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ORIGINAL RESEARCH

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The Role of Magnetic Resonance Imaging in Predicting Pathological Complete Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

Neoadjuvan Kemoterapi Alan Meme Kanseri Hastalarında Patolojik Tam Yanıtı Tahmin Etmede Manyetik Rezonans Görüntülemenin Rolü

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Abstract

Objective: Neoadjuvant chemotherapy (NACT) has been used more frequently in the treatment of non-metastatic breast cancer. Achieving a pathological complete response (pCR) after NACT provides us with information about the prognosis of the disease. We aimed to investigate the diagnostic accuracy of preoperative magnetic resonance imaging (MRI) in predicting pCR in patients with breast cancer.

Method: The charts of patients who received NACT for breast cancer between 2018 and 2024 were retrospectively analyzed. Factors associated with radiologic complete response (rCR) and pCR were analyzed in univariate and multivariate settings. The correlation between rCR and pCR according to MRI interpretation was analyzed.

Results: A total of 153 patients were included in this study; 26 (17%) of these patients achieved rCR, and 39 (25.5%) achieved pCR. A statistically significant correlation was found between pCR and rCR assessed on MRI. Sensitivity, specificity, accuracy, pCR predictive value (PPV) and non-pCR predictive value were estimated at 51.3%, 94.7%, 83.7%, 76.9% and 85%, respectively. Statistically significant correlations between rCR and pCR were found in Luminal A ($p<0.05$), Luminal B ($p<0.05$), HER2-positive ($p<0.05$), but not in triple negative subtypes ($p>0.05$). In univariate and multivariate analysis, tumor characteristics significantly associated with both rCR and pCR were tumor size, lymph node metastasis and molecular subtypes.

Öz

Amaç: Neoadjuvan kemoterapi (NACT), metastatik olmayan meme kanserinin tedavisinde daha sık kullanılmaktadır. NACT sonrasında patolojik tam yanıt (pCR) elde etmek, bize hastalığın prognozu hakkında bilgi sağlar. Meme kanseri hastalarında pCR'yi tahmin etmede preoperatif manyetik rezonans görüntülemenin (MRI) tanısal doğruluğunu araştırmayı amaçladık.

Yöntem: 2018-2024 yılları arasında meme kanseri nedeniyle NACT alan hastaların çizelgeleri retrospektif olarak analiz edildi. Radyolojik tam yanıt (rCR) ve pCR ile ilişkili faktörler tek değişkenli ve çok değişkenli ortamlarda analiz edildi. MRI yorumlamasına göre rCR ve pCR arasındaki korelasyon analiz edildi.

Bulgular: Bu çalışmaya toplam 153 hasta dahil edildi; bu hastaların 26'sı (%17) rCR'ye ulaşırken, 39'u (%25,5) pCR'ye ulaştı. pCR ve MRI'da değerlendirilen rCR arasında istatistiksel olarak anlamlı bir korelasyon bulundu. Duyarlılık, özgüllük, doğruluk, pCR öngörü değeri (PPV) ve pCR dışı öngörü değeri sırasıyla %51,3, %94,7, %83,7, %76,9 ve %85 olarak tahmin edildi. rCR ve pCR arasında istatistiksel olarak anlamlı korelasyonlar Luminal A'da ($p<0,05$), Luminal B'de ($p<0,05$), HER2 pozitif ($p<0,05$) bulundu, ancak üçlü negatif alt tiplerde ($p>0,05$) bulunmadı. Tek değişkenli ve çok değişkenli analizde, hem rCR hem de pCR ile önemli ölçüde ilişkili tümör özellikleri tümör boyutu, lenf nodu metastazı ve moleküler alt tiplerdi.

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Abstract

Conclusion: MRI evaluation varies according to the subtype and after NACT showed a correlation between rCR and pCR.

Keywords: Breast cancer, magnetic resonance imaging, neoadjuvant chemotherapy, pathologic complete response, radiologic complete response

Öz

Sonuç: MRI değerlendirmesi alt tipe göre değişmekte ve NAKT'den sonra rCR ve pCR arasında bir korelasyon göstermektedir.

Anahtar kelimeler: Manyetik rezonans görüntüleme, meme kanseri, neoadjuvan kemoterapi, patolojik tam yanıt, radyolojik tam yanıt

Introduction

Breast cancer remains the most commonly diagnosed type of cancer worldwide (1). Traditional treatment methods (surgery + adjuvant chemotherapy) have an important place in the treatment approach, but neoadjuvant chemotherapy (NACT) is increasingly discussed and implemented in current breast cancer treatment guidelines.

NACT refers to systemic chemotherapy administered prior to planned surgery for patients with locally advanced breast cancer. Its primary goal is to transform initially inoperable tumors into operable ones, thereby offering patients the chance for surgical intervention and improving breast conservation rates. Additionally, NACT enables early assessment of the chemotherapy's impact on cancer tissue, which helps guide the selection of the most effective chemotherapy agents for the patient's future treatment (2).

When the data, in the literature, are examined, it has been observed that high pathological complete response (pCR) rates are achieved, when effective targeted therapies and chemotherapeutic agents are preferred in first-line treatment (3,4).

Currently, no standardized methods or imaging biomarkers are available in clinical practice to accurately predict pCR after NACT. Magnetic resonance imaging (MRI) is considered the most sensitive imaging modality that can be used to assess treatment response in patients undergoing NACT (5).

Radiomics is a feature extraction and analysis method commonly used in medical imaging. Radiomics analyzes pixel values in medical images and inter-pixel relationships.

It is thought that the application of radiomics techniques to MRI imaging will contribute positively to all stages of breast cancer with the additional data it will provide to the diagnosis, treatment and prognosis processes of breast cancer (6).

Scientific studies suggest that patients with radiologic complete response (rCR) show significant correlation with pCR (7).

Nevertheless, there is a limited number of studies investigating the relationship between rCR and pCR across various molecular subtypes, particularly where the Ki-67% proliferation index is used as a criterion.

In this study, we aimed to evaluate the effectiveness of post-treatment breast MRI in forecasting pCR following NACT using a large dataset from a single center.

Material and Methods

Patient Characteristics

We retrospectively analyzed breast MRI data of breast cancer patients with four or more cycles of NACT, at University of Health Sciences Turkey, İstanbul Training and Research Hospital between March 2018 and May 2024. The baseline data for our study were collected from the hospital's medical records database. We received approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital's Clinical Research Ethics Committee (date: 19.07.2024, number: 36).

The study included patients with histopathologically confirmed, radiologically non-metastatic breast cancer who had received NACT. Patients who underwent MRI to monitor tumor response to NACT and had at least two MRI evaluations was incorporated into the study. The initial MRI was conducted following the diagnosis and prior to NACT, and the second MRI was performed after completion of NACT, before surgery.

Patients who could not complete the NACT process had incomplete follow-up data were excluded. In Table 1, the baseline characteristics of the patients are displayed.

Most patients in the study received a combination of anthracycline and cyclophosphamide followed by taxane chemotherapy.

Along with these chemotherapeutic agents, HER2-positive breast cancer patients were also treated with targeted therapy using pertuzumab and trastuzumab. Some patients with triple-negative breast cancer received a carboplatin regimen combined with paclitaxel chemotherapy.

Pathological Classification

According to receptor positivity, tumors were categorized as estrogen receptor (ER) positive or progesterone receptor (PR) positive if the immunohistochemical (IHC) staining of the tumor tissue showed 1% or more positivity in tumor cell nuclei. The HER2 status (positive or negative) was assessed through IHC and/or fluorescence *in situ* hybridization (FISH) analysis of biopsy samples. In the IHC analysis, a score of 3+ was deemed positive, while scores of 0 to 1+ were considered negative. For tumors that received a 2+ score, further evaluation via FISH was conducted to check for *HER2* gene amplification.

The Ki-67% index was divided into three categories based on values: Less than 15%, between 15% and 40%, and more than 40%. Tumors were classified into molecular subtypes using IHC markers. The subtypes included Luminal A (ER-positive, PR ≥20%, HER2-negative, Ki-67% ≤15%), Luminal B (ER-positive, PR <20% or both ER and PR-positive, HER2-negative, or ER/PR/HER2-positive, with Ki-67% >15%), HER2-positive (ER and PR-negative, HER2-positive), and triple-negative (ER/PR/HER2-negative) groups. The Luminal B group was further divided into two subgroups based on the Ki-67% index: Those with Ki-67% <40% were classified as Luminal B low Ki-67%, while those with Ki-67% ≥40% were labeled as Luminal B high Ki-67%.

In postoperative pathology, the Miller-Payne grading system was utilized to assess the response to NACT. Grades 1 and 2 were classified as stable response; grades 3 and 4 as partial pathological response; and grade 5 as pCR. Residual ductal carcinoma *in situ* was excluded from the definition of pCR, irrespective of lymph node metastasis presence.

Breast MRI and Evaluation

MRIs were obtained using a 1.5 T MAGNETOM Aera device (Siemens, GERMANY). According to the breast

Table 1. Patient characteristics

Menopause	Premenopause	60	39.2%
	Postmenopause	93	60.8%
MR-T tumor size	T0	32	20.9%
	T1 (<2 cm)	41	26.8%
	T2 (2-5 cm)	39	25.5%
	T3 (>5 cm)	26	17.0%
	T4 (>5 cm)	15	9.8%
MR-N stage	N0	87	56.9%
	N1	44	28.8%
	N2	18	11.8%
	N2	1	0.7%
	N3	3	2.0%
Radiologic complete response	(-)	127	83.0%
	(+)	26	17.0%
Pathological tumor size	T0	42	27.5%
	T1 (<2 cm)	32	20.9%
	T2 (2-5 cm)	52	34.0%
	T3 (>5 cm)	21	13.7%
	T4 (>5 cm)	6	3.9%
PN-N stage	N0	67	43.8%
	N1	45	29.4%
	N2	22	14.4%
	N3	18	11.8%
Pathological complete response	(-)	114	74.5%
	(+)	39	25.5%

MR: Magnetic resonance, SD: Standard deviation

MRI protocol, axial anterior contrast T1 with 3 mm slice thickness, axial STIR T2, sagittal T2 with 4 mm slice thickness for both breasts, and ADC maps and DWI b values (50-400-800 s/mm^2) were obtained. Dynamic sequences were acquired six times at 60-second intervals after contrast agent injection, and subtraction images were obtained from these sequences. Finally, a contrast fat-suppressed sagittal T1 VIBE sequence was obtained. MRI examinations were performed in a prone position using a breast coil. To minimize background contrast, patients were imaged between the tenth and fourteenth day of their menstrual cycle.

Statistical Analysis

SPSS 28.0 software system was used for the analyses, and a p-value of less than p<0.05 was considered statistically significant. Statistics of the data included mean, maximum, minimum, median, ratio values, frequency, and standard deviation. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used for assessing the distribution of variables. The Mann-Whitney U test was used to analyze independent quantitative data with abnormal distribution. The chi-square test was used for analyzing qualitative independent data, and if the chi-square test was not satisfied, Fischer's test was applied. Specificity, sensitivity and accuracy were calculated to evaluate the effectiveness of MRI after NACT. Multivariable regression was used to examine the simultaneous effects of multiple factors. The accuracy of MRI was measured using predictive values, including negative predictive value (NPV) and positive predictive value (PPV).

Results

The files of 570 patients who underwent NACT for breast cancer at the Oncology Clinic of University of Health Sciences Turkey, İstanbul Training and Research Hospital were analyzed. One hundred fifty-three patients with available MRI images and postoperative pathology results were included. Table 1 shows the baseline characteristics of the patients. The average age of the patients was 57.4±12.9 years, with 88.9% diagnosed with invasive ductal carcinoma. Among them, 22 patients (14.4%) were HER2-positive, 24 patients (15.7%) were triple-negative, and 107 patients (69.9%) were hormone receptor-positive.

Following NACT, all patients underwent surgery. The tumor diameter measured on pretreatment MRI was 4.26±1.95 cm (ranging from 1.5 to 10.6 cm), while the residual tumor diameter measured on post-NACT MRI was 2.41±1.31 cm (ranging from 0 to 6.5 cm).

Out of the cohort, 39 patients achieved pCR, and 26 patients had rCR, a statistically significant finding (p<0.05). The sensitivity, accuracy (ACC), specificity, PPV for pCR, and NPV were estimated to be 51.3%, 83.7%, 94.7%, 76.9%, and 85%, respectively (Table 2).

Additionally, we explored the correlation between rCR and pCR across different breast cancer subtypes. Statistically significant correlations between pCR and rCR were observed in the Luminal A, Luminal B, and HER2-positive groups, whereas no significant correlation was found in the triple-negative group.

Discussion

NACT plays a crucial role in managing locally advanced breast cancer. One study has clearly demonstrated that pCR achieved with NACT improves survival and is a key endpoint for improved prognosis (8). However, the definition of pCR continues to be debated, and there seems to be a lack of consensus in the literature, which complicates the objective comparison of results. In our study, we considered the lack of DCIS or malignant cells in the sections taken from the tumor site as pCR. In our study, we found that rCR rates and pCR rates were similar. We aimed to evaluate whether rCR had a significant relationship with pCR. We also wanted to determine the factors that may affect rCR and pCR.

Table 2. Comparison of breast MRI performance among tumor subtypes after NAC

Molecular subtype	Accuracy	Sensitivity	Positive PV	Specificity	Negative PV	p
All patients	83.7%	51.3%	76.9%	94.7%	85.0%	0.000
Luminal A	100.0%	100.0%	100.0%	100.0%	100.0%	0.025
Luminal B low Ki-67	93.3%	100.0%	50.0%	92.9%	100.0%	0.000
Luminal B high Ki-67	85.7%	25.0%	100.0%	100.0%	85.0%	0.003
HER 2 positive	68.2%	56.3%	100.0%	100.0%	46.2%	0.017
Triple negative	66.7%	40.0%	66.7%	85.7%	66.7%	0.151

MRI: Magnetic resonance imaging, NAC: Neoadjuvant chemotherapy

From Table 3, we determined that tumor size measured by MRI after NACT was the most significant factor associated with both pCR and rCR. Other factors, including primary tumor size by MRI, nodal metastasis, and molecular subtype, were also significantly linked to pCR and rCR. This correlation may be attributed to the fact that smaller tumor size, earlier clinical classification, and higher proliferation rates are associated with a greater likelihood of response and a higher chance of achieving pCR and rCR post-NAC (9).

We also aimed to evaluate the precision of MRI in predicting pCR after NACT, particularly for each breast cancer subtype. We based our classifications on IHC markers used in both literature and clinical practice (10). Additionally, we categorized Luminal B breast cancer into two groups based on Ki-67% scores: Ki-67 >20% and Ki-67 <20%. Our findings indicated that rCR was significantly correlated with pCR, especially in the Luminal B, low and high Ki-67%, HER2-positive, and Luminal A subtypes. Nonetheless, we observed notable differences among these three groups.

Moreover, Luminal B, high Ki-67% and HER2-positive subtypes exhibited low NPV, but high PPV. This implies that residual lesions identified by MRI serve as reliable markers of non-pCR for these subtypes; however, the rCR diagnosed by MRI in these groups may be overestimated. Conversely, MRI predicted pCR in the triple-negative subtype with lower sensitivity, specificity, accuracy, PPV, and NPV, compared to the other subtypes, which is contrary to the findings reported in existing literature (11,12).

In our study, Luminal A and Luminal B breast cancers with low Ki-67% (<20%) were less likely to exhibit pCR or rCR following NACT. However, they achieved high specificity, sensitivity, ACC, NPV and PPV. These data were similar to the results of studies in the literature (13). Certainly, multicenter studies with a larger cohort of patients are needed to speak more precisely. However, MRI still demonstrated a good NPV for these two molecular subtypes. It indicates that the accuracy remains high if the MRI reveals a residual tumor. Some studies have shown that rCR assessed on MRI is not a clear marker for pCR (14,15). The biggest difference between our data and the data in these studies was that we applied the IHC classification methods recommended in the guidelines. We also set a more objective standard for evaluating rCR. rCR was described as the lack of DCIS and malignant cells. This may have contributed to the disparity between our study and the previously mentioned studies.

While pCR remains the gold standard for assessing pathology specimens after NACT, rCR can serve as a predictor of improved prognosis in clinical practice (16). However, there are challenges associated with diagnosing rCR following NACT. The treatment can induce reactive changes such as inflammation and fibrosis, which may result in non-specific contrast enhancement, leading to either underestimation or overestimation of tumor diameter on MRI (17).

Moreover, different molecular subtypes of breast cancer exhibit varying capabilities in achieving pCR. Ki-67% is a key marker for gauging response to neoadjuvant treatment, when Ki-67% exceeds 40%, the rate of pCR after

Table 3. The correlation coefficient according to the clinical and tumor characteristics

Variables	rCR	pCR	rCR	pCR
	|R|	p-value	|R|	p-value
Age	0.043	0.45	0.032	0.584
Menopause (yes/no)	0.031	0.56	0.03	0.967
Primary tumor diameter by hand	0.02	0.006	0.024	0.011
Primary tumor diameter by MRI	0.025	<0.00	0.123	0.025
After NAC tumor diameter by MRI	0.32	<0.00	0.232	<0.00
Tumor grade	0.022	0.033	0.452	0.005
Clinical grade	0.143	0.027	0.167	0.02
Receptor status				
HR (positive/negative)	0.147	0.034	0.01	0.004
HER2 (positive/negative)	0.02	0.65	0.033	1.01
Ki-67% (low/medium/high)	0.32	0.23	0.287	0.004
Moleculer subtype	0.178	<0.00	0.02	<0.00

rCR: Radiologic complete response, MRI: Magnetic resonance imaging, NAC: Neoadjuvant chemotherapy, pCR: Pathological complete response

NACT significantly increases, along with a higher rate of rCR diagnoses. In the Luminal B subtype, a Ki-67% ≥40% indicates a higher likelihood of achieving pCR, with rates comparable to those observed in HER2-positive breast cancer. Although the differences in molecular subtype did not significantly impact the diagnosis of rCR, high Ki-67% emerged as a strong predictor of rCR when compared to low Ki-67%.

Study Limitations

Our study has a number of limitations. The limitations are, firstly, a retrospective design and, secondly, a small sample size. As this was a single-center study, we aimed to employ consistent data analysis methods for both radiological and pathological evaluations. Third, our study did not include immunotherapy agents the guidelines.

Conclusion

In conclusion, the precision of breast MRI in estimating pCR was high in patients receiving NACT for breast cancer. NPV, sensitivity, PPV and precision of MRI in predicting pCR differed significantly between molecular subtypes of breast cancer.

Ethics

Ethics Committee Approval: We received approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital's Clinical Research Ethics Committee (date: 19.07.2024, number: 36).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.G., E.Ö., E.S.A., Ö.H., Concept: İ.G., B.G., M.B.U., Ç.U., R.U.G., Design: İ.G., B.G., E.S.A., Ç.U., R.U.G., Data Collection or Processing: İ.G., E.Ö., M.B.U., Analysis or Interpretation: İ.G., E.S.A., Ç.U., R.U.G., Literature Search: İ.G., E.Ö., M.B.U., Writing: İ.G., B.G., Ö.H.

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ORIGINAL RESEARCH

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Comparative Prognostic Value of CHA_2DS_2-VASc Score and Atherogenic Plasma Index for One-year Mortality Prediction in Ischemic Stroke Patients

CHA_2DS_2-VASc Skoru ve Aterojenik Plazma İndeksinin İskemik İnme Hastalarında Bir Yıllık Mortalite Tahminindeki Prognostik Değerlerinin Karşılaştırılması

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Abstract

Objective: The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age, female gender) score is significantly associated with poor outcomes after ischemic stroke. However, the impact of lipid parameters on prognosis remains unclear. This study aimed to investigate the association between lipid parameters and outcomes, and compare them to the CHA_2DS_2-VASc score.

Method: A total of 583 ischemic stroke patients admitted between 2018 and 2022 were retrospectively analyzed. Demographic data, CHA_2DS_2-VASc scores, and lipid parameters, including ratio of triglyceride to high density lipoprotein (HDL-C), light density lipoprotein (LDL-C) to HDL and atherogenic plasma index (API) were recorded. Patients were followed for one year, with all-cause mortality as the primary endpoint. Predictors of mortality were determined using Cox regression analysis.

Results: The mean age of the 583 patients was 71.05±11.83 years, with a one-year all-cause mortality rate of 17.3% (n=101). Total cholesterol, non-HDL-C, and API were significantly higher in patients with poor outcomes (p=0.003, p=0.031, p=0.019, respectively). Both API and CHA_2DS_2-VASc scores were strong mortality predictors [hazard ratio (HR): 1.062, 95% confidence interval (CI): 0.973-1.252, p=0.007] and (HR: 1.567, 95% CI: 1.003-2.174, p=0.004), respectively. Receiver operating curve analysis revealed higher predictive power for CHA_2DS_2-VASc score compared to API (area under the curve: 0.756; p=0.014 vs. 0.568; p=0.045).

Öz

Amaç: CHA_2DS_2-VASc (konjestif kalp yetmezliği, hipertansiyon, ≥75 yaş, diabetes mellitus, inme, vasküler hastalık, 65-74 yaş, kadın cinsiyet) skoru, iskemik inme sonrası kötü sonlanımlarla önemli ölçüde ilişkilidir. Bununla birlikte, lipid parametrelerinin prognoz üzerindeki etkisi net değildir. Bu çalışma, lipid parametrelerinin sonlanımlar üzerindeki ilişkisini araştırmayı ve bunları CHA_2DS_2-VASc skoru ile karşılaştırmayı amaçlamıştır.

Yöntem: 2018 ve 2022 yılları arasında başvuran toplam 583 iskemik inme hastası retrospektif olarak analiz edildi. Hastaların demografik verileri, CHA_2DS_2-VASc skorları ve trigliserid/yüksek yoğunluklu lipoprotein (HDL-C) oranı, düşük yoğunluklu lipoprotein (LDL-C)/HDL-C oranı ve aterojenik plazma indeksi (API) gibi lipid parametreleri kaydedildi. Hastalar bir yıl boyunca takip edildi ve tüm nedenlere bağlı ölüm birincil sonlanım noktaları olarak kabul edildi. Mortalitenin öngördürücüleri Cox regresyon analizi ile belirlendi.

Bulgular: Beş yüz seksen üç hastanın ortalama yaşı 71,05±11,83 olup, bir yıllık tüm nedenlere bağlı mortalite oranı %17,3 (n=101) olarak saptandı. Toplam kolesterol, non-HDL-C ve API, kötü sonlanımları olan hastalarda anlamlı derecede daha yüksek bulundu (p=0,003, p=0,031, p=0,019, sırasıyla). Hem API hem de CHA_2DS_2-VASc skoru, güçlü mortalite öngördürcüleri olarak kabul edildi [tehlike oranı (HR): 1,062, %95 güven aralığı (GA): 0,973-1,252, p=0,007] ve (HR: 1.567, %95 GA: 1,003-2,174, p=0,004). Alıcı çalışma eğri analizinde, CHA_2DS_2-VASc skoru API'ya kıyasla daha yüksek öngörü olarak izlendi (eğri altındaki alan: 0,756; p=0,014 vs. 0,568; p=0,045).

