series. In the literature, two different peak age ranges have been reported, including 45–55 years of age and the seventh decade of life.[12] There were 16 male patients (72.7%) in our series, representing a significant male predominance. The median patient age was 47.5 years (range: 26–69 years). Approximately half of thymoma patients have a diagnosis of MG and thymomas are observed in 15% of MG patients.[13] Eight (36.4%) of our patients had a diagnosis of MG. No significant differences were observed in patients with MG in terms of acute toxicity, late toxicity, or OS. However, DFS was significantly lower in MG patients.

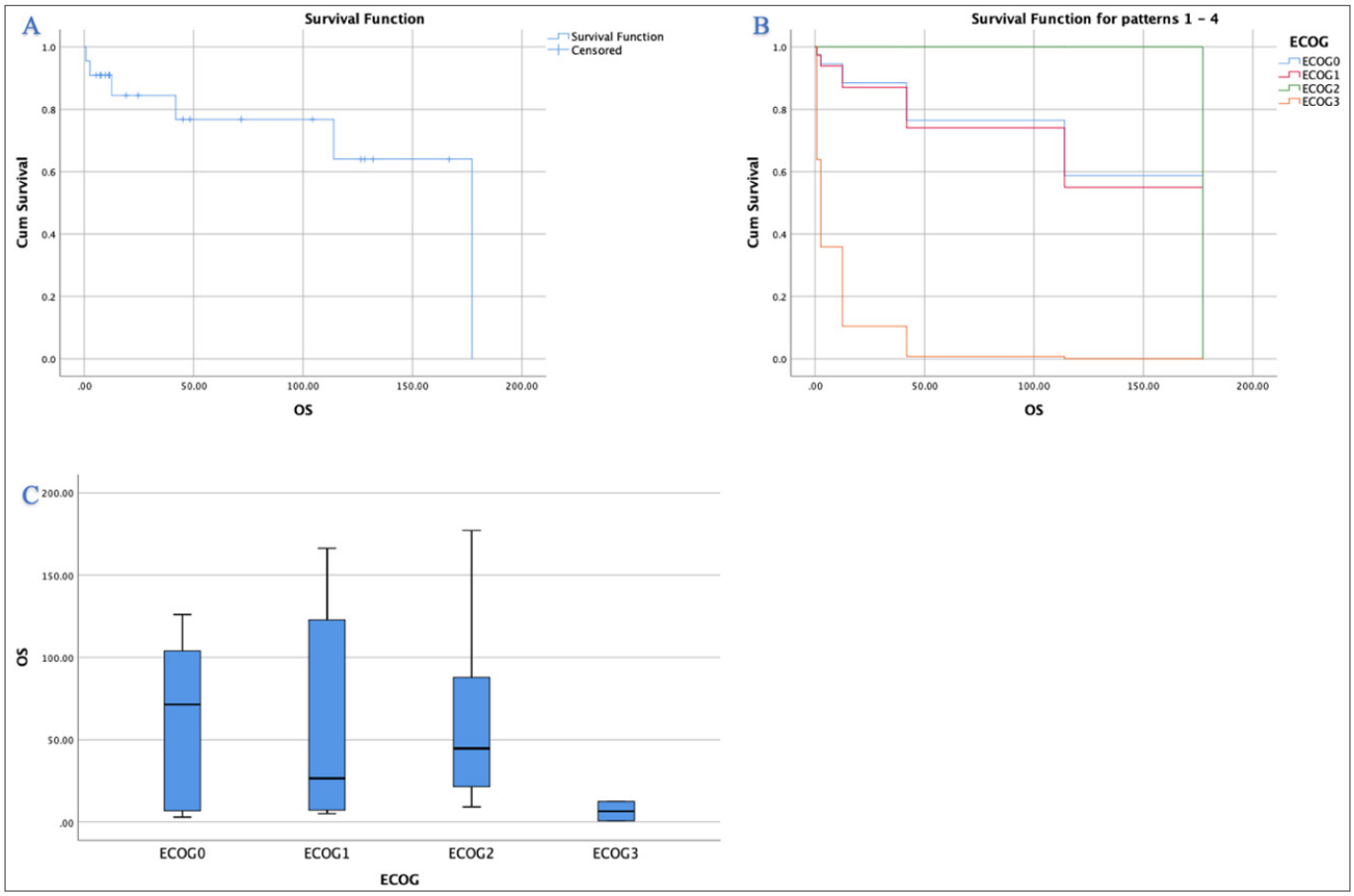

Figure 4. A. Image of OS Kaplan Meier Analysis; B. Lower OS was observed in patients with poor performance status; C. Box blot image evaluating the ECOG - OS relationship.

TCs represent a small fraction of TETs. Pathologically, the distinction between TC and atypical thymoma is important; atypical thymomas differ from TCs in terms of treatment approach and prognosis. The median survival for patients with TC is 6.6 years.[14] Atypical thymoma is a remarkable definition detailed in the 2021 WHO Classification.[5] According to this staging scheme, atypical thymoma is a variant of group A thymomas. In the present study, no atypical variants were noted in the pathology reports. There was also no significant relationship between thymoma histological subtype and survival.