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Conclusion: CHA_2DS_2-VASc and API are valuable predictors of one-year mortality after ischemic stroke. CHA_2DS_2-VASc score, which includes embolism risk factors, has stronger sensitivity and specificity for predicting poor outcomes compared to lipid parameters.

Keywords: Atherogenic plasma index, cholesterol, ischemic stroke, lipoprotein

Sonuç: CHA_2DS_2-VASc ve API, iskemik inme sonrası bir yıllık mortaliteyi öngörmede değerli prediktörlerdir. Tromboembolizm risk faktörlerini içeren CHA_2DS_2-VASc skoru, kötü sonlanımlar açısından lipid parametrelerine kıyasla daha güçlü duyarlılık ve özgünlüğe sahiptir.

Anahtar kelimeler: Aterojenik plasma indeksi, iskemik inme, kolesterol, lipoprotein

Introduction

Stroke is the third most common cause of death worldwide after cancer and coronary artery disease. Ischemic stroke is one of the most common forms of stroke and constitutes approximately 87% of all cases (1). Even if an individual survives a stroke, the risks continue; the incidence of death or recurrent stroke within 5 years is between 25% and 30% (2). Despite current treatment and a wide hospital network that allows rapid intervention, stroke outcomes are still not satisfactory.

The primary pathophysiology of the ischemic stroke involves atherosclerosis. Hyperlipidemia is one of the major contributing risk factors (3). Intimal thickening caused by the accumulation of low-density lipoprotein cholesterol (LDL-C) particles within the endothelium is the first step of atherosclerosis (4). Numerous studies have been conducted on the effects of various cholesterol markers on ischemic stroke and their role in its treatment (5). However, there is no sufficient consensus on the effects of cholesterol present during stroke on outcomes. Various cholesterol parameters, including total cholesterol (T-Chol), LDL-C, triglyceride (Tg), high density lipoprotein (HDL-C), non-HDL-C, Tg/HDL-C and atherogenic plasma index (API), have been studied to predict stroke outcomes (6,7).

CHA_2DS_2-VASc is a scoring system that includes the variables of congestive heart failure, hypertension, age ≥75, diabetes, previous stroke, vascular disease, age 65 to 74, and sex category (female). It has been used in cardiology guidelines for a long time to predict the risk of cardio-embolism in atrial fibrillation (AF) (8).

CHA_2DS_2-VASc score was found to be statistically significant in predicting 1-year major cardiovascular events in acute myocardial infarction (9). CHA_2DS_2-VASc score predicted all cause of mortality for both in hospital and medium term (one year) in patients underwent primary percutaneous coronary intervention due to ST-elevation myocardial infarction (10).

The CHA_2DS_2-VASc score is feasible in predicting stroke, but there are not enough clinical studies to support its use as a risk predictor independent of AF in ischemic stroke. AF is a risk factor that negatively affects one-year outcomes in ischemic stroke; however, isolated effects of the CHA_2DS_2-VASc score on prognosis in ischemic stroke are not clear (11). Scoring systems can provide important information about the patient's prognosis and current risks without creating additional costs for clinicians. In scoring systems and prognosis assessments, different lipid parameters and their ratios are frequently monitored in cardiovascular risk studies. Although many cardiovascular risk factors are included in the CHA_2DS_2-VASc score, there is no marker that directly shows lipid metabolism. For this reason, in our study lipid parameters were compared with the CHA_2DS_2-VASc score, despite the lack of a direct relationship between them. The aim of the study was to compare the effects of initial CHA_2DS_2-VASc and lipid parameters on one-year outcomes in patients with ischemic stroke.

Materials and Methods

Study Design and Population

This study was designed retrospectively and the raw data were obtained from the health care recording system between January 2018 and December 2022. Patients who were admitted to hospital with ischemic stroke were enrolled in this study. According to a medical database, 878 patients were hospitalized due to cerebrovascular events and 610 of those patients were hospitalized due to ischemic stroke. Twenty-seven patients were excluded due to hemorrhagic transformation during follow-up, missing data, and refusal to participate in the study. The absence of medical records or patients' permission, patients under eighteen years old, severe kidney, liver or congestive heart failure, simultaneous myocardial infarction or pulmonary embolism, end stage cancer, previous carotid artery intervention, were exclusion criteria. Patients who could not undergo magnetic resonance imaging (MRI) due to pacemakers or various body implants were not included in the study.

Every individual participant signed informed consent in accordance with regulations. The study protocol was approved by the Siir University's Ethics Committee

(no: 2022/12/01/02, date: 13.12.2022). The study was conducted in line with the ethical considerations set forth in the Declaration of Helsinki and Good Clinical Practice Guidelines. All participants included in this study were contacted by phone. Information about the individuals' conditions was obtained from them or their relatives. Data on those included in the study were obtained from the Ministry of Health's "e-pulse" system and hospital database.

Management of Stroke Patient

All patients presenting to the emergency department with a diagnosis of acute cerebrovascular accident were evaluated in accordance with the specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic algorithm (12). All patients underwent cranial computed tomography and MRI scans under the direction of neurology consultants. Cranial intracerebral and subarachnoid hemorrhages were excluded with neuroimaging. Neurological dysfunctions with symptoms lasting less than 24 hours were evaluated as transient ischemic attacks. Stroke severity was determined by neurology consultants according to the national institute of health stroke scale (NIHSS). Intravascular fibrinolysis and/or anti-platelet anti-coagulant treatment was decided in line with acute stroke guidelines. Patients with NIHSS score 6 and above and internal carotid artery or middle cerebral artery segment 1 occlusion were directed to mechanical thrombectomy if there were no contraindications. Fibrinolytic treatment was applied to patients younger than 80 years of age who presented within the first 3 hours of symptom onset, with NIHSS >25, with no previous stroke history, and not using oral anti-coagulants (13).

Data collection and clinical outcomes

Patient follow-up continued until death from any cause occurring after hospital admission. Demographic information, hemogram, lipid parameters, and other routine laboratory findings were obtained from the hospital database and recorded. Hemogram parameters, markers related to lipid metabolism, and their ratios were calculated and compared between groups. To prevent the possibility of bias, individuals with more than 20% missing data were not included in the study. All-cause mortality during the one-year follow-up period was accepted as the primary outcome. Subgroups of all-cause mortality were not specifically identified.

Statistical Analysis

All the statistical analysis was performed using SPSS version 23.0 (IBM SPSS Statistics, USA). Mean ± standard deviation was used for continuous variables, and for categorical variables, percentage and numbers were used. The distribution characteristics of variables were determined by Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-normally distributed variables were presented as median, with minimum and maximum values. Normally distributed continuous variables were evaluated with paired samples t-test. Non-normally distributed variables were examined with the Mann-Whitney U test or the Kruskal-Wallis test. Categorical variables were compared with chi-square tests. Multi-variable Cox regression analysis was used to determine the independent predictors associated with primary outcomes. Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) including variables of total-C, non-HDL cholesterol, API, Mon/HDL and CHA_2DS_2-VASc score. Receiver operating characteristic (ROC) curve analysis was applied to demonstrate the predictive power of variables for mortality in stroke follow-up. The area under the curve (AUC) was calculated with a 95% CI. Probability p-values of <0.05 were considered to indicate statistical significance.

Results

This study consisted of 583 patients who suffered from ischemic stroke. The mean age was 71.05±11.83 and 50.0% (n=292) of them were male. Mortality was defined during the one-year follow-up period among patients divided into two groups based on the primary end-point. The total mortality rates during one-year follow-up were 17.3% (n=101). The mean age was significantly higher in the mortality group (76.88±10.25 vs. 69.78±13.44; p=0.010). In the demographics of the population, hypertension, diabetes mellitus, atrial fibrillation, obesity, heart failure and atherosclerotic cardiovascular diseases had statistically higher prevalence in the non-survivor group (Table 1). T-Chol was significantly higher in mortality group (181.00±44.92 vs. 172.21±51.83, p=0.003). Tg and LDL-C were higher in the group with mortality, however, the difference is not statistically significant (p=0.511, 0.064, respectively). HDL-C was higher in the survival group, but not statistically significant (p=0.191). Non HDL-C and API were significantly higher in patients who had mortality in one year follow-up (138.58±42.51 vs. 131.34±49.04, p=0.031 and 0.52±0.25 vs. 0.48±0.27, p=0.019). Monocyte (MON) to HDL ratio was higher in survival group (0.013±0.19 vs. 0.03±0.39, p=0.047). The hemogram parameters were similar in each group except neutrophil which was higher in mortality group (7.14±4.35 vs. 6.10±3.25, p=0.006). The CHA2DS2-VASc score was found higher in patient who

had primary outcomes in one year rather than survival (5.16±1.49 vs. 4.94±1.68, p=0.005).

A multivariable logistic regression model was prepared with the variables of T-Chol, non-HDL-C, API, MON/HDL, and CHA2DS2-VASc score to determine the independent predictors increasing the mortality rate in the first year of stroke (Table 2). API and CHA_2DS_2-VASc were found to be independent variables to predict mortality during follow-up in the first year (HR: 1.062, 95% CI: 0.973-1.252, p=0.007; HR: 1.567, 95% CI: 1.003-2.174, p=0.004).

ROC analysis was used to compare the predictive power of API and CHA_2DS_2-VASc for predicting mortality during

Table 1. Initial demographics and laboratory findings of patients at admission and comparison according to 12-months follow-up

Variable	Mortality (n=101)	Survival (n=482)	p-value
Age, years	76.88±10.25	69.78±13.44	0.010
Male gender, % (n)	47.5 (48)	50.6 (244)	0.571
Hypertensiyon, % (n)	72.3 (73)	32.4 (156)	<0.001
Diabetes mellitus, % (n)	58.4 (59)	22.8 (110)	<0.001
Smoking habbits, % (n)	24.8 (25)	6.8 (33)	<0.001
Atrial fibrillation, % (n)	41.6 (42)	23.4 (113)	<0.001
Morbid obesity, % (n)	15.8 (16)	1.2 (6)	<0.001
Peripheral vascular disease, % (n)	15.8 (16)	3.9 (19)	<0.001
Heart failure, % (n)	32 (32)	9.5 (46)	<0.001
Coronary artery disese, % (n)	53.5 (54)	16.2 (78)	<0.001
Total-C, mmol/L	181.00±44.92	172.21±51.83	0.003
Triglyceride, mmol/L	194.14±75.26	188.79±69.64	0.511
HDL-C, mmol/L	40.87±11.20	42.41±10.70	0.191
LDL-C, mmol/L	113.70±37.71	106.01±38.93	0.064
Non-HDL-C, mmol/L	138.58±42.51	131.34±49.04	0.031
Tg/HDL-C	3.75±2.62	3.53±2.65	0.040
API	0.52±0.25	0.48±0.27	0.019
LDL/HDL	2.77±1.14	2.75±1.52	0.853
MON/HDL	0.013±0.19	0.03±0.39	0.047
WBC, cells/μL	9.77±4.28	9.08±3.78	0.105
Hemoglobin, g/dL	13.26±2.37	13.60±1.93	0.125
Platelet, cells/μL	235.92±87.97	249.63±76.79	0.112
RDW, cells/μL	52.39±10.51	50.24±10.65	0.065
Neutrophil, cells/μL	7.14±4.35	6.10±3.25	0.006
Lymphocyte, cells/μL	1.91±1.27	2.14±1.08	0.054
Monocyte, cells/μL	0.52±0.28	0.52±0.23	0.867
CHA_2DS_2-VASc, n	5.16±1.49	4.94±1.68	0.005

Total-C: Total cholesterol, HDL-C: High density lipoprotein, LDL-C: Light density lipoprotein, Tg: Triglyceride, MON: Monocyte, RDW: Red cell distribution width, WBC: White blood cell, API: Atherogenic plasma index

Table 2. Multivariable adjusted regression analysis for mortality in 12-months follow-up period

Variable	Exp (B)	Confidence interval	p-value
T-Chol	0.795	0.963-1.745	0.068
Non-HDL	1.051	0.996-1.125	0.084
API	1.062	0.973-1.252	0.007
MON/HDL	1.125	0.967-1.424	0.073
CHA_2DS_2-VASc	1.567	1.003-2.174	0.004

Total-C: Total cholesterol, HDL-C: High density lipoprotein, LDL-C: Light density lipoprotein, Tg: Triglyceride, MON: Monocyte

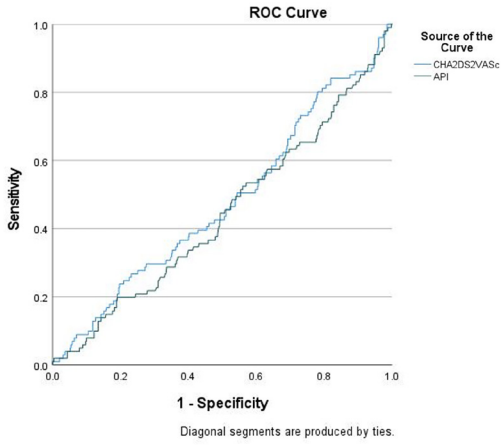

Figure 1. ROC analysis of CHA_2DS_2-VASc and API to compare their predictive ability for mortality after ischemic stroke

API: Atherogenic plasma index, ROC: Receiver operating characteristic

the first follow-up year (Figure 1). Accordingly, the API cut-off value of 0.48 predicted the development of with a sensitivity and specificity of 75.6% and 72.4%, respectively, (AUC: 0.568; 95% CI: 0.410-0.723; p=0.045). The CHA_2DS_2-VASc score was better than API to predict mortality (AUC: 0.756, 95% CI: 0.602-0.953; p=0.014). The sensitivity was 82.5%, and the specificity was 79%, with a cut-off value of 4.4.

Discussion

The average one-year mortality rate following ischemic stroke has been reported in the literature as 13-20% (14). In our study, the one-year all-cause mortality rate was observed to be 17.3%. This study aimed to predict one-year mortality after ischemic stroke using lipid parameters and the CHA_2DS_2-VASc score both API and CHA_2DS_2-VASc scores were identified as significant predictors of mortality. In the ROC analysis, API demonstrated a sensitivity of 75.6%, while the CHA_2DS_2-VASc score showed a higher sensitivity of 82.5%.

AF negatively affects outcomes in patients with ischemic stroke. Previous studies have reported that AF is an independent predictor of both mortality and cardiac embolism, particularly in cases involving large infarct territories (10). The CHA_2DS_2-VASc scoring system was developed to determine the risk of stroke in patients with AF. Recent studies have shown that a higher CHA_2DS_2-VASc score is associated with worse outcome after ischemic stroke. In a 3-month follow-up of 6,612 ischemic stroke patients, those with a CHA_2DS_2-VASc score of 2 or above experienced higher mortality and morbidity rates (15). In a 5-year follow-up study of 1,756 ischemic stroke patients without AF, intermediate and high-risk CHA_2DS_2-VASc scores were significantly associated with increased mortality risk compared to low-risk scores (HR: 3.56, 95% CI: 1.89-6.70) (16). Yang et al. (17) demonstrated that the CHA_2DS_2-VASc score lacks sufficient prognostic value after lacunar stroke in patients without AF. However, in patients with AF, a strong relationship between higher scores and poor outcomes was emphasized (17). In our study, the entire patient population was evaluated without distinguishing AF status, and the CHA_2DS_2-VASc score, was identified as a statistically significant predictor of one-year mortality in multivariate analyses (OR: 1.567, 95% CI: 1.003-2.174, p=0.004). The CHA_2DS_2-VASc scoring system serves as a valuable tool for clinicians in assessing thromboembolic risk and managing anticoagulation in cases of persistent or paroxysmal AF. Clinical studies have shown that the variables included in the CHA_2DS_2-VASc score are also useful for predicting patient prognosis. Its predictive power has been demonstrated in conditions such as heart failure and acute coronary syndromes, and recent studies have supported its feasibility in predicting post-stroke outcomes (18). In our study, the CHA_2DS_2-VASc score was significantly higher in the group with poor outcomes (p=0.005). It was also identified as a strong independent predictor of mortality within one year (HR: 1.567, p=0.004). These findings align with existing literature, supporting the use of the CHA_2DS_2-VASc score as a reliable variable for predicting poor outcomes in ischemic stroke follow-up.

Lipoproteins, Tg, and the API contribute to an increased frequency of athero-thromboembolic events in both coronary and cranial systems. However, their relationship with mortality after ischemic stroke remains unclear. While high LDL-C is linked to increased mortality in the general population, evidence in ischemic stroke patients is limited (19).

The widely accepted approach, “lower is better,” is contradicted by studies showing mixed results. In a 30-day follow-up of 45,669 ischemic stroke patients, those with T-Chol <120 mg/dL had a higher risk of mortality (HR: 1.29, p<0.001) (20). Among dialysis patients, both T-Chol <120 mg/dL and >200 mg/dL were associated with increased mortality (HR: 2.64 and 3.58, p<0.05) (20). High cholesterol contributes to inflammation and cytokine release; it increases thrombogenicity and reperfusion injury, making patients more vulnerable during recovery. A study by Tirschwell et al. (21) showed high T-Chol levels, increased

the mortality risk by 1.6 times, while another retrospective analysis reported a 2.17-fold increase in mortality with T-Chol >5.2 mmol/L (22).

TG, and TG derived metabolic indices were good predictors of cardiovascular events and demonstrated significant predictive ability during the follow-up period in terms of major adverse events. Liu et al. (7) compared different lipid metabolic markers as 3-month prognosis predictors in a prospective study including 1463 acute ischemic stroke patients. In the study, Tg (p=0.001), non-HDL-C (p=0.003), and API (p<0.001) were observed to be statistically significant and higher in groups with poor outcomes. HDL was found to be inversely correlated with outcomes (p=0.021) (7), suggesting that higher HDL levels were associated with less favorable outcomes.Our study is also in direct correlation with the literature in which T-Chol, non-HDL-C, Tg/HDL ratio and API were observed to be statistically significantly higher in the group with poor outcome. In the analysis in which mortality predictor variables were examined with Cox regression analysis, only API was statistically significant.

The CHA_2DS_2-VASc score is a widely applicable scoring system that offers valuable insights into the surveillance of diseases driven by athero-thromboembolic pathophysiology, impacting both the cardiac and vascular systems. Its ease of use and cost-effectiveness have contributed to its widespread adoption in clinical studies exploring patient outcomes. The variables included in the CHA_2DS_2-VASc scoring model are primarily established cardiovascular risk factors, with the exception of gender. While cardiovascular events are generally less frequent in women, their outcomes tend to be more severe and fatal, which explains this exception. Notably, the CHA_2DS_2-VASc score lacks any direct indicators related to cholesterol or its derivatives. However, cholesterol sub-derivatives, easily accessible and routinely measured, have been shown in the literature to provide valuable prognostic information. In our study, we evaluated the effects of the CHA_2DS_2-VASc score and cholesterol sub-derivatives on medium-term survival after ischemic stroke. While the API emerged as a strong predictor among cholesterol sub-groups, the CHA_2DS_2-VASc score proved to be an even stronger predictor of one-year mortality, likely due to its inclusion of a broader range of demographic and clinical variables.

Study Limitations

The main limitations of the study are that it was not designed prospectively, separate subgroups were not created for AF, and secondary outcomes such as recurrent stroke and hemorrhage were not included alongside the primary outcome points. The most significant limitation of the study is the lack of scoring systems that indicate the severity of stroke in patients. We believe that classifying patients based on stroke severity could have an impact on the results. The one-year follow-up is long enough to introduce bias into the study in terms of drug-patient compliance. In addition, the use of anticoagulant and/or antiplatelet agents was not specified in the study.

Conclusion

In ischemic stroke, both in-hospital and post-discharge mortality, as well as adverse events, affect more than one-fourth of the patients. It is important for clinicians to determine the patients' risks of adverse outcomes and to identify the factors that may lead to these risks. In patients with ischemic stroke, cholesterol levels detected at baseline were found to be higher in the group with poor outcomes. API was found to be a strong predictor that can be used in one-year follow-ups. CHA_2DS_2-VASc score is a stronger predictor than all cholesterol parameters in both determining the risk of thromboembolic events and predicting post-event prognosis. The CHA_2DS_2-VASc score is a more sensitive model in predicting mortality than the API.

Ethics

Ethics Committee Approval: The study protocol was approved by the Siir University's Ethics Committee (no: 2022/12/01/02, date: 13.12.2022). The study was conducted in line with the ethical considerations set forth in the Declaration of Helsinki and Good Clinical Practice Guidelines.

Informed Consent: Every individual participant signed informed consent in accordance with regulations.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A., Y.E.Y., Concept: D.O., Design: D.O., Y.E.Y., Data Collection or Processing: M.A., Analysis or Interpretation: D.O., Y.E.Y., Literature Search: M.A., Writing: D.O.

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

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ORIGINAL RESEARCH

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Uric Acid as a Biochemical Marker of Metabolic Dysfunction in Polycystic Ovary Syndrome: Its Association with Insulin Resistance and Adiposity

Polikistik Over Sendromunda Metabolik Disfonksiyonun Biyokimyasal Bir Belirteci Olarak Ürik Asit: İnsülin Direnci ve Adipozite ile İlişkisi

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Abstract

Objective: The association between polycystic ovary syndrome (PCOS), a widespread endocrine disorder in childbearing-aged women, and elevated serum uric acid levels, along with its connection to metabolic disorders, remains an ongoing area of research. This study aimed to examine the associations between serum uric acid, adiposity, body composition, and hormonal parameters in patients with PCOS, while identifying independent predictors and evaluating uric acid's role in metabolic disorders.

Method: The retrospective study included 123 women with PCOS, aged 18 to 35, diagnosed according to the Rotterdam criteria, and 41 age-and body mass index (BMI)-matched controls without PCOS or hyperandrogenism. Exclusion criteria included having chronic diseases and receiving medications that affect hormonal and metabolic parameters or uric acid. Data collected comprised menstrual histories, anthropometric measurements, hormonal, metabolic, and body composition parameters.

Results: Serum uric acid was significantly greater in patients with PCOS than controls (p=0.008). While age and BMI were similar across groups, waist-to-hip ratio was greater in PCOS group (p=0.009). Fasting insulin (p=0.026) and dynamic insulin indices (p=0.001) were elevated in the PCOS group, although homeostasis model assessment of insulin resistance (HOMA-IR) was comparable (p=0.064). No major differences were observed in the body composition or metabolic parameters, including lipid profiles, visceral adiposity index, and lipid accumulation product (LAP). A multiple regression analysis demonstrated that HOMA-IR (B=0.16, p<0.001), BMI (B=0.03, p=0.017), and LAP (B=0.01, p=0.035)

Öz

Amaç: Doğurganlık çağındaki kadınlarda yaygın bir endokrin bozukluk olan polikistik over sendromu (PKOS) ile yüksek serum ürik asit seviyeleri arasındaki ilişki ve bunun metabolik bozukluklarla bağlantısı ilgi çekici araştırma alanı olmaya devam etmektedir. Bu çalışmanın amacı, PKOS hastalarında serum ürik asit düzeyi ile yağlanma, vücut kompozisyonu ve hormonsal parametreler arasındaki ilişkiyi incelemek, bağımsız belirleyicileri tanımlamak ve ürik asidin metabolik bozukluklardaki rolünü değerlendirmektir.

Yöntem: Retrospektif çalışmaya, yaşları 18 ila 35 arasında değişen ve Rotterdam kriterlerine göre tanı konulmuş 123 PKOS hastası kadın ile PKOS veya hiperandrojenizmi olmayan, yaş ve vücut kitle indeksi (VKİ) açısından eşleştirilmiş 41 sağlıklı kadın dahil edilmiştir. Dışlama kriterleri, kronik hastalıklara sahip olunması ve hormonsal ve metabolik parametreleri veya ürik asit seviyelerini etkileyen ilaçların alınmasıdır. Elde edilen veriler hastaların adet geçmişlerini, antropometrik ölçümleri, hormonsal, metabolik ve vücut kompozisyonu parametrelerini içermektedir.

Bulgular: PKOS hastalarında serum ürik asit düzeyleri kontrollere göre anlamlı olarak yüksek saptanmıştır (p=0,008). Yaş ve VKİ açısından gruplar benzer özellikte olmasına rağmen, PKOS hastalarında bel-kalça oranı daha büyüktür (p=0,009). PKOS grubunda açlık insülini (p=0,026) ve dinamik insülin indeksleri (p=0,001) anlamlı derecede yüksek olmasına rağmen insülin direnci için homeostaz model değerlendirmesi (HOMA-IR) benzer bulunmuştur (p=0,064). Lipid profilleri, visseral adipozite indeksi ve lipid birikim ürünü (LAP) dahil olmak üzere metabolik veya vücut kompozisyonu parametrelerinde anlamlı bir farklılık gözlenmemiştir. Çoklu regresyon analizi, HOMA-IR (B=0,16, p<0,001), VKİ (B=0,03,

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Abstract

were independent determinants of uric acid, collectively explaining 48.4% of the variance (R^2=0.484, adjusted R^2=0.467).

Conclusion: The study revealed a significant association between increased serum uric acid levels and metabolic problems in PCOS, particularly with insulin resistance and adiposity. Uric acid may be a potential biochemical marker for early metabolic risk assessment in PCOS.

Keywords: Adiposity indices, insulin resistance, polycystic ovary syndrome, uric acid

Öz

p=0,017) ve LAP'nin (B=0,01, p=0,035) ürik asidin bağımsız belirleyicileri olduğunu ve bunların varyansın %48,4'ünü açıkladığını göstermiştir (R^2=0,484, düzeltilmiş R^2=0,467).

Sonuç: Bu çalışma, PKOS hastalarındaki metabolik bozukluklar ile serum ürik asit yüksekliği arasında, özellikle insülin direnci ve adipozite ile anlamlı bir ilişki olduğunu ortaya koymuştur. Ürik asit PKOS'de erken metabolik risk değerlendirmesinde bir potansiyel biyokimyasal belirteç olabilir.

Anahtar kelimeler: Adipozite indeksleri, insülin direnci, polikistik over sendromu, ürik asit

Introduction

Polycystic ovary syndrome (PCOS) is a widespread endocrine disorder that affects women at all stages of their reproductive journey. It is characterized not only by its effects on fertility and physical appearance but also by the associated metabolic disorders. These problems are related to several factors, including hormonal imbalances, ovulation disorders, chronic inflammation, and difficulties with weight management in people with PCOS (1).

Uric acid, a metabolic byproduct of purine degradation, serves a protective role by maintaining oxidative balance within the body under normal physiological conditions. However, when uric acid levels rise, they can exhibit pro-oxidant and pro-inflammatory effects, potentially leading to damage across multiple organ systems. Elevated serum uric acid is linked to increased risks of renal and cardiovascular diseases (2,3). Additionally, it is strongly associated with various metabolic conditions, including diabetes, insulin resistance, obesity, hypertension, and metabolic syndrome conditions often seen in individuals with PCOS (4-8). Furthermore, growing evidence suggests that serum uric acid is frequently elevated in patients with PCOS (9-11).

Hyperandrogenemia, obesity, and hyperinsulinism, all associated with PCOS, are thought to contribute to elevated uric acid levels. While the metabolic complications of PCOS are well documented, the specific role of uric acid in this context remains unclear. Uric acid is not only linked to metabolic risks but also actively participates in a vicious cycle that is believed to mediate the development of insulin resistance and hyperandrogenemia. This may be occurring through mechanisms such as increased oxidative stress, inflammation, and mitochondrial dysfunction (10,12).

To our knowledge, there are no studies that have investigated the combined effects of adiposity indices, body composition, and hormonal parameters established cardiovascular risk indicators on uric acid in women with PCOS. This research aimed to explore the connection between serum uric acid levels and adiposity indicators, body composition, and hormonal factors in patients with PCOS, to identify independent predictors, and to evaluate the potential of uric acid as an early marker of metabolic risk. This could facilitate the development of early intervention strategies to manage hyperuricemia and prevent metabolic disorders.

Materials and Methods

Study Design

The retrospective study involved 123 women aged 18 to 35 years, diagnosed with PCOS according to the Rotterdam criteria, who attended our tertiary outpatient clinic between 2017 and 2019. A control group consisting of 41 age and body mass index (BMI)-matched women without PCOS was also included, with a ratio of one control for every three patients. The data collected encompassed comprehensive menstrual histories, anthropometric measurements, as well as hormonal and metabolic parameters for all participants. Ovarian function in the control group was evaluated by confirming regular menstrual cycles (occurring every 24-36 days) and the absence of signs or symptoms of hyperandrogenism. Furthermore, none of the participants in the control group had any clinical history of endocrine or reproductive disorders, and their hormonal parameters fell within the normal range for reproductive-age women. The study was conducted in agreement with the Declaration of Helsinki II and was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (reference number: 0l0.99/59, date: 24.02.2024). The requirement for written informed consent was waived by the Declaration of Helsinki, as only medical data from patient records were used in this retrospective study.

The exclusion criteria included: i) secondary causes of hyperandrogenemia such as non-classical congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors for patients diagnosed with PCOS; ii) a history of hypertension, diabetes, cardiovascular events, oncological diseases, thyroid dysfunction, or hyperprolactinemia; iii) the use of oral contraceptives, anti-androgens, insulin sensitizers, or medications that influence uric acid levels, such as thiazide diuretics or aspirin, within the six months prior to the study; iv) insufficient data.

PCOS Definition Criteria

PCOS was diagnosed in accordance with the 2003 Rotterdam criteria after excluding other potential causes of hyperandrogenemia. The diagnosis required the presence of at least two of the following criteria: [1] Clinical hyperandrogenism or hyperandrogenemia: Clinical hyperandrogenism is assessed using the modified Ferriman-Gallwey score (with hirsutism indicated by a score exceeding 8), while hyperandrogenemia is confirmed through laboratory tests that reveal elevated serum testosterone and dehydroepiandrosterone sulfate (DHEAS) levels. [2] Oligo-ovulation or anovulation, characterized by fewer than nine menstrual cycles per year, cycle lengths outside the range of 26 to 35 days, or luteal phase progesterone levels below 4 ng/mL in regular cycles. [3] Polycystic ovarian morphology, identified via ultrasound as the presence of 12 or more antral follicles (ranging from 2 to 9 mm) or an ovarian volume exceeding 10 mL in at least one ovary.

Measurements and Calculations

Height, weight, waist circumference (measured at the narrowest point between the rib cage and iliac crest during expiration while standing), and hip circumference (measured at the widest point over the femoral trochanters) were recorded. Various adiposity indices, including BMI, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), visceral adiposity index (VAI), and lipid accumulation product (LAP) were calculated. BMI was determined by dividing weight (in kg) by height squared (in m^2). The VAI was calculated using the formula: [(waist circumference in cm/36.58)+(1.89xBMI)x(triglycerides (TG)/0.81) x(1.52/high-density lipoprotein cholesterol (HDL-C) in mmol/L)]. The LAP was calculated using the formula: [(waist circumference in cm-58)xTG in mmol/L]. The free androgen index (FAI) was derived by dividing total testosterone (TT) by sex hormone-binding globulin (SHBG) and multiplying by 100. Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated using fasting insulin (μIU/mL) and fasting plasma glucose (mg/dL) with the formula fasting insulin x fasting plasma glucose/405. An oral glucose tolerance test (OGTT) was performed to measure plasma insulin and glucose levels at 0, 30, 60, 90, and 120 minutes after administering 75 g of glucose. The areas under the glucose and insulin curves from the OGTT were used to calculate the dynamic insulin secretion index [insulin/glucose area under the curve $(AUC)_{OGTT}$]. Body composition and basal metabolic rate (BMR) were measured using a bioelectrical impedance analysis (BIA) system.

Laboratory Analysis

Laboratory evaluations were conducted between the second and fifth days of spontaneous menstrual cycles, following a minimum fasting period of 10 hours. In individuals with amenorrhea, pregnancy was ruled out before testing. Glucose, total cholesterol (TC), TG, HDL-C, and uric acid levels were determined using an enzymatic colorimetric method on the AU5800 Clinical Chemistry System Analyzer (Beckman Coulter, Florida, USA). The Friedewald formula, TC – HDL-C – (TG/5), was used to calculate low-density lipoprotein cholesterol (LDL-C). Insulin levels were measured using an electrochemiluminescence immunoassay on the E-170 Immunological Analyzer System (Roche Diagnostics, Osaka, Japan). Hormonal assessments included TT, SHBG, DHEAS, estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), 17-hydroxyprogesterone, and prolactin, which were analyzed using the UniCel DXI 800 Access Immunoassay System (Beckman Coulter, Florida, USA). Body composition was evaluated using a BIA system (Tanita BC-418 MA, Tanita Corporation, Tokyo, Japan).

Statistical Analysis

Statistical analyses were conducted using statistical package for the social sciences (SPSS) software version 17.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was applied to assess the normality of the data. Categorical variables were presented as frequencies and percentages, parametric variables were expressed as mean ± standard deviation (SD), and non-parametric variables were presented as median and interquartile range (IQR, 25^{th}-75^{th} percentiles). For group comparisons, the independent samples t-test was employed for parametric data, and the Mann-Whitney U test was utilized for non-parametric data. Correlations were analyzed using Spearman's rank correlation. A multiple linear regression analysis was conducted to identify independent predictors of uric acid levels. Model fitting and residual diagnostics confirmed the validity of the regression model, with residual normality

supporting its appropriateness. The predictor variables included BMI, WHR, WHtR, FAI, HOMA-IR, TG/HDL, VAI, LAP, and body composition parameters, all of which were significantly correlated with uric acid levels. However, due to multicollinearity, VAI, TG/HDL, and body composition parameters were excluded from the analysis. Analysis of variance results were statistically significant across models, highlighting the impact of predictors on uric acid levels, with 5% types-I error level applied to assess statistical significance. The Ins AUC120/Glu AUC120 ratio was analyzed using receiver operating characteristic (ROC) curves. A power analysis was performed using the G*Power (v.3.1.9) program to calculate the power of the study. The analysis was conducted based on the number of patients included in the study, with an effect size of 0.3, an alpha error of 0.05, and a statistical power of 99%.

Results

Clinical Characteristics of Patients with PCOS

In a cohort of patients diagnosed with PCOS, 94% (n=115) exhibited evidence of hyperandrogenism, with 78% (n=96) presenting clinical hyperandrogenism and 66% (n=81) demonstrating hyperandrogenemia. Also, ovulatory dysfunction was observed in 72% (n=89) of the patients, and 87% (n=107) displayed polycystic ovarian morphology through ultrasound imaging.

Adiposity Indices, Hormonal, and Metabolic Features of the PCOS and Control

The characteristics of the PCOS and control groups were comparable in terms of age, BMI, waist circumference, and WHtR. However, WHR was notably greater in patients with PCOS (p=0.009). Hormonal analysis revealed that individuals with PCOS exhibited elevated levels of LH/FSH, TT, and DHEAS (p=0.028, p=0.019, p=0.001), along with decreased levels of SHBG when compared to the controls (p=0.001).

Fasting insulin levels (p=0.026), as well as early-phase and total insulin secretion (Ins AUC30/Glu AUC30 and Ins AUC120/Glu AUC 120) as assessed by the OGTT (p=0.001), were significantly higher in patients with PCOS. However, HOMA-IR values were comparable between the two groups (p=0.064). Figure 1 displays the ROC curve for Ins AUC120/Glu AUC120 with an AUC of 0.695. The metabolic parameters and adiposity indices, including lipid profiles, VAI, and LAP, did not show significant differences. Notably, serum uric acid was elevated in women with PCOS compared to the control group (p=0.008) (Table 1).

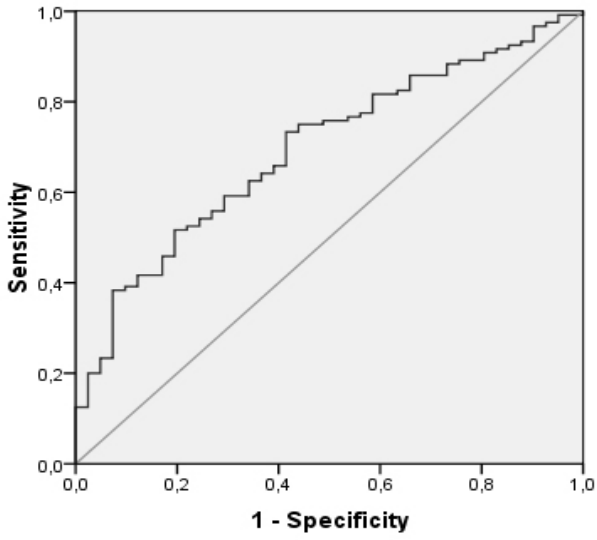

Figure 1. Graph of the InsAUC120/GlucAUC120 ratio (AUC=0.695)

ROC: Receiver operating characteristic, AUC: Area under the curve

Body Composition Parameters of PCOS and Control Groups

In a comparison of body composition parameters between the PCOS group and the control group, no significant differences were observed in fat mass (FM), body fat percentage (PBF), soft lean mass (SLM), total body water (TBW), Trunk FM, or Trunk SLM. However, patients with PCOS demonstrated a higher BMR compared to the control (p=0.033) (Table 2).

Correlations Between Serum Uric Acid and Adiposity Indices, Hormonal Levels, and Body Composition Parameters in Patients with PCOS

In patients with PCOS, a significant positive association was observed between uric acid and various measures of adiposity, including BMI, WHR, and WHtR (p<0.01, r=0.548, 0.374, 0.544 respectively). Furthermore, metabolic parameters and adiposity indices such as the HOMA-IR, TG/HDL ratio, VAI, and LAP showed positive correlations with serum uric acid levels (p<0.01, r=0.511, 0.399, 0.430, 0.587 respectively). Additionally, all body compartments measured by BIA (PBF, FM, SLM, TBW, Trunk FM, Trunk SLM) displayed positive correlations with serum uric acid levels (p<0.01, r=0.448, r=0.532, r=0.503, r=0521, r=0.518, r=0.499 respectively) (Table 3).

Table 1. Adiposity indices, hormonal, and metabolic characteristics of the PCOS and control groups

	PCOS	Control	p-value
	(n=123)	(n=41)	
Age (years)	25 (19-28)	25 (21-28)	0.118
BMI (kg/m²)	27.2 (22.5-31.5)	23.9 (21.1-32.5)	0.347
WC (cm)	85 (77-96)	80 (68-92)	0.071
WHR	0.81 (0.75-0.87)	0.78 (0.73-0.82)	**0.009**
WHtR	0.52 (0.47-0.59)	0.49 (0.43-0.57)	0.105
LH/FSH	0.9 (0.64-1.37)	0.76 (0.59-0.99)	**0.028**
TT (ng/dL)	69.5±90	35.5±12.4	**0.019**
SHBG (nmol/L)	29.4 (17.6-40.7)	46.2 (27.5-69.9)	**0.001**
FAI	2.2 (1.4-3.9)	0.8 (0.5-1.2)	**0.001**
DHEA-S (ug/dL)	314.3±143.2	200±83.1	**0.001**
PRL (ng/mL)	16 (11.5-24.1)	16 (10.7-19.5)	0.519
FPG (mg/dL)	88.1±9.4	91.1±9.3	0.080
FI (uU/mL)	14 (10-19)	10 (8-15)	**0.026**
Ins AUC30/Glu AUC30	0.43 (0.33-0.64)	0.33 (0.26-0.41)	**0.001**
Ins AUC 120/Glu AUC120	0.61 (0.42-0.88)	0.42 (0.32-0.58)	**0.001**
HOMA-IR	2.97 (2.01-4.43)	2.35 (1.61-3.43)	0.064
HbA1c (%)	5.1 (4.9-5.3)	5 (4.9-5.3)	0.880
TG (mg/dL)	80 (62-122)	76 (58-105)	0.294
LDL-C (mg/dL)	105.2±30.3	107±29.5	0.751
HDL-C (mg/dL)	48 (43-57)	53 (44-57)	0.207
TG/HDL-C	1.69 (1.13-2.72)	1.46 (0.99-2.19)	0.151
VAI	3.15 (2.14-5.02)	2.7 (1.79-3.96)	0.080
LAP	28.5 (13.2-48.9)	16.9 (7.6-40.1)	0.053
CRP (mg/L)	3.5 (3.4-3.6)	3.5 (3.3-3.5)	0.380
TSH (mIU/L)	2.13 (1.55-2.95)	2.06 (1.5-3.53)	0.566
Creatinine (mg/dL)	0.63±0.08	0.61±0.1	0.259
Uric acid (mg/dL)	4.46±0.91	4.02±0.79	**0.008**

BMI: Body mass index, WC: Waist circumference, WHR: Waist to hip ratio, WHtR: Waist to height ratio, LH/FSH: Luteinizing hormone to follicle-stimulating hormone ratio, TT, Total testosterone, SHBG: Sex hormone binding globulin, FAI: Free androgen index, DHEA-S: Dehydroepiandrosterone sulfate, PRL: Prolactin, FPG: Fasting plasma glucose, FI: Fasting insulin, Ins AUC30/Glu AUC30: Early phase insulin secretion, Ins AUC 120/Glu AUC120: Total insulin secretion, HOMA-IR: Homeostatic model of assessment-insulin resistance, HbA1c: Glycated hemoglobin, TG: Triglyceride, LDL-C: LDL cholesterol, HDL-C: HDL cholesterol, VAI: Visceral adiposity index, LAP: Lipid accumulation product, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, PCOS: Polycystic ovary syndrome, values are mean ± standard deviation and median (interquartile range), and p-values are from the samples t-test and Mann-Whitney U test

Multiple Linear Regression Analysis of Independent Factors Influencing Uric Acid Levels in Patients with PCOS Using Stepwise Selection

A multiple regression analysis was conducted to recognize the independent uric acid determinants in patients with PCOS using the stepwise selection method. To avoid multicollinearity, body composition parameters, VAI, and early and total insulin secretion indices were excluded from the regression model. The independent variables included in the analysis were age, BMI, WHR, WHtR, FAI, HOMA-IR, and LAP. Model 1 includes HOMA-IR as the sole predictor, which demonstrates a significant positive association with uric acid levels (B=0.26, p<0.001), explaining 37.3% of the variance (R^2=0.373, adjusted R^2=0.367). Model 2 incorporates both BMI and HOMA-IR, and both predictors remain significant. Together, HOMA-IR (B=0.18, p<0.001) and BMI (B=0.05, p<0.001) account for 45.8% of the variance (R^2=0.458, adjusted R^2=0.447). Model 3 introduces LAP as an additional predictor. All three predictors HOMA-IR (B=0.16, p<0.001), BMI (B=0.03, p=0.017), and LAP (B=0.01, p=0.035) demonstrate statistical significance. Together, they explain 48.4% of the variance in uric acid (R^2=0.484, adjusted R^2=0.467) (Table 4).

Table 2. Body composition parameters of PCOS and control groups

	PCOS	Control	p-value
	(n=123)	(n=41)	
Basal metabolic rate	1314 (1262-1379)	1284 (1231-1328)	0.033
Percentage of body fat (pbf) (%)	33.1 (27.1-38.6)	32.2 (25.6-39.1)	0.612
Total fat mass (kg) (FM)	22.7 (16.3-32.3)	18.5 (15-32.2)	0.301
Fat-free mass (kg) (FFM)	47.6 (42.1-52.8)	45 (41-51.2)	0.240
Soft lean mass (SLM)	43.9±6.2	42.2±6.4	0.146
Total body water (TBW)	34.4±4.9	33.2±5.3	0.195
Trunk fat mass (kg) (Trunk FM)	11.6 (8.3-16.4)	9.9 (7.6-16.8)	0.430
Trunk soft lean mass (kg) (Trunk SLM)	22.1±2.9	21±2.9	0.054

Values mean ± standard deviation and median (interquartile range), and p-values are from the samples t-test and Mann-Whitney U test, p<0.05 is significant, PCOS: Polycystic ovary syndrome

Table 3. Correlations between serum uric acid and adiposity indices, hormonal and body composition parameters in patients with PCOS

Adiposity indices, biochemical and hormonal parameters		Body composition parameters	
BMI	**0.548**[b]	BMR	**0.440**[b]
WHR	**0.374**[b]	PBF (%)	**0.448**[b]
WHtR	**0.544**[b]	FM (kg) (FM)	**0.532**[b]
LH/FSH	**-0.132**[c]	FFM (kg)	**0.533**[b]
FAI	**0.347**[b]	SLM (kg)	**0.503**[b]
HOMA-IR	**0.511**[b]	TBW	**0.521**[b]
Ins AUC 30/Glu AUC30	**0.331**[b]	Trunk FM (kg)	**0.518**[b]
Ins AUC 120/Glu AUC3120	**0.448**[b]	Trunk SLM (kg)	**0.499**[b]
TG/HDL	**0.399**[b]		
VAI	**0.430**[b]		
LAP	**0.587**[b]		

BMI: Body mass index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, FAI: Free androgen index, Ins AUC30/Glu AUC30: Early phase insulin secretion, Ins AUC 120/Glu AUC120: Total insulin secretion, HOMA-IR: Homeostatic model of assessment-insulin resistance, PCOS: Polycystic ovary syndrome, TG/HDL: Triglyceride/HDL cholesterol, VAI: Visceral adiposity index, LAP: Lipid accumulation product, BMR: Basal metabolic rate, PBF: Percentage of body fat, FM: Fat mass, FFM: Fat-free mass, SLM: Soft lean mass, TBW: Total body water, correlation coefficients are presented, [a]: p<0.05, [b]: p<0.01, [c]: p≥0.05

Discussion

In the current research, we found that serum uric acid levels were elevated in women with PCOS compared to BMI-and age-matched controls. Insulin resistance indices emerged as significant predictors of uric acid levels, with BMI and adiposity indices also playing important roles. These findings indicate that uric acid may serve as a valuable marker for metabolic disturbances in PCOS, particularly in relation to insulin resistance and adiposity.