An important current issue in the field of TET therapy is the identification of patient subgroups that do not require RT.[4] RT indications for TET should be evaluated separately for thymoma and TC. Surgery is usually the initial treatment for these patients. Patients who are candidates for surgery should be evaluated in an experienced RT clinic to determine if they should receive adjuvant RT. Adjuvant RT is not indicated for all thymic epithelial malignancies. According to the European Society for Medical Oncology (ESMO) 2021 guidelines, thymoma patients with PT1aR0 tumours of the A–B1 subtypes and without massive capsular invasion can be observed and adjuvant RT is not indicated. However, postoperative RT (PORT) is indicated in cases of B2–3 tumours or those with massive capsular invasion, even at early stages. For TCs, PORT is recommended for all patients except selected patients with pT1aR0 tumours.[15] In addition to ESMO, the Oncologic Group for the Study of Lung Cancer/Spanish Society of Radiation Oncology (GOECP/SEOR) published another set of important RT guidelines, last updated in 2021. In the GOECP/SEOR 2021 guidelines, the indications for RT are determined according to Masaoka–Koga staging. Specifically, patients for whom PORT is not indicated include those with stage I and stage IIA tumours with R0 resection.16 There was only 1 patient with a stage I tumour (R0, B2) in our study. The patient was evaluated by the multidisciplinary tumour council. The patient's tumour underwent R0 resection and the subtype was B2, but total thymectomy was not performed. Therefore, adjuvant RT was administered.

According to current guidelines, adjuvant RT is indicated for patients with Masaoka–Koga stage IIB and III tumours.[15,16] The necessity of adjuvant RT for this disease in which high OS can be obtained is controversial. According to a study by Song et al.[17] adjuvant RT does not contribute to overall survival in patients with a completely resected stage II thymoma. Additionally, in

an analysis of 65 patients with complete resected stage III (Masaoka–Koga) tumours, the 5- and 10-year OS rates were reported as 91.7% and 71.6%, respectively. In this study, PORT reduced local recurrence but did not contribute to OS.[3] In patients with unresectable or debulked stage III thymoma, the contribution of definitive RT has been reported in the literature and identified as an independent prognostic factor for OS.[18] In an Italian study that evaluated 183 thymoma patients from three different centres, the lowest DFS and OS rates were observed in patients with incompletely resected thymomas. Thus, RT appears to contribute to patients with stage II-III thymoma without complete resection.[7] Further, in a Surveillance, Epidemiology, and End Results program analysis of 2,236 thymoma patients published by Mou et al.[9] in 2020, PORT was recommended for all patients over 60 years of age and who had Masaoka–Koga stage III and IV tumours. However, no strong evidence for the contribution of PORT has been reported in patients with stage II thymoma.[9] In summary, whether or not adjuvant RT should be administered to patients with stage II-III thymoma is controversial, especially in cases of complete resection. In these patients, RT dose varies between 50 and 66 Gy depending on the type of surgery received, residual status, and pathological subtype.

The RT field for thymoma patients is the anterior mediastinum proximal to the heart. For every 1 Gy increase in the mean heart dose, the risk of major cardiac events increases by 7.4%.[19] In our study, the median mean heart dose was 7.2 Gy (range: 1.1–21.3 Gy). No significant relationship was found between mean heart dose and OS, but we predict that RT increases patients' risks of major cardiac events. This rate is a serious late side effect for this disease, which carries a long life expectancy. Thus, the balance of insufficient and over-treatment needs to be correctly evaluated for stage IIB and III thymoma patients.

For stage II and III thymoma patients, an accurate assessment of the balance between local recurrence-associated problems in patients who do not receive RT and the long-term side effects associated with RT—particularly long-term cardiac effects—is needed. For this purpose, "RADIORYTHMIC", a phase III randomized trial that aimed to evaluate the necessity of adjuvant RT in patients with Masaoka–Koga stage IIB/III thymoma, was initiated. In this study, patients with completely resected tumours were randomized to adjuvant RT vs. observation. A total of 50–54 Gy of IMRT or proton therapy are being administered to patients in the RT arm. The results of this study are expected to be presented in 2028. This trial is the first prospective randomized phase III study of PORT in thymoma patients.[6] In our study, nine patients had stage II tumours and two of these patients relapsed. In both patients, R0 resection was achieved and 50.4 Gy of adjuvant RT was administered. In these two patients with local relapse, subtype was the only remarkable unfavourable prognostic factor, as one patient had a B2 tumour and the other patient had a B3 tumour.