Contrary to studies that identified no significant difference in uric acid levels between individuals with PCOS and non-hyperandrogenemic controls (13), our findings are consistent with previous research demonstrating elevated serum uric acid in PCOS (9-11). Although the increase in uric acid levels has been attributed to various factors, the impact of increased uric acid on the development of PCOS remains debated, especially considering that PCOS encompasses a variety of metabolic disorders.

Insulin resistance and hyperinsulinemia, independent of obesity, play a pivotal role in the development of metabolic disorders in individuals with PCOS. Our study emphasizes the significant impact of insulin resistance on elevated uric acid levels among patients with PCOS. Notably, we observed that HOMA-IR emerged as the strongest independent predictor of serum uric acid levels in this population. These findings align with existing research that links elevated plasma uric acid levels to increased insulin resistance (14,15). A possible explanation for this relationship is that insulin promotes the reabsorption of uric acid in the kidneys, thereby reducing its excretion (16).

Table 4. Multiple linear regression analysis of independent predictors for uric acid levels in patients with PCOS using stepwise selection

Model	B	SE	Beta	95% confidence interval		t	p-value
				Lower limit	Upper limit		
1. Constant	3.58	0.14		3.3	3.86	25.53	0.001
HOMA-IR	0.26	0.03	0.61	0.19	0.32	7.56	0.001
2. Constant	2.5	0.31		1.89	3.11	8.12	0.001
HOMA-IR	0.18	0.04	0.44	0.11	0.26	5.06	0.001
BMI	0.05	0.01	0.34	0.02	0.07	3.86	0.001
3. Constant	2.80	0.33		2.14	3.47	8.41	0.001
HOMA-IR	0.16	0.04	0.37	0.08	0.23	4.03	0.001
BMI	0.03	0.01	0.24	0.01	0.06	2.43	0.017
LAP	0.01	0.00	0.22	0.00	0.01	2.14	0.035

BMI: Body mass index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, FAI: Free androgen index, HOMA-IR: Homeostatic model of assessment-insulin resistance, LAP: Lipid accumulation product, SE: Standard error, PCOS: Polycystic ovary syndrome

Stepwise criteria: Probability of F to enter ≤0.05, probability of F to remove ≥0.1. Independent variables included in the analysis: Age, BMI, WHR, WHtR, FAI, HOMA-IR, LAP.

- Model 1 R^2=0.373, adjusted R^2=0.367
- Model 2 R^2=0.458, adjusted R^2=0.447
- Model 3 R^2=0.484, adjusted R^2=0.467

Moreover, elevated uric acid could induce inflammation and oxidative stress, which, as demonstrated in other studies, may contribute to the development of insulin resistance (17).

The literature presents conflicting evidence regarding the influence of insulin resistance on uric acid levels. According to Luque-Ramírez et al. (13), insulin resistance does not appear to have a direct effect on uric acid levels. In their study, 34 patients with PCOS were treated with either anti-androgenic combined oral contraceptives (COCs) or metformin over a period of 24 weeks. A decrease in serum uric acid was observed in those receiving COC treatment. While metformin did enhance insulin sensitivity, it did not have an impact on uric acid levels, indicating that insulin resistance may not be the primary factor influencing serum uric acid concentrations in this population. Furthermore, uric acid levels in individuals with PCOS were found to be comparable to those in the control. However, participants with obesity exhibited significantly higher uric acid levels across all study groups, regardless of their PCOS status. These findings indicate that hyperandrogenemia and obesity are major determinants affecting serum uric acid in patients with PCOS. In their study analyzing 17,753 adults from Korea, Bae et al. (18) demonstrated that increased BMI, waist circumference, and both general and abdominal obesity are significant risk factors for hyperuricemia in both genders. Similarly, research conducted by Mu et al. (9) revealed that the prevalence of hyperuricemia in patients with PCOS significantly increases with higher BMI levels. These results may be attributed to dysfunctional adipose tissue, which can lead to low-grade chronic inflammation associated with obesity. Consistently, in another study of patients with PCOS who were treated with COCs for six months indicated that laboratory changes were evident exclusively in PCOS patients with obesity, reinforcing the connection between obesity and inflammation (19).

The present study revealed a direct association between serum uric acid and body composition parameters assessed through BIA, indicating both general and abdominal obesity. However, it's important to note that BIA does not differentiate between subcutaneous and visceral adipose tissue (VAT). Zhang et al. (20) explored the relationship between body composition, measured by dual-energy X-ray absorptiometry, and elevated uric acid levels. Their study found that increased VAT mass may exacerbate hyperuricemia, while other adipose tissue compartments did not show a similar effect. LAP and VAI are cost-effective, non-invasive, and easily accessible metrics that incorporate BMI, waist circumference, TG, or HDL cholesterol. These indices are useful for predicting metabolic conditions in women with PCOS and serve as valuable tools for assessing and monitoring VAT changes (21,22). Ribeiro et al. (23) demonstrated that both LAP and VAI effectively screen for and help prevent metabolic syndrome and insulin resistance in individuals with PCOS. Furthermore, both our study and recent literature suggest that LAP is more effective than VAI in predicting visceral adiposity and metabolic disorders (23,24).

The relationship between hyperandrogenemia, a key characteristic of PCOS, and uric acid levels has been investigated in several studies. Findings indicate a positive correlation between elevated testosterone and FAI and increased serum uric acid (9,25). A large-scale study involving 1,183 PCOS patients and 10,772 control subjects without PCOS found that androgens might be a significant mediator in uric acid metabolism (9). Androgens may increase uric acid levels by stimulating renal reabsorption and enhancing hepatic purine nucleotide metabolism (26,27). Similarly, Gong et al. (10) studied 603 PCOS patients and 604 controls, demonstrating that hyperandrogenemia, insulin resistance, and dyslipidemia play roles in raising uric acid levels among patients with PCOS.

Our research distinguishes itself from previous studies by integrating various adiposity markers such as LAP and VAI, along with insulin secretion indices, hormonal and metabolic parameters, and body composition. As far as we know, no prior research has evaluated the combined influence of these factors on uric acid in patients with PCOS. After excluding multicollinear body composition parameters, as well as VAI, and TG/HDL cholesterol from the multivariate regression analysis, we identified HOMA-IR, BMI, and LAP as significant mediators of elevated uric acid. Integrating these metabolic indicators provides a more comprehensive understanding of uric acid metabolism in PCOS.

Study Limitations

This study presents several limitations, such as its retrospective design, which restricts the ability to establish causal relationships, and its single-center nature, which may introduce selection bias. Furthermore, the smaller size of the control group is also a limitation of this research. While BIA is a reliable and accessible method for assessing body composition, its precision in distinguishing between visceral and subcutaneous fat compartments is limited. Additionally, although certain variables were excluded to address multicollinearity, their potential additive value should be examined in larger cohorts.

Conclusion

In conclusion, this study emphasizes the significant relationship between elevated uric acid and metabolic disturbances in PCOS, particularly in relation to insulin resistance and adiposity. These findings suggest that uric acid may serve as a valuable marker for metabolic dysfunction, providing a basis for early risk assessment and intervention. To gain a deeper understanding of the role of uric acid in the pathophysiology of PCOS and its potential as an early predictor of metabolic risk, further prospective long-term analysis with larger cohorts is required.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (reference number: 0l0.99/59, date: 24.02.2024).

Informed Consent: The requirement for written informed consent was waived by the Declaration of Helsinki, as only medical data from patient records were used in this retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.G., K.A., Concept: N.G., K.A., Design: N.G., K.A., Data Collection or Processing: N.G., K.A., Analysis or Interpretation: N.G., K.A., Literature Search: N.G., Writing: N.G.

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

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ORIGINAL RESEARCH

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The Effect of Dissociative Symptoms on Anxiety, Depression and Functionality in Patients Diagnosed with Adjustment Disorder

Uyum Bozukluğu Tanısı Almış Hastalarda Disosiyatif Semptomların Anksiyete, Depresyon ve İşlevsellik Üzerindeki Etkisi

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Abstract

Objective: The current study aimed to examine the impact of dissociative symptoms on anxiety, depression, and general functioning in individuals diagnosed with adjustment disorder.

Method: This cross-sectional study was conducted on 58 patients diagnosed with adjustment disorder according to the diagnostic and statistical manual of mental disorders criteria. The patients voluntarily participated in the study and provided written informed consent. Socio-demographic and clinical data were collected through a customized data form. The dissociative experiences scale, Beck anxiety inventory (BAI), Beck depression inventory (BDI), and functioning assessment short test (FAST) were used.

Results: Participants with dissociative experiences had significantly higher BAI, BDI, and FAST scores. Dissociative experiences were also positively correlated with depression (r=0.536, p<0.01) and anxiety (r=0.740, p<0.01), indicating increased levels of anxiety, depression, and functional impairment, and highlighting the negative impact of these symptoms on emotional health and daily functioning.

Conclusion: Dissociative symptoms can significantly aggravate anxiety, depression, and functional impairment in individuals with adjustment disorder. Early detection and targeted treatment of dissociative symptoms are essential for improving both mental health and overall quality of life in these patients.

Keywords: Adjustment disorder, anxiety, depression, dissociative symptoms, functional impairment

Öz

Amaç: Bu çalışma, uyum bozukluğu tanısı konmuş bireylerde disosiyatif semptomların anksiyete, depresyon ve genel işlevsellik üzerindeki etkisini incelemeyi amaçlamaktadır.

Yöntem: Bu kesitsel çalışma, ruhsal bozuklukların tanı ve istatistik el kitabı kriterlerine göre uyum bozukluğu tanısı almış, gönüllü olarak katılım gösterip yazılı onam veren 58 hasta üzerinde gerçekleştirilmiştir. Sosyo-demografik ve klinik veriler, özel olarak hazırlanmış bir veri formu aracılığıyla toplanmıştır. Çalışmada disosiyatif yaşantılar ölçeği, Beck anksiyete ölçeği (BAI), Beck depresyon ölçeği (BDI) ve işlevsellik değerlendirme kısa testi (FAST) kullanılmıştır.

Bulgular: Disosiyatif yaşantıları olan katılımcılar, BAI, BDI ve FAST skorlarında anlamlı olarak daha yüksek puanlar almışlardır; bu durum artmış anksiyete, depresyon ve işlevsellikte bozulmayı göstermektedir. Disosiyatif yaşantılar, depresyon (r=0,536, p<0,01) ve anksiyete (r=0,740, p<0,01) ile pozitif korelasyon göstermiştir; bu da bu semptomların duygusal sağlık ve günlük işlevsellik üzerinde olumsuz etkisini vurgulamaktadır.

Sonuç: Disosiyatif semptomlar, uyum bozukluğu olan bireylerde anksiyete, depresyon ve işlevsellik bozulmasını önemli ölçüde artırmaktadır. Bu semptomların erken tespiti ve hedefe yönelik tedavisi, bu hastaların hem ruh sağlığını hem de yaşam kalitesini iyileştirmek için önemlidir.

Anahtar kelimeler: Anksiyete, depresyon, disosiyatif semptomlar, işlevsellikte bozulma, uyum bozukluğu

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Introduction

Adjustment disorder, as outlined by the the diagnostic and statistical manual of mental disorders-5 (DSM-5) diagnostic criteria, may develop in response to a stressful life event and typically resolves within six months once the stressor is removed (1). Although there is no specific standard for the stressor that can lead to the development of adjustment disorder, the literature frequently highlights precipitating events such as financial difficulties, health problems, or issues related to social relationships. The prevalence of adjustment disorder in the general population has been reported to range from 7% to 35% (2,3). A large-scale study conducted with patients diagnosed with adjustment disorder identified common co-occurring symptoms such as depressed mood, low self-esteem, suicidal thoughts, and behaviors, increased motor activity, hypervigilance, impulsivity, and substance use (2).

The DSM-5 stipulates that the symptoms of adjustment disorder must be manifested within three months of exposure to a stressor (1). These symptoms must either be clinically significant, presenting a reaction beyond what would typically be expected, or cause significant impairment in social or occupational functioning. The duration of exposure to the stressor, whether the event is reversible, and the individual's characteristics can all influence the clinical presentation (4). An individual may struggle to fulfill their daily responsibilities, leading to a notable decline in their quality of life. Furthermore, impairments in interpersonal relationships may be exacerbated during this disorder, further weakening the individual's social support networks.

Dissociation is a defense mechanism that helps an individual to cope with distressing situations (5). Dissociative disorders, historically referred to as hysteria, are among the most prevalent mental health conditions globally. According to the DSM-5, these disorders involve disruptions in consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior. Dissociative disorders are characterized by symptoms affecting voluntary motor or sensory function, leading to distress or functional impairment, without any underlying medical or mental condition that may explain the symptoms (APA, 2013). This mechanism develops as a cognitive and emotional protective response to challenging life events. Studies have demonstrated a positive association between stressful life events and adjustment difficulties, along with the subsequent development of dissociative symptoms (6,7).

Dissociative symptoms can alter the clinical presentation of depression by aggravating depressive symptoms and deepening the severity of the condition. Sar et al. (8) emphasized that dissociative symptoms are a critical factor in the worsening of depression, potentially complicating the treatment process. Dissociative symptoms can cause significant impairment in both social and occupational functioning, severely limiting an individual's capacity to maintain their daily life. Moreover, dissociative symptoms may weaken an individual's capacity to cope with stress, intensifying both anxiety and depression symptoms (9).

The presence of dissociative symptoms therefore can profoundly affect the individuals emotional health and overall functioning, making the diagnosis and treatment processes more challenging in such patients. Furthermore, the course of dissociative disorder (AD) itself is a critical issue. A study conducted on Danish soldiers reported that approximately 25% of individuals initially diagnosed with adjustment disorder continued to experience adjustment disorder or another mental health disorder ten years later (10). O'Donnell et al. (11) reported that 56% of participants diagnosed with adjustment disorder within three months of a stressful event received a mental health diagnosis nine months later.

The current study was based on the hypothesis that dissociative symptoms can exacerbate anxiety and depression in individuals diagnosed with adjustment disorder, thereby contributing to further impairment in overall functioning. Accordingly, the primary objective of the current research was to assess the specific impact of dissociative symptoms on anxiety, depression, and general functioning in patients' with adjustment disorder. A comprehensive analysis of the severity and effect of these symptoms on psychosocial adaptation may provide valuable insights for clinical practice. The findings are expected to guide the development of more targeted therapeutic interventions for this patient population.

Materials and Methods

Procedures and Materials

The current study was designed as a cross-sectional investigation to evaluate the effects of dissociative symptoms on anxiety, depression, and functionality in individuals diagnosed with adjustment disorder according to DSM-5 criteria (1). The study included 58 outpatients who volunteered to participate, provided informed verbal and written consent, and met the inclusion and exclusion

criteria. The inclusion criteria of the study were as follows: Signing the informed consent form; meeting the diagnostic criteria for AD according to DSM-5; age between 18 and 65 years; lack of any neurological disease; history of head trauma; substance or alcohol abuse or dependence in the past six months; in addition to the absence of any illness that could affect the course of psychiatric symptoms.

The study was conducted at University of Health Sciences Turkey, Erzurum City Hospital, and the relevant scales and forms were completed or administered during interviews with the patients who presented to the hospital and agreed to participate in the study. Socio-demographic and clinical data were collected via a data form specifically designed for the study. The patients were administered the dissociative experiences scale (DES), Beck anxiety inventory (BAI), Beck depression inventory (BDI), and short form of the functioning assessment scale.

Socio-demographic Data Form

This form included questions that addressed the descriptive characteristics of the patient population. Questions regarding the participants' age, income status, place of residence, medication use, presence of additional psychiatric disorders, and history of psychiatric disorders in first-degree relatives were answered.

Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)

The SCID-5-CV is a structured clinical interview scale that was developed as a tool for clinical diagnosis and is administered by the interviewer. It investigates disorders according to the diagnostic criteria outlined in DSM-5. The Turkish adaptation, as well as the validity and reliability studies of the scale, have been conducted (12). The SCID-5-CV was used to confirm the diagnoses of patients participating in the research and to investigate the presence of comorbid psychiatric disorders.

DES

The DES is a self-report instrument that was developed to measure the frequency and severity of dissociative symptoms in individuals. The scale was created by Bernstein and Putnam (13) in 1986 and consists of a global scale with 28 items. Each item is scored using a visual analog scale ranging from 0 to 100, and it assesses how frequently the individual experiences dissociative symptoms (e.g., memory loss, depersonalization, identity confusion). The DES is widely used, particularly in the diagnosis and assessment of post-traumatic stress disorder and other dissociative disorders. It has been validated in multiple languages, and its reliability has been confirmed, making the DES an important tool for the clinical assessment of and research on dissociative symptoms (14).

BAI

The BAI was developed by Beck et al. (15) in 1988 to measure anxiety symptoms in individuals. The BAI is a 21-item self-report scale where each item is scored in a range from 0 (not at all) to 3 (severely). The scale assesses both somatic anxiety symptoms (e.g., heart palpitations, trembling) and subjective anxiety symptoms (e.g., fear, worry). The BAI is widely used in various clinical and research settings and is considered to be an effective tool in the diagnosis and treatment of anxiety disorders. Researchers have reported the validity and reliability of the scale to be high across different cultural and demographic groups (16).

BDI

The BDI is a self-report scale that was developed by Beck et al. (17) in 1961 to assess the severity of depression. The scale consists of 21 items, each evaluating a different symptom of depression, and is scored from 0 to 3. The BDI covers the cognitive, emotional, and somatic symptoms of depression, and therefore effectively measures both general and specific symptoms of depression. It is widely used in clinical practice and research, with numerous validation and reliability studies conducted in various languages (18).

Short Functioning Assessment Scale

This clinical assessment tool measures an individual's level of functionality in various domains of daily life (e.g., autonomy, occupational functioning, cognitive functioning, financial management, interpersonal relationships, and leisure activities). Each item is scored from 0 to 3, providing a quantitative assessment of the individual's functional difficulties in specific areas. The scale is commonly used in clinical practice and measures parameters that may help identify the areas that require support during the treatment process (19,20).

Ethical Approval

The research protocol was approved by the Scientific Research Ethics Committee of the University of Health Sciences Turkey, Erzurum City Hospital (decision no: 2024/09-177, date: 11.09.2024), and strictly adhered to the principles outlined in the Helsinki Declaration.

Statistical Analysis

The clinical characteristics and demographic data were analyzed using descriptive statistics, with frequencies and

percentages (n, %) for categorical variables and means and standard deviations for continuous variables. The Pearson correlation test was used to evaluate the relationship between variables that met parametric assumptions. Comparisons of parametric variables were conducted using the Student's t-test, while comparisons of non-parametric binary groups were carried out using the chi-square test. All analyses were carried out with IBM SPSS software, version 25.0. The significance level for all statistical tests was set as $p<0.05$.

Results

The participants were divided into two groups based on the presence or absence of dissociative experiences: Absence of dissociative experiences (n=20) and presence of dissociative experiences (n=38). Table 1 summarizes the socio-demographic and clinical characteristics of the two groups. The mean age of participants in both groups was comparable, with no significant difference (p=0.856). All participants were male, ensuring no variability due to sex (p=1.0).

An evaluation of the education levels revealed that a larger proportion of participants with dissociative experiences received only middle school education (78.9% vs. 60.0%) compared to those without, although the difference did not reach statistical significance (p=0.087). Employment status was predominantly regular in both groups, with 97.4% of those with dissociative experiences being regularly employed compared to 90.0% in the group without dissociative experiences (p=0.228).

Significant differences were observed in marital status, with a higher percentage of the patients lacking dissociative experiences being married (30.0% vs. 7.9%, p=0.027). The history of self-harm was also significantly more frequent in the group that lacked dissociative experiences (90.0% vs. 65.8%, p=0.045). Differences in variables such as smoking status, history of alcohol or substance use, or family history of mental disorders did not reach statistical significance (p>0.05).

Table 2 compares the BAI, BDI, and FAST scores between the participants with and without dissociative experiences.

Table 1. Socio-demographic and clinical characteristics of the participants

	Dissociative experiences		
Variables	**Absence (n=20)**	**Presence (n=38)**	
	Mean ± SD n (%)	**Mean ± SD n (%)**	**p**
Age (years)	22.5±2.98	22.3±2.40	856.0
Sex (male)	20 (100.0)	38 (100.0)	1.0
Education levels			0.087
Middle school	12 (60.0)	30 (78.9)	
High school	8 (40)	6 (15.8)	
University	0 (0.0)	2 (5.3)	
Employment			0.228
No/irregular	2 (10.0)	1 (2.6)	
Regular	18 (90.0)	37 (97.4)	
Marital status			**0.027**
Not married	14 (70.0)	35 (92.1)	
Married	6 (30.0)	3 (7.9)	
Smoker (yes)	20 (100.0)	35 (89.5)	0.133
Lifetime history of alcohol use (yes)	2 (10.0)	8 (21.1)	0.503
Lifetime history of substance use (yes)	2 (10.0)	8 (21.1)	0.368
Medical history (yes)	0 (0.0)	0 (0.0)	
Family history of mental disorders (yes)	4 (20.0)	13 (34.2)	0.258
History of self-harm (yes)	18 (90.0)	25 (65.8)	**0.045**
History of suicide attempt (yes)	4 (20.0)	10 (26.3)	0.593

Student's t-test and chi-squared test were used for statistical analyses. $p<0.05$ statistically significant (bold values)
SD: Standard deviation

The group that underwent dissociative experiences had significantly higher scores on the FAST scale (34.86±12.91 vs. 26.05±12.49, p=0.015), indicating greater functional impairment. Similarly, the dissociative experiences group also displayed higher BAI (40.57±15.74 vs. 25.00±19.40, p=0.002) and BDI (40.65±9.63 vs. 23.50±15.35, p<0.001) scores, reflecting higher levels of anxiety and depression. The DES score was also significantly higher in patients with dissociative experiences (60.19±14.44 vs. 20.12±6.08, p<0.001).

Table 3 presents the correlation analysis between the BAI, BDI, FAST, and DES scores. Significant positive correlations were found between the BAI and both the BDI (r=0.740, p<0.01) and the FAST (r=0.401, p<0.01) scores. The BDI score also showed significant positive correlations with the DES (r=0.536, p<0.01) and the FAST (r=0.514, p<0.01) scores. However, the correlation between the FAST and the DES scores was not statistically significant (r=0.115, p>0.05).

Discussion

To the best of our knowledge, the current study is the first to examine the effects of dissociative symptoms on anxiety, depression, and overall functioning in individuals diagnosed with adjustment disorder. The findings of our study suggest that dissociative symptoms not only aggravate anxiety and depressive symptoms but also negatively affect the overall level of functioning of an individual. Adjustment disorder develops in response to stressful life events and can lead to a significant decline in social and occupational functioning. Various studies suggest that adjustment disorder can progress over time into more severe psychiatric disorders such as depression and anxiety (10,11). Our data suggest that dissociative symptoms may accelerate this process and further impair function of the individual.

Cases with adjustment disorder comorbid with depression and anxiety disorders were reported to carry a higher risk of functional impairment (21); moreover, treatment processes in the presence of such co-morbidities were reported to be longer and more complex (22,23). We report in the current study, that dissociative symptoms may further aggravate depression. Additionally, depression was reported to become more severe and resistant to treatment in individuals experiencing dissociative symptoms, indicating that such symptoms may exacerbate depression (8). Thus, the negative impact of dissociative symptoms on the treatment process highlights the need for careful planning of treatment strategies in individuals with such symptoms.

Previous studies examining the relationship between anxiety disorders and dissociation have shown that individuals with anxiety disorders experience higher rates of dissociation (24). In particular, individuals with panic disorder frequently exhibit dissociative symptoms such

Table 2. Comparison of beck anxiety inventory, Beck depression inventory, and functioning assessment short tests in the presence and absence of dissociative experiences

	Dissociative experiences (n=58)			
	Absence (n=20)	Presence (n=38)		
	Mean ± SD	Mean ± SD	t	p
Functioning assessment short test	26.05±12.49	34.86±12.91	-2.498	**0.015**
Beck anxiety inventory	25.00±19.40	40.57±15.74	-3.303	**0.002**
Beck depression inventory	23.50±15.35	40.65±9.63	-5.224	**<0.001**
DES	20.12±6.08	60.19±14.44	-11.831	**<0.001**

A Student's t-test was used for statistical analyses, p<0.05 statistically significant (bold values), SD: Standard deviation, DES: Dissociative experiences scale

Table 3. Correlation analysis of Beck anxiety inventory, Beck depression inventory, functioning assessment short test, and DES scores

Correlations				
r	1	2	3	4
Functioning assessment short test	1			
Dissociative experiences scale	0.115	1		
Beck anxiety inventory	0.401**	0.384**	1	
Beck depression inventory	0.514**	0.536**	0.740**	1

r: Correlation coefficient, **: Correlation is significant at the 0.01 level (2-tailed), DES: Dissociative experiences scale, FAST: Functioning assessment short test

as depersonalization and de-realization (25). Dissociative symptoms can weaken the ability of individuals with high levels of anxiety to cope with stress, thereby exacerbating their anxiety levels (9). Studies investigating the relationship between generalized anxiety disorder and dissociative symptoms similarly demonstrate that dissociation can intensify anxiety responses, making individuals more vulnerable to stress (26,27). In this context, several authors have emphasized that the presence of dissociative symptoms in adjustment disorder can lead to challenges in managing anxiety and therefore can prolong the treatment process.

The impact of dissociative symptoms on the overall functionality of an individual is particularly striking. Dissociation significantly impairs social and occupational functioning, leading to a decreased quality of life and disruptions in social relationships. It can be argued that the loss of functionality becomes even more severe when considered in conjunction with depression and anxiety. The negative effects of dissociation increase the challenges that individuals face in their daily lives and pose a serious threat to their quality of life. This highlights the need for greater consideration of dissociative symptoms in treatment planning.

Considering the effects of dissociative symptoms in depression, anxiety, and functionality, it is clear that treatment processes should be approached more holistically. Dissociative symptoms are not merely a defense mechanism, but also a factor that is highly likely to negatively impact an individual's overall functionality in life. Therefore, it is important to develop a more comprehensive approach to treatment that takes into account the interaction of dissociation with depression and anxiety.

Study Limitations

The study limitations include its cross-sectional design, small sample size, and the use of self-report scales, all of which decrease the generalizability of the findings.

Conclusion

The current study examined the effects of dissociative symptoms on anxiety, depression, and functionality in individuals with adjustment disorder. Dissociative symptoms were found to play a significant role in both the worsening of anxiety and depression levels and the deterioration of functionality in individuals diagnosed with adjustment disorder. The negative impact of dissociation on treatment processes can lead to an increase in depressive and anxiety symptoms as well as pronounced functional impairment, which can additionally complicate the individual's response to treatment. In this context, the early diagnosis of dissociative symptoms and their targeted management during the treatment process are of great importance for improving both the psychological and functional health of individuals and supporting the recovery process.

Ethics

Ethics Committee Approval: The research protocol received approval from the Scientific Research Ethics Committee of the University of Health Sciences Turkey, Erzurum City Hospital (decision no: 2024/09-177, date: 11.09.2024), and strictly adhered to the principles outlined in the Helsinki Declaration.

Informed Consent: The patients voluntarily participated in the study and provided written informed consent.

Footnotes

Authorship Contributions

Concept: U.T., H.B., Design: U.T., Data Collection or Processing: U.T., Analysis or Interpretation: U.T., H.B., Literature Search: U.T., H.B., Writing: U.T., H.B.

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ORIGINAL RESEARCH

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Effect of Pulmonary Recruitment Maneuver on Postlaparoscopic Shoulder Pain, Postoperative Pain and Outcomes in Gynecologic Laparoscopic Surgeries

Jinekolojik Laparoskopik Cerrahilerde Pulmoner Recruitment Manevrasının Postlaparoskopik Omuz Ağrısı, Postoperatif Ağrı ve Sonuçlara Etkisi

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Abstract

Objective: Post-laparoscopic shoulder pain (PLSP) is a significant occurrence after laparoscopic surgery. This study investigated the effects of pulmonary recruitment maneuvers (PRM) on PLSP, postoperative pain, and patient outcomes in patients undergoing laparoscopic gynecologic surgery.

Method: Patients who underwent laparoscopic gynecological surgery for benign reasons between April 2023 and October 2023 were retrospectively examined. The patients were divided into the PRM group (group PRM, n=45) and the control group (group C, n=46). In group PRM, five recruitment maneuvers were performed manually at the end of the operation with 40 cm H_2O pressure. The PLSP visual analog scale (VAS) scores were compared with VAS scores at the 6th, 12th, and 24th postoperative hours, postoperative wound VAS scores, ambulation times, postoperative nausea and vomiting (PONV), bowel movement times, and hospital stay.

Results: The study included 91 patients with a mean age of 49.4±9 years. The most commonly performed operations were total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. The PLSP rate in Group PRM was significantly lower than in Group K (31.1% vs. 63%,

Öz

Amaç: Laparoskopik cerrahi sonrasında önemli oranda postlaparoskopik omuz ağrısı (PLSP) görülmektedir. Bu çalışmanın amacı, laparoskopik jinekolojik cerrahi gerçekleştirilen hastalarda pulmoner rekruitment manevrasının (PRM) PLSP, postoperatif ağrı ve hasta sonuçlarına etkisini araştırmaktır.

Yöntem: Nisan 2023 ile Ekim 2023 tarihleri arasında benign sebeplerle laparoskopik jinekolojik operasyon gerçekleştirilen hastalar retrospektif olarak incelendi. Hastalar PRM uygulanan grup (grup PRM, n=45) ve uygulanmayan kontrol grubu (grup K, n=46) olarak iki gruba ayrıldı. Grup PRM'de operasyon bitiminde manuel yöntemle 40 cmH_20 basınçlı 5 rekruitment manevrası gerçekleştirildi. Postoperatif 6, 12 ve 24. saatlerdeki PLSP vizüel analog skala (VAS) skorları, postoperatif yara yeri VAS skorları, ambülasyon süreleri, postoperatif bulantı-kusma (PONV) mevcudiyeti, bağırsak hareketleri zamanı ile hastanede kalış süreleri karşılaştırıldı.

Bulgular: Çalışmaya yaş ortalaması 49,4±9 yıl olan toplam 91 hasta dahil edildi. En çok gerçekleştirilen operasyon, total laparoscopic hysterectomy, bilateral salpingo-oophorectomy idi. Grup PRM'de PLSP oranı Grup K'ye göre anlamlı olarak düşük idi (%31,1 vs. %63, p=0,002). Grup PRM'de postoperatif 6 (3,6 vs. 5,8), 12 (3,3 vs. 4,9) ve 24. saatteki

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Abstract

p=0.002). In Group PRM, mean PLSP VAS scores at 6 (3.6 vs. 5.8), 12 (3.3 vs. 4.9), and 24 hours (2.8 vs. 3.9) postoperatively were significantly lower (p<0.001 for all). In Group PRM, postoperative 6th-hour wound pain scores were significantly lower (4.8 vs. 5.7, p=0.009). In Group PRM, ambulation time (6.6±0.9 vs. 7.5±1.5 hours, p=0.002) and bowel movement recovery time (14.2±4 vs. 16.4±5 hours, p=0.038) were also significantly lower. In Group PRM, the PONV rate (28.9% vs. 37%) and hospital stay (2.2±0.4 vs. 2.3±0.5 days) were lower, but no statistically significant difference was found.

Conclusion: PRM, which can be easily applied at the end of benign laparoscopic gynecological surgeries, effectively reduces PLSP and early wound pain. It is also helpful in reducing postoperative ambulation time and in the return of bowel functions.

Keywords: Early ambulation, laparoscopy, pneumoperitoneum, postoperative pain, pulmonary recruitment maneuver, shoulder pain

Öz

(2,8 vs. 3,9) ortalama PLSP VAS skorları anlamlı olarak düşük saptandı (hepsi için p<0,001). Grup PRM'de aynı zamanda postoperatif 6. saat yara ağrı skorları da anlamlı olarak düşüktü (4,8 vs. 5,7, p=0,009). Grup PRM'de ambülasyon süresi (6,6±0,9 vs. 7,5±1,5 saat, p=0,002) ile bağırsak hareketlerinin geri gelme süresi de anlamlı olarak düşük idi (14,2±4 vs. 16,4±5 h, p=0,038). Grup PRM'de PONV oranı (%28,9 vs. %37) ve hastanede kalış süresi (2,2±0,4 vs. 2,3±0,5 gün) düşük olmakla birlikte anlamlı farklılık saptanmadı.

Sonuç: Benign laparoskopik jinekolojik cerrahilerde operasyon bitiminde kolayca uygulanabilen PRM, PLSP ve erken dönem yara ağrısının azaltılmasında etkilidir. Bununla birlikte postoperatif ambülasyon süresinin ve bağırsak fonksiyonlarının geri dönmesinde de faydalıdır.

Anahtar kelimeler: Erken ambülasyon, laparoskopi, omuz ağrısı, pnömoperitoneum, postoperatif ağrı, pulmoner rekruitman manevras

Introduction

With the development of minimally invasive surgery (MIS) techniques, these methods have increasingly been used to diagnose and treat various diseases. MIS, including laparoscopic surgery (LS), has been widely accepted instead of traditional laparotomy in the treatment of various benign gynecological diseases (1). LS has advantages over laparotomy, such as shorter hospital stays, smaller incisions, earlier return to daily activities, less postoperative pain, and better cosmetic results (2). However, it is crucial to note that despite the advantages of LS, conditions such as post-laparoscopic shoulder pain (PLSP) are frequently encountered and bother patients. In the literature, the incidence of shoulder or abdominal pain after laparoscopy has been reported to be between 35% and 80% (3,4), highlighting the prevalence of these complications. In addition, postoperative nausea and vomiting (PONV) is seen after LS and negatively affects patient comfort.

During laparoscopy, pneumoperitoneum is created, increasing intra-abdominal pressure. As a result of this pressure increase, the diaphragm is displaced upwards. Functional residual capacity and lung compliance decrease, and patients may develop atelectasis. There needs to be a consensus on the mechanism of PLSP. The generally accepted view is that carbon dioxide (CO_2) causes referred pain in the C4 dermatome due to phrenic nerve irritation (5). Another possible mechanism, is shoulder pain due to CO_2 accumulation between the liver and the right diaphragm. Another perspective is the tissue trauma theory. Stretching or injury of the peritoneum and diaphragm due to pneumoperitoneum causes rupture of blood vessels, traction of nerves (e.g., the phrenic nerve), and release of inflammatory mediators that cause referred pain to the shoulder (6). PLSP may increase postoperative analgesic consumption, lengthen hospital stays and, rarely, may lead to rehospitalizations. Therefore, necessary precautions should be taken to reduce the intensity of PLSP. Although various methods are used to reduce PLSP, the most widely accepted method is to perform a pulmonary recruitment maneuver (PRM) at the end of the surgical procedure to evacuate the remaining CO_2 (7). PRM, with its potential to prevent PLSP and reduce postoperative pain scores, also significantly reduces PONV, providing a comprehensive solution to this issue (8).

This study aimed to investigate the effects of PRM performed at the end of the operation on PLSP, postoperative pain, PONV, ambulation time, and hospital stay in patients who underwent laparoscopic gynecological surgery due to benign gynecological reasons.

Materials and Methods

This retrospective cohort study was initiated after the approval of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Trials Review Board and Ethics Committee (KAEK/2023.11.166, 29.11.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients who underwent laparoscopic gynecological surgery for indications other than malignancy (e.g., total laparoscopic hysterectomy, laparoscopic cystectomy, laparoscopic myomectomy) at the University of Health Sciences Turkey, Kanuni Sultan

Süleyman Training and Research Hospital between April 2023 and October 2023 were included in the study. Patient data and patient files were accessed from the hospital information system. Data that were prospectively recorded were analyzed retrospectively.

Inclusion criteria are as follows: (1) American Society of Anesthesiologists (ASA) physical status I-II; (2) 18-65 years old; (3) laparoscopic gynecological surgery performed for non-malignant indications. Exclusion criteria included: (1) chronic shoulder or epigastric pain; (2) previous lung or shoulder surgery; (3) lung diseases such as chronic emphysema; (4) previous pneumothorax; (5) pregnancy; (6) conversion to laparotomy after laparoscopy; (7) missing data.

Patients were retrospectively divided into the pulmonary recruitment maneuver group (PRM) and the control group (K). No randomization method was used to form the groups. The demographic characteristics of the patients, the duration of anesthesia and surgery, preoperative hemoglobin (Hb) and difference (preoperative Hb-postoperative Hb) Hb levels, ASA status, surgical procedure, PLSP, and wound pain VAS scores at 6, 12, 24 hours, postoperatively (0=no pain, 10=the most severe pain ever) were recorded. The postoperative ambulation time, PONV, the time until passage of flatus (time to return of bowel functions), and the duration of hospital stay were analyzed.

Ambulation or mobilization is any activity in which the patient is out of bed, such as standing at the bedside, sitting in a chair, or walking in the hallway. Gastrointestinal motility is the movement of the stomach and intestines (9). In our study, the first gas exit time was assessed and recorded in the evaluation of gastrointestinal motility. Similarly, patients are encouraged to mobilize early and are routinely mobilized at the 6th hour postoperatively.

Anesthesia Management and Pulmonary Recruitment Maneuver

All patients brought to the operating theatre underwent a similar general anesthesia procedure. Following standard anesthetic monitoring (electrocardiography, non-invasive blood pressure, end-tidal carbon dioxide-$EtCO_2$ pressure), premedication was performed with 0.03 mg/kg midazolam. General anesthesia induction was performed with 2-3 mg/kg propofol, 1 mg/kg fentanyl, and 0.6 mg/kg rocuronium. Anesthesia was maintained with 2-3% sevoflurane and 0.5 µg/kg/min remifentanil infusion. Ventilation was performed in volume-controlled mode with a tidal volume of 6-10 mL/kg and an $EtCO_2$ level of 30-40 mmHg. Positive end-expiratory pressure (PEEP) was not applied to the patients. One of the aims of the present study is to assess the effects of pulmonary recruitment maneuvers on oxygenation and hemodynamics, with an expectation of no significant effects. Therefore, the findings, including peripheral oxygen saturation, blood pressure, and heart rate, of the patients included in the study were not evaluated.

All laparoscopic procedures were performed using four ports. A single 10-mm port was placed through the umbilicus, and a 5-mm port was placed through the suprapubic regions and the lateral lower abdominal wall. To ensure laparoscopic vision, 12 mmHg intra-abdominal pressure was achieved by insufflating CO_2 with a flow rate of <3 L/min. The pneumoperitoneum was passively evacuated in the control group. In Group PRM, a recruitment maneuver consisting of five manual inflations to a maximum pressure of 40 cmH_2O was performed in the 30° Trendelenburg position with a fractional oxygen concentration of 100%. The anesthesiologist performed the recruitment maneuver by holding each positive pressure inflation for 5 seconds while the valves in the ports were open.

Diclofenac sodium (Dikloron, Deva Pharma, Turkey) is administered 75 mg intramuscularly, 2x1, intramuscularly as an analgesic in the postoperative period to patients, who undergo gynecological LS in our hospital's obstetrics and gynecology clinic. Tramadol hydrochloride (Tradolex, Menta Pharma, Turkey) is infused intravenously into 100 mL of physiological saline for patients whose pain is not relieved with diclofenac. If patients had moderate pain (VAS ≥4); diclofenac and tramadol were administered.

Sample Size

A previous study was used to calculate the sample size (3). The authors estimated that in the study, PLSP would decrease from 80% to 50% with the effect of PRM. Using the G*Power 3.1 program, they calculated that there should be 45 patients in each group to obtain $p<0.05$ and 80% power (1-β) for chi-square tests. In our study, with significant implications for the statistical analysis, it was determined that there should be at least 45 patients in each group.

Statistical Analysis

Version 26.0 of SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) was used to analyze the data. The conformity of the data to a normal distribution was tested using the Shapiro-Wilk test and histogram. An independent samples t-test was used to analyze normally distributed data. The Mann-Whitney U test was used to analyze data

that did not show a normal distribution. Pearson chi-square tests and Fisher's exact tests were used to analyze categorical data. Descriptive data were expressed as the number of patients, percentage, mean, standard deviation, and median (interquartile range). The repeated measures ANOVA test with Bonferroni post hoc comparisons was used to analyze VAS scores within and between groups. The significance level for all results was set at $p<0.05$.

Results

The study included 91 patients who underwent laparoscopic gynecological surgery between April 2023 and October 2023 (Figure 1). The mean age of the entire population was 49.4±9 years, and 86.8% (n=79) were in ASA II status. The mean operation time in the entire population was 136±38 minutes. The most commonly performed surgical procedures were total laparoscopic hysterectomy and bilateral salpingo-oophorectomy (TLH+BSO). No significant difference was found between the groups in terms of demographic characteristics, anesthesia and operation time, and perioperative Hb levels (Table 1).

The PLSP rate in Group PRM was significantly lower than that in the control group (31.1% vs. 63%, p=0.002). In Group PRM, mean PLSP VAS scores at 6 (3.6 vs. 5.8), 12 (3.3 vs. 4.9) and 24 hours (2.8 vs. 3.9) postoperatively were significantly lower ($p<0.001$ for all). In addition, the postoperative 6th-hour wound pain scores were significantly lower in Group PRM (4.8±1.5 vs. the 5.6±1.1, p=0.004). However, the 12th and 24th-hour wound pain scores did not differ significantly between the groups (p=0.075 and p=0.089, respectively) (Table 2, Figures 2, 3).

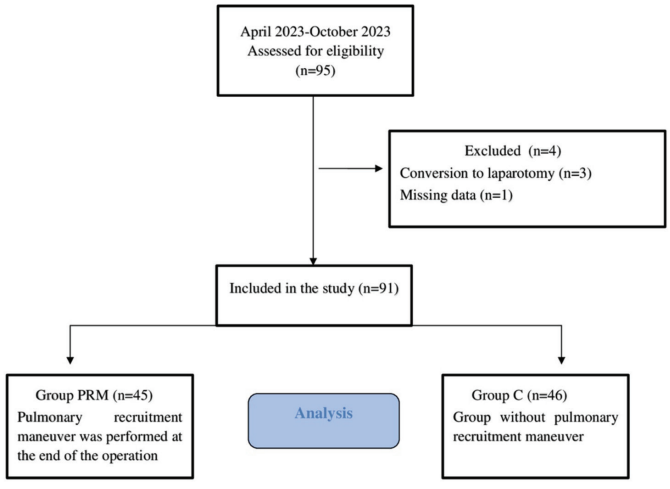

Figure 1. Flow chart of the study
PRM: Pulmonary recruitment maneuver

PONV was detected in 33% of the whole population (n=30). Although the PONV rate was low in Group PRM, there was no significant difference detected (28.9% vs. 37%, p=0.413). Postoperative ambulation time was significantly lower in Group PRM (6.6±0.9 vs. 7.5±1.5 hours, p=0.002). The time to recovery of bowel functions was also significantly lower in Group PRM (14.2±4.7 hours vs. 16.4±5.9 hours, p=0.038). The length of hospital stay was also low in Group PRM, but no significant difference was detected (2.2±0.4 vs. 2.4±0.5 days, p=0.075) (Table 3). No severe cardiovascular instability or pulmonary complications were observed in any patient associated with the recruitment maneuver.