In addition to cardiac toxicity, pulmonary fibrosis is another important RT-related toxicity. Radiation pneumonitis and pulmonary fibrosis may be observed as acute and late RT-related side effects, respectively. Radiation pneumonia is also one of the most frequently observed RT-related toxicities. In an analysis by Kirakli et al.[2] radiation pneumonia was reported in 52% of patients with grade 1 and 2 tumours. However, in an Italian study, there were no significant differences in terms of side effects between patients in the PORT and observation arms.[7] In our study, RT-related late toxicity was noted in 8 patients (36.4%), but no such data were available for 14 patients (63.6%). Thus, cancer registries should contain more detailed data about the long-term side effects of RT, especially for patients with rare diseases for whom long survival periods are expected. Among the patients in our study for whom these data were available, late side effects were as follows: chronic aspiration and dysphagia (1 patient; 4.5%), pulmonary fibrosis (1 patient; 4.5%), chronic pain (1 patient; 4.5%), and secondary malignancy (1 patient; 4.5%).

Modern RT techniques (e.g. IMRT, image-guided RT [IGRT], and four dimensional (4D) computed tomography) should be used in thymoma patients because the RT field is adjacent to many vital organs.[4] In the literature, RT techniques such as 3D approaches, IMRT, IGRT, VMAT, stereotactic body RT [SBRT], and proton therapy have been administered to thymoma patients.[20] In a prospective analysis of proton therapy for TET patients, Mercado et al.[21] reported a 3% local recurrence rate after a median of 13 months of follow-up. In addition, no patients had grade 3 or higher side effects. Although side effects are reduced in patients who receive proton therapy, standard IMRT techniques are more accessible to patients. With IMRT techniques, effective doses can be applied to target volumes while protecting surrounding organs. Stereotactic radiosurgery for TET patients is experimental and there is limited available data in the literature. In a prospective study by Hao et al.[22] in which SBRT was administered to 39 lesions in 32 patients, the response rate was 96.9% and the local control rate was 81.25%. Thus, this study concluded that SBRT may be an alternative for patients with unresectable tumours who are not candidates for conventional RT. However, SBRT is not the standard approach for thymoma patients.[22] In our case series, no patients preferred SBRT. IMRT/VMAT was administered to the most of the patients.

The target volume for thymoma and TC includes the surgical bed and risk area and there is no elective nodal irradiation.4 Gross tumour volume is defined by positron emission tomography fusion imaging and the clinical target volume margin is usually 5 mm.[16] Typically, conventional fraction doses of 1.8 and 2.0 Gy are preferred. Johnstone et al.[4] suggested the following doses in their research presented in 2022, 45–50.4 Gy for R0 patients, 50–54 Gy for R1 patients, and 60–70 Gy for R2 and inoperable patients. The National Comprehensive Cancer Network (NCCN) and GOECP/SEOR guidelines also recommend the same doses.[16,23] However, doses below 40 Gy are also under investigation in early-stage thymoma patients and those with completely resected tumours.[10,24] In addition, although some approaches recommend doses above 56 Gy in patients with R2 resection or unresectable tumours, there is no consensus on this issue.[25] If concurrent CT is to be administered, 54 Gy is also an effective dose and is often preferred.[26] In our study, the median dose was 50 Gy and only 3 patients (13.6%) were treated with concurrent CT. There were no significant relationships between RT technique and acute side effects or survival.

In patients with resectable thymomas, the first treatment choice is surgery. The optimal surgery is en bloc resection of the entire thymus and peritumoral adipose tissue. Minimally invasive surgical procedures should only be attempted by experienced thoracic surgeons for small tumours but they are not recommended as standard approaches. In cases of locally advanced disease, the surrounding organs (cardiac main vessels, lung parenchyma, etc.) into which the tumour has invaded should also be resected. If maximal reduction surgery is performed, surgical risk areas should be marked with clips.[15] Clips are important tools that enhance compliance between surgeons and radiation oncologists. In our study, 17 patients (77.3%) underwent surgery and R0 resection was achieved in 8 patients (47.1%).

The majority of TET RT data are based on studies of TC wherein CT response rates are low. NCCN guidelines recommend carboplatin/paclitaxel as a first-line therapy, with an overall response rate of 22–36%. A total of six additional defined protocols can be administered. ADOC, administered to 3 patients (13.6%) in our case series, is also effective in thymic tumours but is more toxic than carboplatin/paclitaxel. Second-line systemic therapy can be used in patients who cannot tolerate or progress from first-line therapy. Second-line systemic treatment options include sunitinib, pemetrexed, everolimus, paclitaxel, gemcitabine with or without capecitabine, 5-fluorouracil, etoposide, ifosfamide, lenvatinib, and pembrolizumab. Response rates were 22.5% with pembrolizumab but severe immune toxicity rates (15%) were observed.[23]

Study Limitations

The most important limitation of the study is its retrospective nature. In addition, CT preference and RT dose/technique were heterogeneous. For thymoma, which is a rare disease, there is a need for prospective studies with a large series of patients using standard treatments.

CONCLUSION

Side effects were more frequently observed in patients younger than 40 years of age. Poor prognostic factors were identified as MG for DFS and poor performance status for OS. Thymoma patients have high OS, studies are needed to identify subgroups that do not require RT. The patients were evaluated with a multidisciplinary approach before their treatment commenced.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 11.01.2023, Decision No: E1-23-3183).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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