Discussion

In this study, we found that PRM performed manually at 40 cmH_2O pressure, at the end of the operation in benign gynecological laparoscopic surgeries, significantly reduced

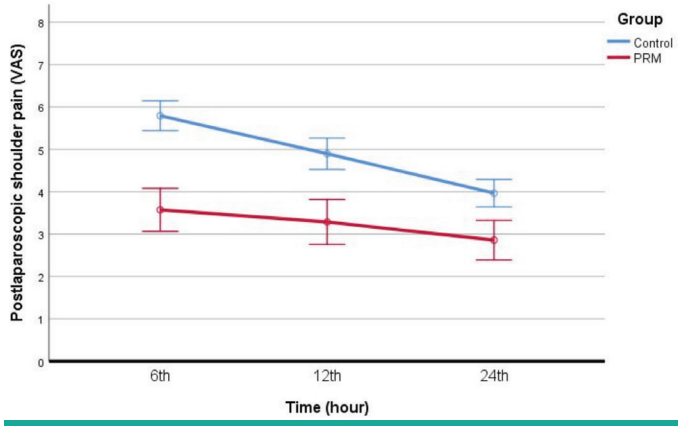

Figure 2. The mean postlaparoscopic shoulder pain VAS scores of the groups in the first 24 hours
VAS: Visual analog scale, PRM: Pulmonary recruitment maneuver

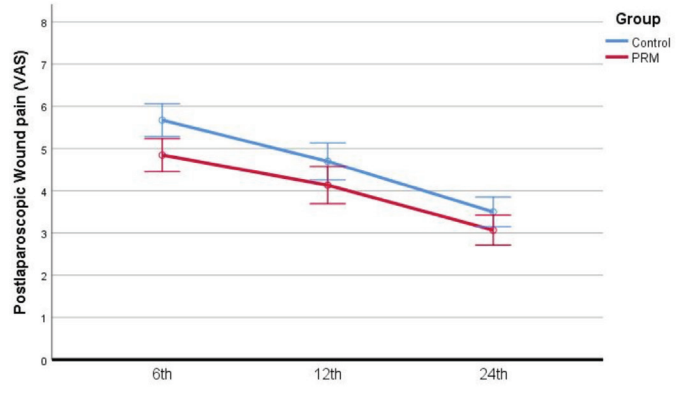

Figure 3. The mean wound pain VAS scores of the groups in the first 24 hours
VAS: Visual analog scale, PRM: Pulmonary recruitment maneuver

Table 1. Clinical characteristics of patients

	Overall (n=91)	Group PRM (n=45)	Group C (n=46)	p-value
Age (years)				0.254
Mean ± SD	49.4±9.0	48.4±8.4	50.5±9.3	
Median (Q1-Q3)	49 (44-54)	49 (44-52)	49 (43-56)	
ASA status				0.967
I	12 (13.2)	6 (13.3)	6 (13)	
II	79 (86.8)	39 (86.7)	40 (87)	
BMI (kg/m²)				0.204
Mean ± SD	29.8±4.7	30.1±3.9	29.6±5.4	
Median (Q1-Q3)	29 (26-33)	30 (27-33)	29 (25-31)	
Parity				0.915
Mean ± SD	2.9±2.0	2.8±1.9	2.9±2.0	
Median (Q1-Q3)	2 (2-3)	2 (2-3)	2 (2-3)	
Operation duration (min)				0.498
Mean ± SD	136±38	131±32	140±42	
Median (Q1-Q3)	135 (110-150)	135 (110-148)	135 (118-156)	
Anesthesia duration (min)				0.845
Mean ± SD	157±37	154±29	160±42	
Median (Q1-Q3)	150 (135-170)	150 (135-170)	153 (136-171)	
Preoperative Hb (g/dL)				0.162
Mean ± SD	12.2±1.5	12.5±1.5	12.1±1.5	
Median (Q1-Q3)	12.4 (11.2-13.4)	13.l (11.2-13.4)	12 (10.9-13.4)	
Δ Hb (g/dL)				
Mean ± SD	1.4±0.7	1.4±0.7	1.5±0.6	0. 173
Median (Q1-Q3)	1.5 (0.8-1.9)	1.3 (0.8-1.6)	1.6 (1.1-2.0)	
Type of surgery				0.309
TLH+BSO	52 (57.1)	24 (53.3)	28 (60.9)	
TLH+BS	24 (26.4)	15 (33.3)	9 (19.6)	
TLH	4 (4.4)	2 (4.4)	2 (4.3)	
LS cystectomy	3 (3.3)	1 (2.2)	2 (4.3)	
LS myomectomy	8 (8.3)	4 (8.9)	4 (8.7)	
PLSP, n (%)	43 (47.3)	14 (31.1)	29 (63.0)	**0.002**

Values are the number of patients, percentage, mean ± standard deviation, median (interquartil range, Q3-Q1), PRM: Pulmonary recruitment maneuver, C: Control, ASA: American Society of Anesthesiologists status, BMI: Body mass index, Hb: Haemoglobin, Δ Hb: Difference between preoperative and postoperative haemoglobin levels, TLH: Total laparoscopic hysterectomy, TLH+BSO: Total laparoscopic hysterectomy+bilateral salpingo-oophorectomy, TLH+BS: Total laparoscopic hysterectomy+bilateral salpingo, LS: Laparoscopic shoulder, PLSP: Post-laparoscopic shoulder pain

the PLSP rate and PLSP VAS scores at 6, 12, and 24 hours. We also found that PRM significantly reduced postoperative 6th-hour wound site VAS scores, ambulation time, and the time to return of bowel functions. Although PONV rates were low in the PRM group, no significant difference was observed compared to the control group.

The main goal of enhanced recovery after surgery (ERAS) protocols is to reduce the length of hospital stay. ERAS protocols mainly focus on reducing perioperative stress, early return of gastrointestinal function, less postoperative pain, and early mobilization. For this purpose, minimally invasive techniques, such as LS, recommended in ERAS protocols, have advantages such as less postoperative pain in gynecological diseases, shorter hospital stays, early ambulation, and early return of gastrointestinal functions (10). However, in addition to the advantages of LS, undesirable conditions, including PLSP, are observed. Although the underlying mechanism of PLSP has not yet been established, neuropraxia of the phrenic nerve is attributed to factors such as distension, an acidic

Table 2. Postoperative pain scores (visual analog scale score)

	Group PRM (n=45)				Group C (n=46)				
	Mean	SD	SE	95% CI	Mean	SD	SE	95% CI	p-value
PLSP (6th h)	3.6	1.1	0.2	3.27-3.87	5.8	1.1	0.2	5.38-6.20	**<0.001**
PLSP (12th h)	3.3	0.5	0.1	3.02-3.56	4.9	1.1	0.2	4.46-5.33	**<0.001**
PLSP (24th h)	2.9	0.4	0.1	2.65-3.07	4.0	1.0	0.2	3.58-4.35	**<0.001**
WP (6th h)	4.8	1.5	0.2	4.38-5.31	5.7	1.1	0.2	5.35-5.99	**0.004**
WP (12th h)	4.1	1.3	0.2	3.73-4.54	4.7	1.6	0.2	4.22-5.18	0.075
WP (24th h)	3.1	1.1	0.2	2.73-3.41	3.5	1.3	0.2	3.13-3.87	0.089

SD: Standard deviation, SE: Standard error, CI: Confidence interval, PLSP: Post-laparoscopic shoulder pain, WP: Wound pain, PRM: Pulmonary recruitment maneuver, C: Control

Table 3. PONV status, ambulation and length of hospital stay

	Overall (n=91)	Group PRM (n=45)	Group C (n=46)	p-value
PONV, n (%)	30 (33)	13 (28.9)	17 (37)	0.413
Ambulation duration (h)				**0.002**
Mean ± SD	7.0±1.3	6.6±0.9	7.5±1.5	
Median (Q1-Q3)	7 (6-8)	7 (6-7)	8 (6-9)	
Recovery time bowel function (h)				**0.038**
Mean ± SD	15.5±5.4	14.2±4.7	16.4±5.9	
Median (Q1-Q3)	16 (10-19)	15 (10-18)	18 (13-20)	
Hospital stay duration (days)				0.075
Mean ± SD	2.3±0.5	2.2±0.4	2.4±0.5	
Median (Q1-Q3)	2 (2-3)	2 (2-2)	2 (2-3)	

Values are the number of patients, percentage, mean ± standard deviation (SD), median (interquartil range, Q3-Q1), PONV: Postoperative nausea and vomiting, PRM: Pulmonary recruitment maneuver, C: Control

intraperitoneal environment, and residual abdominal gas. These conditions are believed to cause C4 pain referred to the shoulder (11,12). Jackson et al. (13) reported that the remaining CO_2 gas bubble size after laparoscopy correlates with the severity of PLSP. The authors stated that the length and height of the subdiaphragmatic gas measured on chest X-ray are related to the severity of PLSP. Different rates of PLSP have been reported in various laparoscopic surgeries. PLSP lasting up to 7 days has been reported in 63% of laparoscopic cholecystectomy (14), in 83% of laparoscopic gynecological surgery (3), and in 66% of laparoscopic gastric band surgery (15). Considering the hospital costs, evaluating the patient's remaining gas volume with a chest X-ray is not cost-effective. Therefore, our study did not pursue this evaluation method. Shoulder pain observed in the patients, was evaluated in the first 24 hours.

Various methods have been used to prevent PLSP, which is believed to occur due to phrenic nerve irritation by CO_2 used in pneumoperitoneum. Methods such as alternative inflation gas in the pneumoperitoneum, heated or humidified insufflation gas, low-pressure pneumoperitoneum, intraperitoneal fluid instillation, intraperitoneal local anesthetic use, intraperitoneal drainage, and active gas absorption at the end of surgery have been used (16,17). It has been reported that patients experience less pain when pneumoperitoneum is created using nitrous oxide instead of CO_2 (18). Tsai et al. (19) investigated the role of the recruitment maneuver applied at the end of the operation and the role of the intra-abdominal injection of saline in removing residual CO_2. The authors reported a significant decrease in shoulder pain. Intraperitoneal local anesthetic application has also been reported to be associated with a decrease in the incidence of shoulder pain and postoperative opioid consumption. PLSP may vary depending on the patient's position. It has been reported that standing causes phrenic nerve irritation and increased pain, which is referred to as shoulder pain, due to the CO_2 bubble moving under the diaphragm. The supine position relieves pain (20). It has been reported

that the semi-Fowler position significantly reduces PLSP after laparoscopy with the recruitment maneuver, which increases intra-abdominal pressure (21). The literature has also investigated the effects of gasless laparoscopy and low-pressure pneumoperitoneum on PLSP and postoperative pain. It has been reported that low-pressure pneumoperitoneum reduces postoperative pain scores, but there is no change in PLSP with gasless laparoscopy (22,23). However, these methods have yet to be widely adopted due to additional costs and potential adverse effects. In our study, CO_2 was used to create pneumoperitoneum. After the operation, PRM was applied in the supine position at safe pressure limits. PLSP and wound pain were evaluated while the patients were in a sitting position.

PRM is used to open collapsed alveoli by applying high airway pressures and increasing oxygenation. It is frequently used in intensive care units and has been reported to be helpful in laparoscopic surgeries for preventing atelectasis, reducing hypercapnia, and improving oxygenation (7). Hemodynamic instability, bullous lung disease and pneumothorax, high intracranial pressure, and congestive heart failure are conditions in which recruitment maneuvers are contraindicated (24). PRM is one of the most effective methods in preventing PLSP, caused by pneumoperitoneum (3-5,8). Phelps et al. (3), investigated the effect of 5 manual recruitment maneuvers with 60 cm H_2O pressure in the Trendelenburg position on PLSP in laparoscopic gynecological surgery. The authors reported that PRM significantly reduced both the incidence of PLSP (63% vs. 31%) and VAS scores at 12, 24, 36, and 48 hours. Güngördük et al. (25) investigated the effect of 2 manual recruitment maneuvers at 40 cmH_2O pressure on PLSP and wound pain in laparoscopic gynecologic oncologic surgery. The authors reported that PRM significantly reduced PLSP and upper abdominal wound pain at 12 and 24 hours postoperatively. However, it should be noted that complications related to PRM, including barotrauma and hemodynamic deterioration, may occur when higher pressures are used (26,27). Yilmaz et al. (28) suggested that a maximum inspiratory pressure of 15 cm H_2O may be preferred to avoid possible complications of PRM by using higher pressures. In our study, 5 manual recruitment maneuvers were applied at 40 cmH_2O pressure in the 30° Trendelenburg position, with the laparoscopy ports in place, at the end of the operation. The PLSP rate decreased, as well as PLSP scores 6, 12, and 24 hours, and the postoperative pain score at 6 hours decreased. However, postoperative 12-hour and 24-hour pain scores were similar between the groups. The recruitment maneuver can reduce shoulder and early postoperative pain by reducing air trapping due to pneumoperitoneum. Since relatively few studies have been conducted on using PRM at low pressures, the optimum pressure level of PRM that minimizes the severity of PLSP and the incidence of adverse events should be investigated. Based on our clinical experience, PRM application with a pressure of 40 cmH_2O is safe. Pressure levels of 15 cmH_2O are low.

It has been reported that PRM reduces postoperative pain scores and the PONV rate in laparoscopic surgeries (3,24). Phelps et al. (3) reported that PRM significantly reduced PONV in the first 24 hours in patients undergoing laparoscopic gynecological surgery. The authors stated that in the control group, greater PLSP and more opioid consumption may have been effective in increasing the PONV rate. However, studies also report that no significant differences were found in the incidence of PONV. Güngördük et al. (25) reported that PRM reduced the PONV rate in patients undergoing laparoscopic gynecological oncological surgery, but no statistically significant difference was found. Another study stated that gas drainage to remove residual CO_2 did not significantly change the frequency and severity of PONV up to 72 hours after laparoscopic cholecystectomy (29). A meta-analysis of 14 randomized controlled trials stated that PRM could significantly reduce PLSP scores at postoperative 12, 24, and 48 hours. However, it did not significantly affect postoperative wound pain, upper abdominal pain, and PONV (30). In our study, PONV was lower, although not significantly, in the PRM group (28.9% vs. 37%). We believe that the residual effect of pneumoperitoneum and opioid analgesics may cause this situation. In our clinic, NSAIDs and tramadol hydrochloride are used for analgesic purposes in postoperative gynecological patients. Although the quantity of analgesics consumed postoperatively was not evaluated in our study, we think, that the higher VAS scores of the patients in the control group increased the quantity of opioids consumed. In addition, the ambulation time in the recruitment group was significantly lower than in the control group (6.6±0.9 vs. 7.5±1.5 h). The return of bowel movements was rapid, and the duration of hospital stay was also short, although not significant. The lower rate of PLSP in the PRM group, along with lower early pain scores, early mobilization, and less opioid consumption, may lead to the observed effects.

Study Limitations

The study has some limitations. First, the study is conducted in a single-center setting and is retrospective. Second, PLSP and wound pain scores were evaluated within the first 24

hours. The shoulder pain of the patients after discharge was not evaluated. Third, diclofenac sodium 2x1.75 mg intramuscularly is administered as an analgesic to patients in the postoperative period. However, tramadol was administered to patients with moderate pain (VAS) pain. Tramadol consumption in the postoperative period was not analyzed in the study. PLSP and wound pain VAS scores may have been affected.

Conclusion

In conclusion, PRM, a technique easily implemented in clinical practice, has been shown to significantly reduce PLSP and early pain scores in laparoscopic gynecological operations. Importantly, PRM aligns with the goals of ERAS protocols, aiming to expedite recovery, promote early ambulation, and restore gastrointestinal function, thereby reducing hospital stays.

Ethics

Ethics Committee Approval: This retrospective cohort study was initiated after the approval of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Trials Review Board and Ethics Committee (KAEK/2023.11.166, 29.11.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.A., H.Ç.A., Concept: K.A., H.Ç.A., N.Y., A.S.Ş., Design: K.A., H.Ç.A., N.Y., A.S.Ş., Data Collection or Processing: K.A., H.Ç.A., N.Y., A.S.Ş., Analysis or Interpretation: K.A., H.Ç.A., Literature Search: K.A., Writing: K.A., H.Ç.A.

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

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ORIGINAL RESEARCH

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Effect of Donor Ages on Long-term Graft and Recipient Survival in Liver Transplantation

Karaciğer Naklinde Uzun Dönem Alıcı ve Graft Sağkalımında Donör Yaşının Etkisi ve Karaciğer Naklindeki Önemi

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Abstract

Objective: Long waiting time and higher mortality rate are major problems for patients waiting for liver transplantation (LT). Many efforts expanding the liver donor pool are being made to increase the feasibilty of living donor liver transplantation (LDLT).

Method: We planned to examine the effect of living donors used in LDLT recipients on survival in different age groups. The study included a retrospective analysis of patients who had undergone LDLT. LDs were divided into multiple forms. Accordingly, three different LD age groups were established: 18-39, 40-49 and 50-59 years. The primary outcomes of the study were long-term recipient and graft survival and early recipient complications.

Results: The number of LDLTs performed by donor age category were as follows: Age 18-39 (n=95), age 40-49 (n=46) and age 50-59 (n=26). The first degree relative rate was significantly lower in the 50-59-year age group. The ≥5% steatosis rate (macro or micro) was significantly higher in the 50-59 year age group (42.3%). One-year LDLT recipient survival was 100% in all groups. The five-year survival rates of 18-39, 40-49 and 50-59 year age groups were 100%, 94.3% and 86.7%, respectively. However, 10 year survival rate was significantly higher in 18-39 year age group than others groups.

Conclusion: Recipient and graft survival rates of up to five years did not vary among age groups. From the recipient's perspective, the decision to use elderly LD should outweigh the risks for different LD options or DDLT waiting period.

Keywords: Donor age, living liver donor, liver transplantation, survival

Öz

Amaç: Uzun bekleme süresi ve yüksek ölüm oranı karaciğer nakli bekleyen hastalar için önemli sorunlardır. Canlı donör karaciğer naklinin (LDLT) uygulanabilirliğini artırmak için karaciğer donörü havuzunu genişletmek için birçok çaba sarf edilmektedir.

Yöntem: LDLT alıcılarında kullanılan canlı donörlerin farklı yaş gruplarında sağkalım üzerindeki etkisini incelemeyi planladık. Çalışma, LDLT geçiren hastaların retrospektif analizini içeriyordu. LDLT'ler birden fazla forma ayrıldı. Buna göre, üç farklı LD yaş grubu belirlendi: 18-39, 40-49 ve 50-59 yaş. Çalışmanın birincil çıktıları uzun vadeli alıcı ve greft sağkalımı ve erken alıcı komplikasyonlarıydı.

Bulgular: Donör yaş kategorisine göre gerçekleştirilen LDLT sayıları şu şekildeydi: 18-39 yaş (n=95), 40-49 yaş (n=46) ve 50-59 yaş (n=26). Birinci derece akraba oranı 50-59 yaş grubunda önemli ölçüde daha düşüktü. ≥%5 steatoz oranı (makro veya mikro) 50-59 yaş grubunda önemli ölçüde daha yüksekti (%42,3). Bir yıllık LDLT alıcı sağkalımı tüm gruplarda %100'dü. On sekiz-otuz dokuz, 40-49 ve 50-59 yaş gruplarının beş yıllık sağkalım oranları sırasıyla %100, %94,3 ve %86,7 idi. Ancak, 10 yıllık sağkalım oranı 18-39 yaş grubunda diğer gruplara göre önemli ölçüde daha yüksekti.

Sonuç: Alıcı ve greft sağkalım oranları beş yıla kadar yaş grupları arasında değişmedi. Alıcının bakış açısından, yaşlı LD kullanma kararı farklı LD seçenekleri veya DDLT bekleme süresi için risklerden daha ağır basmalıdır.

Anahtar kelimeler: Canlı karaciğer donör, donör yaşı, karaciğer nakli, sağkalım

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Introduction

Long waiting times and higher mortality rates are major problems for patients waiting for liver transplantation (LT). Many efforts expanding the living donor (LD) pool are being made to increase the feasibility of living donor liver transplantation (LDLT) in patients who have no other option due to massive organ shortages. In modern transplantation surgery, elderly LDs can be used to meet the needs and fulfill the expectations of patients, given the rapid increase in average life expectancy in the general population. The functional effect of aging was less pronounced in the liver than in the heart and kidney. The liver tends to have a 20-40% volume decrease with aging. This is more pronounced in women than in men. The hepatic arteriolar wall becomes thinner with a decrease in endothelial cell fenestration, resulting in decreased liver inflow. Bile acid secretion is also reduced, but most of the liver functions are generally protected in older individuals. In these individuals, metabolic changes are also observed. A decrease in gluconeogenic capacity and a physiological elevation of liver lipid accumulation increase lipotoxicity and steatosis (1-3). The ageing process is governed by imbalanced immune response and by imbalanced immune stimulation. As a result, the regeneration capacity of the elderly liver decreases. Insights into the mechanisms involved in normal liver aging are important for a better understanding of donor age in LT. In the context of deceased donor liver transplantation (DDLT), the independent effect of using aged donor grafts on graft and recipient survival has been extensively published in many studies, but this issue remains controversial (4,5). Deceased donor shortages increase the number of LDLTs. The use of elderly living donors in high-volume LDLT centers, raises some concerns for donor safety. Conversely, the relevance of increased donor age to ischemia perfusion injury on allograft endurance in LDLT is less worrisome (6-9). In 2021, one-third of liver transplants in the United States (US) used liver grafts from donors older than 50. Exclusion criteria for living liver donor are improving to further expand the liver donor pool for LDLT. Although the number of LDLTs using elderly donors is expected to increase in parallel with the aging population, the use of elderly donor grafts is still controversial (10). Thus, the upper limit of donor age in LDLT is recently regulated.

We aimed in this study that analysis the trend in option of grafts from elderly living donors is refered to the change in a parameter over a period of time between 2012 and 2018. 2) To evaluate the long-term recipient and graft survival relationship of elderly and young LDs, one needs to consider various factors, including age-related variables. 3) Analyze the relationship between donor age and recipient complications. In this context, we also aimed to analyze whether grafts taken from older donors can be used without creating a significant difference in survival and morbidity compared to younger donors. LT is a effective treatment for end-stage liver disease including primer liver cancers, metabolic diseases and infections. We hypothesized that outcomes of LT with older grafts have amended over time and the discrepancy in survival between elderly and younger.

Currently, LD has narrowed. Allocating donated livers across patients is a challenging process for the transplantation team. Using elderly donors would solve this gap.

Materials and Methods

A total of 520 liver transplants were performed in our center between December 2012 and January 2018. The study consecutively included a retrospective analysis of patients who had undergone LDLT. For LDLT, LDs were divided into multiple forms. Accordingly, three different LD age groups were established: young (18-39), middle-aged (40-49) and elderly (50-59) years. As descriptive analyses, t the following categories were used: <40 y, 40-49 y, 50-59 y. We did not evaluate donor age continuously (e.g., per decile) for donors under the age of 40. LD parameters included age, sex, relationship to liver recipient, steatosis rate based on donor liver biopsy, type of hepatectomy, estimated liver graft volume was defined as preoperative assessment of graft size by computed tomography, duration of operation. Recipient parameters included model for end-stage liver disease (MELD) score, etiology of liver disease, sex, age, duration of operation, length of postoperative hospital stay (day), graft rejection, post-transplantation complications (according to Clavien-Dindo classification), graft-to-recipient weight rate (GRWR), and body mass index (BMI). Our institute follows specific preoperative criteria for graft sizing. We have used left or right-lobe grafts. Patients were required following inclusion criteria: LDLT for any indication. Patients were excluded deceased donor liver transplantation, receiving simultaneous solid organ transplants, child recipients (<18 y), recipients with perioperative mortality in the first 30 days and cases with missing survival data or donor age.

Pre-LT assessment protocol should be performed to identify underlying cardiovascular disease. Comprehensive blood tests, imaging, endoscopy and pulmonary examinations

were also performed all of liver recipients. Recipients received standard immunosuppression treatment after transplantation. The determination of older donors typically varies in other centers. In the present study, we defined donors who were older than 50 years as elderly. Donor selection criteria included healthy individuals and aged 60 years or younger. Donors with comorbidities or underlying medical diesases were also excluded from living liver donations. Living donors were also followed with laboratory tests and abdominal ultrasonography at months 1, 3, and 6 during the first year after surgery and annually hereafter. Postoperative management and follow-up have been described previously (11,12). Indications for LDLT have been described previously (13). The primary outcome of the study was long-term survival (1, 3, 5 and 10 years) of the recipient and the graft. Recipient survival was the time from LDLT to death occurring or to the last follow-up time. Graft survival was determined as the loss of graft function due to HCV recurrence, infection, sepsis, ischemia, or vascular complications after LDLT, and it was also determined by the time to HCC recurrence. This study protocol was reviewed and approved by the Ethics Committee of Acıbadem University (no: ATADEK 2023-18/617) on 16.11.2023. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the individual(s) for the publication.

Statistical Analysis

The distribution of variables was controlled with Kolmogorov-Smirnov test. In comparing basic recipient characteristics according to donor age groups, the Kruskal-Wallis test was used for continuous variables. Categorical variables among the 3 age categories of donors were compared using chi-square test or Fisher's exact tests.

Time-to-event analyses were used the relationship between LD age and recipient and graft survival. For comparison of normally distributed data among the three groups of donor age categories (18-39, 40-49, 50-59), the Student t-test was used. The Mann-Whitney U test was used for non-normally distributed data, and comparison of quantitative data. Kaplan-Meier curves were used for graft and recipient survival. Graft and recipient survival were compared using the logrank test. All analyses were performed using SPSS 28.0.

Results

The study included a total of 168 LDLT recipients. LDLTs numbers according to donor age categories were as follows: Young (n=95), middle-aged (n=47), and elderly (n=26). Recipient disease etiology was cryptogenic (25%), HBV (20.2%), HCV (14.3%), HCC (8.3%), autoimmune (7.7%), alcoholic (6.5%) and others (18%) (Table 1). There were few significant differences in recipient characteristics among the LD age groups. Table 2 shows recipient demographic characteristics. The proportion of female patients in the younger age group was significantly higher than in the elderly group. There was no difference in gender distribution between the young and elderly age groups. Graft liver volume was significantly higher in the 50 to 59-year-old age group than in the young and middle-aged groups. There was no significant difference in graft liver volume between the young and middle-aged groups. The first-degree relative rate was significantly lower in the elderly group than in the middle-aged group. The other biological relative rate and non-biological relative rate were significantly higher in the elderly group than in the young and middle-aged groups. The degree of biological closeness did not differ significantly between the young and middle-aged (Table 2). The relationship between donor and recipient differed by donor age. In the >50 year age group, 34.6% of donors were non-biological relationship with the recipients whereas 72.6% of donors in the <40 year age group and 59.6% of donors in the middle-aged groups were first-degree relatives with recipients.There was no significant difference between the young, middle-aged and elderly groups for the Clavien-Dindo complication rate, recipient MELD score and duration of operation for recipients. But the ≥5% steatosis rate (macro or micro) was significantly higher in the 50-59 year age group (42.3%) than in the 18-39 year (22.2%) and middle-aged groups (31.9%). However, the rate of steatosis did not differ significantly between the young and middle-aged groups. Median recipient survival, graft survival, and duration of operation for the recipients did not differ significantly between the young and middle-aged groups, but were significantly lower in the elderly group than in the young and middle-aged groups. The GRWR value was significantly higher in 50-59 year age group than in young and middle-aged groups. There was no significant difference in GRWR value between the young and middle-aged groups. Length of hospital stay was significantly shorter in elderly group than in young and middle-aged groups for recipient. There was no significant difference in length of hospital stay between young and middle-aged groups (Table 3). One-year LDLT recipient survival was 100% in all groups, while three-year survival rate was 100% in young, middle-aged groups, and 95.8% in the elderly group. The five-year survival rates of

young, middle-aged and elderly groups were 100%, 94.3% and 86.7%, respectively. However, 10-year survival rates were significantly higher in the young group (48.5%) than in the middle-aged and elderly groups (22.9% and 0%, respectively). Five-year graft survival rate of young, and middle-aged groups was 72.6 and 76.6%, respectively. But an 84.3% graft survival rate was observed in elderly group. After five years, donor age remained associated with recipient overall survival. In terms of the survival rates of LDLT recipient age groups, the predicted survival rate in the elderly group (68.3%) was significantly lower than that in middle-aged and young groups. The predicted survival time was significantly lower in the middle-aged and the elderly groups than in the young age group (Figure 1). In the graft survival analysis, the predicted graft survival times of young, middle-aged and elderly groups did not differ significantly (Figure 2). We showed the study population in a flow diagram (Figure 3).

Discussion

While previously considered highly risky, LT using elderly LD grafts has been increasing over time due to the significant

Table 1. Recipient demographic characteristics

		Min-max			Median	Mean ± SD/n-%		
Age		6.0	-	57.0	37.0	37.0	±	10.1
Recipient age		0.60	-	71.0	54.0	50.5	±	14.9
Gender	Female					84		50.0%
	Male					84		50.0%
BMI		14.0	-	47.0	26.0	26.6	±	4.8
Liver volume		10.0	-	71.0	64.0	60.7	±	12.4
First degree relative	(No)					66		39.3%
	(Yes)					102		60.7%
Other biological relative	(No)					123		73.2%
	(Yes)					45		26.8%
Non-biological relative	(No)					144		85.7%
	(Yes)					24		14.3%
Diagnosis								
Cryptogenic						42		25.0%
Hepatitis B virus						34		20.2%
Hepatitis C virus						24		14.3%
Hepatocelluler carcinoma						14		8.3%
Autoimmune						13		7.7%
Alcoholic						11		6.5%
Biliary cirrhosis						6		3.6%
Budd chiari						5		3.0%
Primer biliary sclerosis						4		2.4%
Biliary atresia						4		2.4%
Hyperoxa luria						2		1.2%
Primer biliary cholangitis						2		1.2%
Wilson disease						2		1.2%
Non-alcoholic steatohepatitis						2		1.2%
Caroli disease						1		0.6%
Liver failure						1		0.6%
Progresissive familial intrahepatic cholestasis						1		0.6%

SD: Standard deviation, BMI: Body mass index

gap in demand and supply. With increasing experience, elderly deceased donor transplantations, including those from octogenarian donors, are being achieved with excellent results in many centers around the world (14-16). LDLT is performed in LT centers with very few LDs who are ≥50 years of age. In this regard, there are only minor relative differences between the centers. Overall acceptance of centers of elderly living liver donors has not markedly changed. Studies from Asia with a high prevalence of HCC showed an inconsistent effect of increased LD age on graft and recipient outcomes (17-21). Again, although some studies showed that LDLT with carefully selected elderly LD is safe even with LDs over 60 years of age, well experienced LDLT centers' point of view, there are still major concerns about this (10,22). In Japan, the percentage of donor graft use for donors over the age of 50 is 18%, and for those over 60, it is 4%, respectively. According to volumetric measurements made with computed tomography after LDLT, impaired liver regeneration was shown in elderly donors (≥50 years of age) compared to younger donors (<30 years) (23). Donor age is a strong and independent prognostic factor in LDLT. However, some researchers have showed that LD grafts can be used safely even in donors older than 50 years, although the regeneration capacity is impaired (19,24-27). Compared to Europe and Asia, use of LD among the elderly in the US has lagged behind. This is likely due to multifactorial reasons including the increased risk perception from previous studies. The most recent study showed excellent results in the use of elderly LDs over 70 years of age in selected recipients (28). However, that study conducted an analysis of elderly DCD (donation after cardiac death) donors in the United Network for Organ Sharing (UNOS) database. In contrast, the US study showed a significant unfavorable effect of an elderly LD on graft results, reporting that 1/10 recipients with LD >50 were retransplanted within the first year. Nevertheless, 5- and 10-year long-term graft survival outcomes of 71.4% and 58.6%, respectively, were still acceptable. Interestingly, it was found that increasing donor age in LDLT compared to DDLT had deeper negative consequences for graft results (29). The data regarding the association of older LD age and outcomes in LDLT, came from the adult to adult living LDLT (A2ALL) study (30). The A2ALL study showed that older donor age was associated with early graft dysfunction (EAD) and high recipient mortality (31). However, A2ALL studies were performed during a period when selection criteria in LDLT centers were conservative, and the use of LDs over 50 years of age was rare. In fact, although long-

Table 2. Donor demographic characteristics

			Age 18-39[1]			Age 40-49[2]			Age 50-59[3]			p	
			Mean ± SD/n-%			Mean ± SD/n-%			Mean ± SD/n-%				
Age (year)	Mean ± SD		30.0	±	5.5	42.5	±	6.1	52.6	±	2.3		
	Median		31.0			43.0			52.0				
Recipient age (year)	Mean ± SD		50.0	±	14.6	49.5	±	18.4	54.1	±	6.9	**0.745**	K
	Median		53.0			55.0			54.0				
Gender	Female	n-%	39[2]		41.1%	36.0		76.6%	9[2]		34.6%	**0.000**	X^2
	Male	n-%	56		58.9%	11.0		23.4%	17		65.4%		
Body mass index	Mean ± SD		27.1	±	4.9	26.0	±	5.0	25.6	±	3.5	0.407	K
	Median		26.0			26.0			25.5				
Liver volume	Mean ± SD		60.0	±	12.3	59.3	±	15.1	65.9	±	3.5	**0.005**	K
	Median		63.0[3]			65.0[3]			66.0				
First degree relative	(No)	n-%	26		27.4%	19		40.4%	21		80.8%	**0.000**	X^2
	(Yes)	n-%	69[3]		72.6%	28[3]		59.6%	5		19.2%		
Other biological relative	(No)	n-%	70		73.7%	39		83.0%	14		53.8%	**0.026**	X^2
	(Yes)	n-%	25		26.3%	8[3]		17.0%	12		46.2%		
Non-biological relative		n-%	91		95.8%	36		76.6%	17		65.4%	**0.000**	X^2
	(Yes)	n-%	4[23]		4.2%	11		23.4%	9		34.6%		

X^2: Chi-square test, K: Kruskal-Wallis (Mann-Whitney U test), [2]: Difference with age 40-49 group p<0.05, [3]: Difference with age 50-59[3] group p<0.05, SD: Standard deviation

Table 3. Recipient characteristics and posttransplantation outcomes in the comparison study using elderly donors and younger donors in the living donor liver transplantation

			Age 18-39[1]			Age 40-49[2]			Age 50-59[3]			p	
			Mean ± SD/n-%			Mean ± SD/n-%			Mean ± SD/n-%				
Liver steatosis	0%	n-%	61[23]		64.2%	21		44.7%	8		30.8%	0.004	X^2
	1%	n-%	13		13.7%	11		23.4%	7		26.9%		
	5%	n-%	19		20.0%	10		21.3%	8		30.8%		
	10%	n-%	0		0.0%	4		8.5%	2		7.7%		
	15%	n-%	1		1.1%	0		0.0%	1		3.8%		
	20%	n-%	0		0.0%	1		2.1%	0		0.0%		
	100%	n-%	0		0.0%	0		0.0%	0		0.0%		
Clavien-Dindo complication	I	n-%	71		74.7%	38		80.9%	22		84.6%	0.479	X^2
	II	n-%	10		10.5%	8		17.0%	4		15.4%		
	III	n-%	13		13.7%	1		2.1%	0		0.0%		
	IV	n-%	1		1.1%	0		0.0%	0		0.0%		
MELD	Mean ± SD		19.1	±	6.4	18.8	±	6.0	19.8	±	4.3	0.349	K
	Median		17.0			17.0			19.0				
Operation time of donor (minute)	Mean ± SD		382.2	±	69.7	413.4	±	82.4	390.0	±	57.9	0.058	K
	Median		370[2]			410			388				
Graft survival (month)	Mean ± SD		77.8	±	46.0	68.4	±	36.8	62.0	±	20.3	**0.003**	K
	Median		92.0[23]			73.0			65.5				
Recipient survival (month)	Mean ± SD		77.8	±	46.0	66.8	±	38.0	62.0	±	20.3	**0.002**	K
	Median		92.0[23]			72.0			65.5				
Recipient operation time (minute)	Mean ± SD		643	±	106	596	±	104	556.0	±	76.7	**0.000**	K
	Median		630[23]			570			535				
Right hepatectomy	(No)	n-%	8		8.4%	5		10.6%	0		0.0%	0.247	X^2
	(Yes)	n-%	87		91.6%	42		89.4%	26		100%		
Left lateral hepatectomy	(No)	n-%	87		91.6%	42		89.4%	26		100%	0.247	X^2
	(Yes)	n-%	8		8.4%	5		10.6%	0		0.0%		
Live	(No)	n-%	26		27.4%	11		23.4%	4		15.4%	0.444	X^2
	(Yes)	n-%	69		72.6%	36		76.6%	22		84.6%		
Graft rejection	(No)	n-%	71		74.7%	39		83.0%	18		69.2%	0.368	X^2
	(Yes)	n-%	24		25.3%	8		17.0%	8		30.8%		
GRWR	Mean ± SD		0.99	±	0.22	1.1	±	0.33	1.1	±	0.17	**0.008**	K
	Median		0.97[23]			1.00			1.00				
Hospital stay	Mean ± SD		22.2	±	11.5	19.2	±	12.6	16.2	±	4.0	**0.004**	K
	Median		20.0[23]			14.0			15.5				
Died	(No)	n-%	68		71.6%	35		74.5%	22		84.6%	0.402	X^2
	(Yes)	n-%	27		28.4%	12		25.5%	4		15.4%		

X^2: Chi-square, K: Kruskal-Wallis (Mann-Whitney U test), [2]: Difference with age 40-49 group p<0.05, [3]: Difference with age 50-59[3] group p<0.05, SD: Standard deviation, GRWR: Graft-to-recipient weight rate, MELD: Model for end-stage liver disease

term survival outcomes in LDLT are believed to be better than DDLT, our study showed that this advantage is lost at advanced donor age. Several factors may contribute to this phenomenon. The meticulous selection of older donors is crucial. Age-related comorbidities may be more prevalent in older donors, potentially impacting post-transplant complitaions and long-term survival. Surgical difficulties and morbidites can be more frequent in the transplantation

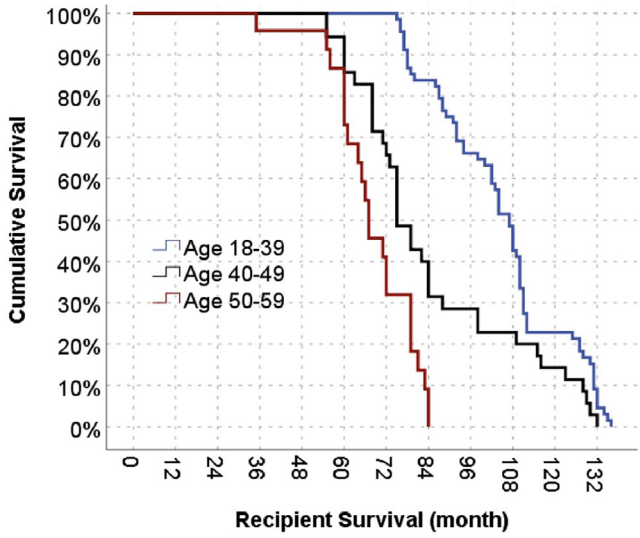

Figure 1. Recipient's overall survival graphic in different living age groups

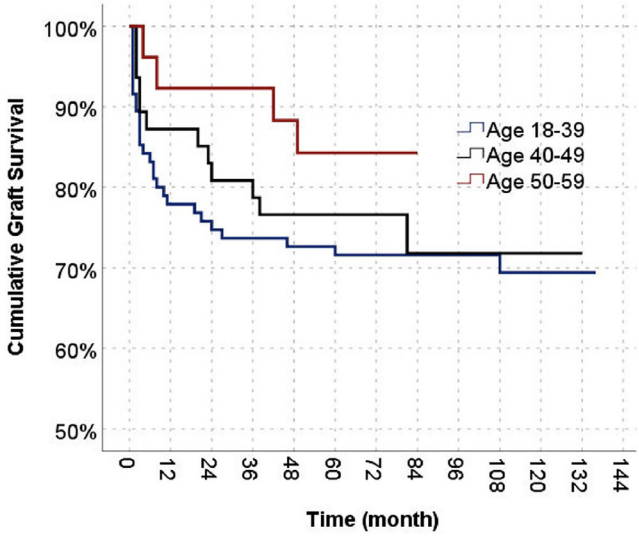

Figure 2. Graft survival curve in the recipient after liver donor graft using in different age groups

of livers from older donors. Immunological differences in older donors might affect the recipient's ability to accept the transplanted liver. Recipient characteristics and comorbidities play a vital role. The response of older donors' liver to immunosuppressive drugs may differ, influencing post-transplant survival. The combination of these factors may contribute to the observed trend where the advantage of superior long-term survival outcomes in LDLT diminishes with advanced donor age. We reported that the graft survival rate did not differ significantly among the groups for the long term. We evaluated this as graft failure if the graft failure due to HCV, NASH, HCC

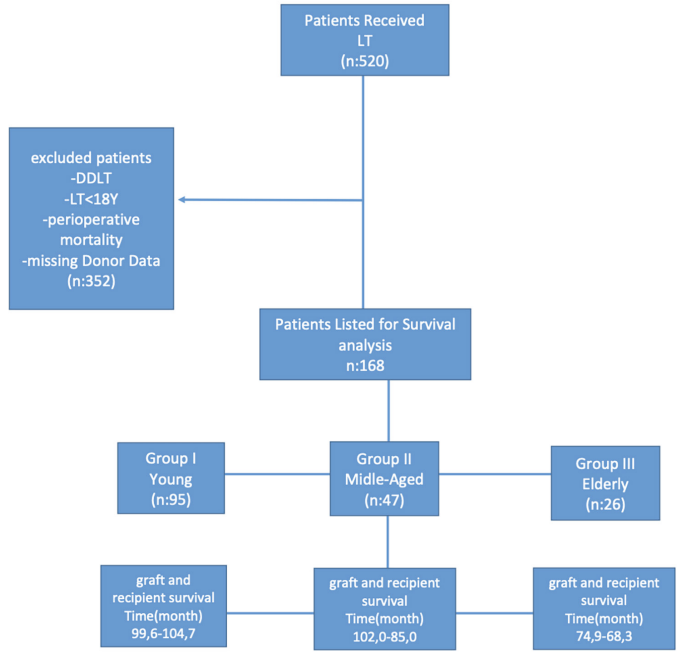

Figure 3. Flow chart illustrating our study population

DDLT: Donor liver transplantation, LT: Liver transplantation

recurrence, non-compliance with immunosuppressive treatment, graft rejection, infectious causes as sepsis or arterial-venous and biliary complications can not reversed with treatment. Therefore no patients in each cohort were diagnosed with small-for-size syndrome (SFSS). We did not assess portal venous pressure (PVP) during transplantation. Previous studies have shown that elevated PVP necessitates portal inflow modulation to prevent SFSS. No cases of EAD were observed in this study. These complications are frequently encountered during the early post-LT period. It was less common in recipient (50> LD). Recipient losses due to any other reason were not considered as graft loss in this statistics. Further graft liver volume and GRWR were significantly higher in the elderly group than in other groups. The GRWR could improve the prediction of 90-day graft survival (32). The decision to continue LDLT with elderly LD must take into account the clinical status of the recipient, the risk of death on the waiting list, and especially alternative donor availability. In this context, there is also a need to determine the appropriate recipient and donor selection practices in the elderly LD arrangement. The centers did not perform LDLT for more severe disease, nor with an elderly LD suitable for an elderly recipient. There was also no difference in the prevalence of normal weight compared to obese or overweight elderly LD. This finding was in line with the present study. Although the increased age of

LDs did not influence the decision to perform pre-LT liver biopsy, we found that the rate of steatosis was significantly higher in elderly donors than in younger donors in our study. This suggested preoperative liver biopsy in elderly donors. However, in our analysis, the inclusion of liver biopsy in LD for all LDLT could have resulted in selection bias because of the restrictive nature of the biopsy. The use of non-invasive measurement methods such as MR spectroscopy as an alternative to invasive liver biopsy could have made the steatosis evaluations more effective and safer in assessing the results of increased LD age (33-35). In our study, there were differences in recipient-donor relationships. Non-biological status was more common in the LD group of individuals over 50 years of age. This reflected the inability of potentially younger biologically-related donors to serve as suitable donors. Based on UNOS data, a study reported that early postoperative donor complications were not affected by donor age, but biliary complications were more common in LDs older than 55 years of age, although the age difference was not statistically significant (29).

One of the inherent challenges with UNOS data is that there may be less propensity for centers to report complications directly. A recent study, showed that elderly LD was associated with a higher risk of major morbidities (36). Some other studies showed that LDLT using elderly donor grafts induced more serious postoperative complications and resulted in higher mortality rates in recipients than those who received younger donor grafts (37,38).

In our study, we evaluated early (≤6 weeks) postoperative complications, including biliary and vascular complications, using the Clavien-Dindo classification for the first time. In this context, we did not observe a negative effect of donor age. Additional studies are needed to determine more comprehensively whether older liver donors are related to potential long-term effects on recipient survival. With the recent increase in the demand for LT in parallel with LD limitation, there is a need for updated donor results on a wide scale in the world LDLT community. Although many side effect discussions for donors are directly transferred from the seminal A2ALL studies, they do not fully reflect the concerns in the current era, when there is more LDLT experience. Experienced centers are now expanding their donor selection criteria and performing more LDLT. Due to some reservations about using LD in the elderly, it seems intuitively more prudent to prioritize patients with severe clinical conditions due to increased likelihood of graft dysfunction and decreased organ physiological reserve capacity. In the present study, the median recipient ages were 53, 55 and 54 years and MELD scores were 17, 17 and 19 in young, middle-aged and elderly groups, respectively. Although the MELD score, was higher in the elderly LD group, there was no statistically significant difference compared to the other groups. We observed a relatively stable MELD score over time in this study. Contrary to programs that tend to use elderly LD at lower MELD scores, the present study observed no difference in early complications, and graft and recipient survival, was observed between LDLT performed with elderly LD at high MELD values and younger age groups, at the same MELD value. There was no significant difference in recipient ages among the study groups. LT is technically more difficult in obese recipients. This may increase the operative time and the need for transfusion, as well as the risk of perioperative complications such as uncontrolled major bleeding in the inferior vena cava, bleeding adjacent to the liver, or damage to the hepatic artery (39). Noteworthy is the classification of our study participants as overweight (BMI: 25-29.9) without any individuals falling into the obese category (BMI: 30 and above), which is noteworthy. we observed that there were no significant differences in BMI among the groups.

In our study, we reported a significant difference in long-term recipient survival after five years. It is important to optimize donor-recipient matching here. Our findings also support the idea of discouraging the use of older LD grafts in younger recipients to benefit from the graft for a long time. In recent years, several studies have examined the long-term outcomes of using elderly LDs from the recipient's perspective. These reports stated that donor age is a factor affecting recipient survival (18,37-42). A number of studies indicated a difference in post-transplant survival between the use of old and young donors in the first year after the transplantation, which stabilizes thereafter (43). Our study is the first to evaluate the use of the LD graft in the LDLT simultaneously in three different age groups for long-term recipient and graft survival outcomes, and to include GRWR and Clavien-Dindo classification parameters in the analysis. An important aspect of LDLT safety is GRWR and donor graft volume. These parameters are predominant factors in the LD selection process. Dayangac in Turkey reported increased concerns about the relationship among high LD age, donor graft volume and recipient outcomes (44). In recent study, the predicted survival time in the elderly group (68.3 months) was significantly ($p<0.05$) lower than in the middle aged and young groups. Furthermore the predicted survival time in the middle- aged group was significantly ($p<0.05$) lower than in the young group. Our study also eliminated concerns about this relationship by more

accurately determining the impact of increased donor age. Considering the center heterogeneity in LDLT applications, large multicenter studies are essential to overcome this problem. Our study is likely to encourage these efforts. For patients awaiting LDLT and without suitable young donors, it is imperative to examine the potential survival benefit of proceeding with LDLT using elderly LD to better guide decision-making for both physicians and patients. This study shows that Length of postoperative hospital stay was significantly shorter in elderly group. The impact of donor age on postoperative hospital stay lengths in LT is significant, as older donors are often subject to more stringent selection criteria. Older donors may be preferentially used for less risky recipients. The meticulous surgical techniques might be used in transplants involving older donors (26,45,46). In fact, although long-term survival outcomes in LDLT are believed to be better than DDLT, our study showed that this advantage is lost at high donor age. Comparative and further studies would be beneficial in understanding these findings.

Study Limitations

Our study is limited by the lack of granularity regarding causes of graft loss or patient mortality. In addition to its single-centered and retrospective nature, the study was not suitable for involving the elderly group in the multivariable model due to the low power of the group. Still, we believe it helped to provide some perspective in terms of the older donor age. Portal inflow modulation was not performed during LT. Apart from GRWR and graft volume, factors including donor comorbidity and graft characteristics that affect early post-transplant mortality and morbidity, such as warm ischemia time, hypertension, diabetes, and use of blood products, were not evaluated. The biliary anatomy of the donor, which posed a potential risk for biliary complications, was also not taken into consideration. However, donor and liver graft factors were evaluated to predict recipient outcomes in LDLT. However, it is not clear to what extent these evaluations consider donor age and how they affect the results. Multiple regression analysis was not used in this study, therefore we could not conclude whether LD age of >50 years was an important predictor in long-term graft and recipient survival. Further studies need to be carried out on this.

Conclusion

The results of our study can be based on the following principles: Elderly donors can be selected for LDLT by paying close attention to donor safety, and with appropriate donor-recipient selection, there was no statistically significant difference between the groups in five-year recipient survival. Similarly, no difference was observed between the groups in long-term graft survival. Despite the increasing use of LDLT around the world, centers remain conservative in accepting the use of elderly donors in LDLT. This could be attributable to the low rate of GRWR and high steatosis in the elderly group compared with the younger groups. Many potential factors, such as improved surgical technique, perioperative care, and patient selection, can contribute to this success. From the recipient's perspective, the decision to use elderly living donors should be made by weighing the risks associated with other LD options or the deceased donor LT waiting period. While the use of elderly living donors could be considered in emergency, life-saving scenarios, it is important to note that long-term graft survival in the elderly group remains suboptimal. Consequently, these donors are typically selected with caution.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Ethics Committee of Acıbadem University (no: ATADEK 2023-18/ 617) on 16.11.2023.

Informed Consent: Approval of the participants included in the study was obtained using a voluntary consent form.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.T., İ.B.B., Concept: U.T., Design: U.T., Data Collection or Processing: İ.B.B., Analysis or Interpretation: İ.B.B., Literature Search: U.T., Writing: U.T.

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ORIGINAL RESEARCH

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Relation Between Primary Tumor Suv$_{max}$ Value, Ki-67 Proliferation Index and Axillary Metastasis in Patients with Triple Negative Breast Cancer

Triple Negative Meme Kanserli Hastalarda Primer Tümör Suv$_{maks}$ Değeri, Ki-67 Proliferasyon İndeksi ve Aksiller Metastaz Arasındaki İlişki

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Abstract

Objective: The aim of our study was to determine the relationship between fluorodeoxyglucose (FDG) uptake, expressed as SUV$_{max}$ of the primary tumor in F-18 FDG positron emission tomography/computed tomography (PET/CT) for staging in triple-negative breast cancer (TNBC) patients, and axillary lymph node (LN) metastasis and Ki-67 expression.

Method: A total of 136 female TNBC patients who underwent F-18 FDG PET/CT imaging at our unit between July 2021 and March 2024 were retrospectively evaluated. Data on age, histopathology, hormone receptor status, Ki-67 levels, tumor location (right/left), the largest diameters of the tumor and axillary LN, axillary LN metastasis status, presence and site of distant metastasis, T stage, and clinical stage were recorded. SUV$_{max}$ values of the primary breast lesions and metastatic axillary LNs were documented.

Results: The mean age of the patients was 51.42±13.14 years (range: 23-86). Axillary LN metastasis was present in 95 patients (69.85%), and distant metastasis was detected in 24 patients (17.65%). No significant differences were observed between patients with and without axillary LN metastasis in terms of age, Ki-67, tumor size, tumor SUV$_{max}$, or T stage. Tumor and metastatic axillary LN sizes were positively correlated with SUV$_{max}$ values. However, no correlation was found between Ki-67 and tumor size, tumor SUV$_{max}$, axillary LN size, or axillary LN SUV$_{max}$ values.

Conclusion: In TNBC, there is no relationship between the SUV$_{max}$ value of the primary tumor in staging F-18 FDG PET/CT and axillary LN metastasis or the Ki-67 proliferation index. As expected in aggressive

Öz

Amaç: Çalışmamızın amacı, triple negatif meme kanseri (TNMK) hastalarında evreleme F-18 florodeoksiglikoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografide (PET/BT) primer tümörün SUV$_{maks}$ olarak tanımlanan FDG tutulumu ile aksiller lenf nodu (LN) metastazı ve Ki-67 ekspresyonu arasındaki ilişkiyi belirlemektir.

Yöntem: Temmuz 2021-Mart 2024 tarihlerinde birimimizde F-18 FDG PET/BT görüntülemesi yapılmış olan TNMK tanılı 136 kadın hasta retrospektif olarak değerlendirildi. Hastaların yaşları, histopatolojileri, hormon reseptör durumları, Ki-67 seviyeleri, tümör lokasyonları (sağ/sol), tümör ve aksiller LN'lerinin en büyük çapları, aksiller LN metastaz durumları, uzak metastaz varlığı ve yeri, T evreleri, klinik evreleri, primer tümör ve metastatik aksiller LN'lerin SUV$_{maks}$ değerleri kayıt edildi.

Bulgular: Hastaların ortalama yaşı 51,42±13,14 yıl (aralık: 23-86) idi. Doksan beş (%69,85) hastada aksiller LN metastazı, 24 hastada (%17,65) uzak metastaz mevcut idi. Aksiller LN metastazı olan ve olmayan hastalar arasında yaş, Ki-67, tümör boyutu, tümör SUV$_{maks}$ veya T evreleri açısından anlamlı bir fark izlenmedi. Tümör ve aksiller LN boyutları SUV$_{maks}$değerleri ile pozitif korelasyon gösterdi. Ki-67 ile tümör boyutu, tümör SUV$_{maks}$ değeri, aksiller LN boyutu veya aksiller LN SUV$_{maks}$ değerleri arasında bir korelasyon bulunamadı.

Sonuç: TNMK'de evreleme F-18 FDG PET/BT'den edilen primer tümör SUV$_{maks}$ değeri ile aksiller LN metastazı veya Ki-67 proliferasyon indeksi arasında bir ilişki yoktur. Agresif malignitelerde beklenildiği gibi, primer

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Abstract

malignancies, primary tumor size was correlated with tumor SUV_{max} and metastatic axillary LN size, while metastatic axillary LN size was correlated with axillary LN SUV_{max}.

Keywords: 18F-fluorodeoxyglucose, axillary lymph node, Ki-67, positron emission tomography, triple-negative breast cancer

Öz

tümör boyutu, tümör SUV_{maks} ve metastatik aksiller LN boyutu ile, aksiller LN boyutu ise aksiller LN SUV_{maks} değeri ile korelasyon göstermiştir.

Anahtar kelimeler: 18F-fluorodeoksiglukoz, aksiller lenf nodu, Ki-67, pozitron emisyon tomografisi, triple negatif meme kanseri

Introduction

Breast cancer, characterized by its various molecular subtypes, is one of the most common malignancies among women (1,2). Triple-negative breast cancer (TNBC) is a subtype accounting for approximately 10-15% of all breast cancers, and is defined by the lack of expression of human epidermal growth factor receptor 2 (HER2), estrogen receptors (ER), and progesterone receptors (PR) (2). This feature makes it a clinically distinct and more challenging entity due to poor prognosis, high mortality risk, and aggressive course with metastases (3), which are largely associated with the inefficacy of targeted treatments in the absence of receptors (1,4).

In breast cancer patients, primary tumor size, axillary lymph node (LN) involvement, and distant metastases play crucial roles in determining treatment strategies and prognosis (5). Ki-67, an indicator of tumor proliferation, is widely used as a pathological marker in numerous malignancies, including certain breast cancer subtypes (6). Ki-67 is utilized in other breast cancer subtypes; however, its prognostic significance in TNBC remains unclear (7).

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography [F-18 fluorodeoxyglucose, positron emission tomography/computed tomography (FDG PET/CT)] is frequently employed in the imaging of breast cancer. Its uses include initial staging of large and locally advanced breast cancers, assessing response to neoadjuvant systemic therapy, detecting distant metastases, identifying locoregional or metastatic recurrences, restaging after treatment, planning radiotherapy, and determining prognosis (8-11). FDG uptake in primary lesions is primarily influenced by histological subtype, receptor status, Ki-67 proliferation index, and tumor size (8). The most commonly used method for quantifying F-18 FDG uptake is the maximum standardized uptake value (SUV_{max}), which reflects the highest FDG uptake in the region of interest (12). Primary TNBC lesions are known to exhibit higher SUV_{max} values compared to other subtypes, and available data demonstrate correlations between SUV_{max}, size, and Ki-67 in TNBC (8,9,13-17).

We aimed to investigate the relationship between FDG uptake, expressed as SUV_{max} of the primary tumor, and axillary LN metastasis, and Ki-67 expression in patients with TNBC.

Materials and Methods

Patient Selection

Patients with a diagnosis of breast cancer who underwent F-18 FDG PET/CT imaging in our nuclear medicine department between July 2021 and March 2024 were retrospectively evaluated. Patients with a histopathological diagnosis of TNBC were examined for inclusion. Those without a histopathological diagnosis, subjects who had undergone surgery or treatment for primary malignancy, and patients with other malignancies were excluded.

Collected data included histopathology, hormone receptor status, Ki-67 levels, tumor side (right/left), largest diameters of the tumor and axillary LN, axillary LN metastasis status, distant metastasis status and location, T stage, and clinical stage. Tumor staging was conducted based on the American Joint Committee on Cancer (AJCC) 8^{th} edition TNM classification system (18). Maximum standardized uptake values (SUV_{max}) derived from F-18 FDG PET/CT for the breast tumor (tumor SUV_{max}) and axillary LN (LN SUV_{max}) were recorded.

This study received approval from the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (decision no: E-96317027-514.10-248478655, date: 10.07.2024). All diagnostic and therapeutic procedures were conducted in accordance with national guidelines and the Declaration of Helsinki. All patients provided informed consent for the procedures.

18F-FDG PET/CT Procedure

An Ingenuity TF 64 scanner (Philips medical systems, USA) was used to perform 18F-FDG PET/CT scans, with whole-body CT settings of 113 mAS, 120 kV and 4-mm section thickness (low dosage). The European Association of Nuclear Medicine version 2 ruleset was the basis for

image acquisition and evaluation (19). All patients were instructed to fast for 6 hours before scanning, and blood glucose was confirmed to be <150 mg/dL for each patient at the time of injection. 18F-FDG was administered intravenously as a standard dose of 3-4 MBq/kg. Patients were taken to the scanner after an interval of around 50 minutes (spent resting in a relaxed position) following intravenous 18F-FDG (3-4 MBq/kg) administration. PET imaging covered the same transverse field of view and employed 3 minutes of acquisition time per bed examined. Attenuation correction was based on CT images, and both corrected and non-corrected images were analyzed through maximum intensity projection as well as cross-sectional views in transaxial, coronal, and sagittal planes. Routine evaluations included checks for image quality, alignment accuracy, and potential artifacts.

Image Interpretation

The images were reviewed by two nuclear medicine physicians with over 10 years of expertise. The SUV_{max} was defined as the maximum SUV from a single voxel in an automated volume of interest that was defined as an is contour of 40% of the maximum reported signal intensity, in the area of a suspected lesion.

Pathological Evaluation

All tissue samples were examined by immunohistochemistry (IHC), and all samples negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 were included. ER-, PR-, and HER2- were defined as ER less than 1%, PR less than 1%, and a score of 0-1+ in HER2 IHC or IHC 2+ and negative silver *in situ* hybridization, respectively. Sections were lightly counterstained with hematoxylin. Sections obtained from LN tissue were used as a positive control for proliferating cells. The evaluation of Ki-67 immunostaining was performed in an area with a high cellular presence. All epithelial cells exhibiting nuclear staining, regardless of intensity, were considered positive. Approximately 500 nuclei were counted on each slide. Proliferative activity was assessed as the ratio of Ki-67 stained nuclei in the sample. Fine-needle aspiration cytology (FNAC) was conducted using a needle and a plastic syringe, guided by ultrasound. Following the FNAC procedure, the aspirates were promptly fixed in 95% ethanol. All FNAC smears were then stained using the Papanicolaou method without additional immunostaining and were evaluated routinely by a pathologist for diagnostic assessment.

Statistical Analysis

Statistics were performed using SPSS version 25.0 (IBM, Armonk, NY, USA) with the classical p-value threshold, considered significant if $p<0.05$. Categorical data were summarized using n and column (dependent) percentages and were analyzed by employing the appropriate chi-square tests or the Fisher-Freeman-Halton test. Histograms and Q-Q plots were used to estimate the presence or absence of normal distribution in numerical data, with deviation from the identity line defined as absence of normality. Descriptive statistics for numerical data included mean ± standard deviation or median (25^{th} percentile-75^{th} percentile) depending on normality or non-normality of the distribution. Between groups analysis of continuous variables was performed using Student's t-test or Mann-Whitney U test, depending on the normality of the distribution. Correlation results were based on Spearman's rho.

Results

We included 136 patients with TNBC into the study; the mean age was 51.42±13.14 years (range 23-86). All patients were diagnosed with invasive ductal carcinoma. Among these subjects, 95 (69.85%) had axillary LN metastasis and 24 (17.65%) had distant metastasis. Other data, including detailed tumor characteristics, are summarized in Table 1.

We found no significant differences between patients with and without axillary LN metastasis in terms of age, lesion side, Ki-67, largest tumor diameter, tumor SUV_{max}, and T stage (Table 2).

The frequency of stage T2 was significantly lower in patients with distant metastasis than in other patients ($p=0.026$). We found no significant differences between patients with and without distant metastasis in terms of age, lesion side, Ki-67, tumor largest diameter, tumor SUV_{max}, axillary LN metastasis, axillary LN largest diameter and axillary LN SUV_{max} (Table 3).

The largest tumor diameter was positively correlated with tumor SUV_{max} ($r=0.397$, $p<0.001$) and the axillary LN largest diameter ($r=0.271$, $p=0.001$). The axillary LN's largest diameter was positively correlated with the axillary LN SUV_{max} ($r=0.783$, $p<0.001$). There were no significant correlations between Ki-67 and largest tumor diameter, tumor SUV_{max}, largest axillary LN diameter, axillary LN SUV_{max} (Table 4).

Table 1. Summary of age and tumor characteristics

Age (n=136)	51.42±13.14
Side (n=136)	
Right	53 (38.97%)
Left	83 (61.03%)
Ki-67 (%) (n=122)	70 (50-80)
Tumor largest diameter, cm (n=136)	3.0 (2.2-4.4)
Tumor SUV_{max} (n=136)	16.6 (9.35-23.0)
Axillary LN metastasis (n=136)	95 (69.85%)
Axillary LN largest diameter, cm (n=136)	1.50 (0.00-2.22)
Axillary LN SUV_{max} (n=136)	5.20 (0.00-11.10)
Distant metastasis (n=136)	24 (17.65%)
Distant metastasis location (1) (n=136)	
Bone	11 (8.09%)
Lung	9 (6.62%)
Liver	7 (5.15%)
Brain	1 (0.74%)
T stage (n=136)	
T1b	3 (2.21%)
T1c	27 (19.85%)
T2	84 (61.76%)
T3	22 (16.18%)

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile-75^{th} percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables (1). Patients may have multiple metastases.
LN: Lymph node, SUV_{max}: Maximum standardized uptake value

Discussion

Poor prognosis and treatment challenges are typical for TNBC; there are few assessment tools that can contribute to patient management (4). Our analysis of SUV_{max} values obtained from staging F-18 FDG PET/CT images aimed to identify potential relationships with metastases (axillary LN or distant) and Ki-67 proliferation index. Our results showed that the size of the main tumor was positively correlated with the size of the metastatic LNs and LN SUV_{max} values. However, neither the axillary LN metastasis status nor the Ki-67 proliferation index was associated with the SUV_{max} value of the primary tumor.

In the present study, SUV_{max} and the largest diameter values of the primary tumor were found to be similar in patients with and without axillary LN metastasis. These results add to the available literature concerning different breast cancer subtypes, which have mostly reported the lack of relationships between the SUV_{max} of the primary lesion and axillary LN metastasis (9,14,20). In contrast, a study by Jung et al. (21) including 428 patients with all breast cancer subtypes, found significantly higher SUV_{max} values for primary tumors in patients with axillary LN metastasis compared to those without (4.93±3.32 vs. 3.22±2.78). Similarly, in a study of 671 patients with invasive breast cancer, higher preoperative primary tumor SUV_{max} values were detected in patients with axillary LN metastasis. However, when the same patients were stratified by molecular subtypes, TNBC patients with and without axillary LN metastasis were found to

Table 2. Summary of age and tumor characteristics with regard to axillary LN metastasis

	Axillary LN metastasis		
	No (n=41)	**Yes (n=95)**	**p**
Age	50.88±13.31	51.65±13.13	0.754†
Side			
Right	14 (34.15%)	39 (41.05%)	0.571§
Left	27 (65.85%)	56 (58.95%)	
Ki-67 (%)	75 (50-80)	62.5 (50-80)	0.086‡
Tumor largest diameter, cm	2.75 (2.0-4.0)	3.2 (2.3-4.5)	0.104‡
Tumor SUV_{max}	16.4 (8.6-22.7)	16.6 (9.8-23.1)	0.744‡
T stage			
T1b	1 (2.44%)	2 (2.11%)	0.182¶
T1c	11 (26.83%)	16 (16.84%)	
T2	26 (63.41%)	58 (61.05%)	
T3	3 (7.32%)	19 (20.00%)	

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile-75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. †: Student's t-test, ‡: Mann-Whitney U test, §: Chi-square test, ¶: Fisher-Freeman-Halton test, LN: Lymph node

Table 3. Summary of age and tumor characteristics with regard to distant metastasis

	Distant metastasis		
	No (n=112)	**Yes (n=24)**	**p**
Age	50.73±12.79	54.63±14.51	0.189†
Side			
Right	43 (38.39%)	10 (41.67%)	0.946§
Left	69 (61.61%)	14 (58.33%)	
Ki-67 (%)	70 (50-80)	70 (45-80)	0.611‡
Tumor largest diameter, cm	3.00 (2.26-4.20)	3.38 (1.97-5.84)	0.489‡
Tumor SUV_{max}	16.67 (9.35-22.80)	15.88 (8.30-30.83)	0.654‡
Axillary LN metastasis	76 (67.86%)	19 (79.17%)	0.395§
Axillary LN largest diameter, cm	1.32 (0.00-2.20)	1.81 (1.05-2.62)	0.092‡
Axillary LN SUV_{max}	4.85 (0.00-11.50)	6.15 (2.95-9.45)	0.598‡
T stage			
T1b	3 (2.68%)	0 (0.00%)	**0.026¶**
T1c	19 (16.96%)	8 (33.33%)	
T2	75 (66.96%)	9 (37.50%)*	
T3	15 (13.39%)	7 (29.17%)	

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile-75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. †: Student's t-test, ‡: Mann-Whitney U test, §: Chi-square test, ¶ Fisher-Freeman-Halton test, * Significantly different category, LN: Lymph node, SUV_{max}: Maximum standardized uptake value

Table 4. Correlations between Ki-67, diameters and SUV_{max} levels

		Tumor largest diameter, cm	Tumor SUV_{max}	Axillary LN largest diameter, cm	Axillary LN SUV_{max}
Ki-67 (%)	r	0.078	0.108	-0.139	-0.070
	p	0.390	0.238	0.126	0.442
Tumor largest diameter, cm	r		0.397	0.271	0.141
	p		<0.001	0.001	0.101
Tumor SUV_{max}	r			0.081	0.159
	p			0.350	0.064
Axillary LN largest diameter, cm	r				0.783
	p				<0.001

r: Spearman correlation coefficient, LN: Lymph node, SUV_{max}: Maximum standardized uptake value

have similar SUV_{max} values, consistent with our findings (22).

The lack of correlation between the high metabolic activity of primary tumors and axillary LN metastasis, in TNBC, a highly aggressive malignancy, remains unclear. However, unlike other subtypes, TNBC is suggested to be more prone to hematogenous spread rather than lymphatic spread (22,23). The lack of correlations between tumor SUV_{max} and axillary LN diameter or SUV_{max} values in our study provides indirect support for the literature data. Nonetheless, our correlation analyses revealed a positive relationship between largest tumor diameter, axillary LNs, and LN SUV_{max} values. This finding aligns with numerous studies in the literature, which have demonstrated that tumor size and SUV_{max} values increase in parallel in multiple subtypes of breast cancer (9,14-16,24). In a study by Arslan et al. (16), a similar positive correlation was attributed to the rapid growth of more aggressive tumors. Considering the aggressive nature of TNBC, our results provide additional evidence concerning the direct impacts on SUV_{max} and tumor growth.

The Ki-67 proliferation index is a commonly used prognostic factor in luminal breast cancer subtypes, where patients are classified into luminal A and B subgroups based on Ki-67 levels (25). However, no specific classification based on Ki-67 expression exists

for TNBC, and its prognostic role in this subtype remains inconclusive (26). A meta-analysis of 39 studies involving 7,716 TNBC patients reported that those with Ki-67 levels ≥40% had significantly higher recurrence and mortality risks compared to those with Ki-67 levels of <40% (7). That being said, a definitive prognostic cut-off for Ki-67 in TNBC has not been established. Notably, our patient population had exceedingly high Ki-67 values (70%, range: 50-80%), and therefore, which might have prevented the detection of significant variations in the evaluation of patients based on axillary LN metastasis. Despite the limited literature data in this respect, there exist several studies which have explored these relationships in patients with TNBC. For instance, similar to our results, Groheux et al. (27) found no correlations between the SUV_{max} of the primary lesion and Ki-67 levels in their study of 55 TNBC patients. There are studies in the literature reporting mild-to-moderate relationships in TNBC (9,17). Particularly notable is the study by Koo et al. (9), which described significantly higher SUV_{max} values in patients with ">20%" Ki-67 values compared to those with lower values. Again, the lack of association between these factors in the present study (especially FDG up-take) might be explained by the overwhelmingly elevated Ki-67 results throughout the study group. As mentioned before, one of the primary issues with Ki-67 assessment is the lack of standardization and significant interobserver variability. Factors such as human error, variations in the selection of tumor regions for evaluation, and the specific antibody used for detection can impact Ki-67 assessments (9).

Expanding upon the scope of studies on this topic, we also analyzed and compared patients with distant metastasis. The only significant difference between patients with and without distant metastasis was found to be T stage, which is an anticipated result. All other parameters, including Ki-67, tumor/LN SUV_{max}, and other tumor properties, were similar. Our findings in this context, which were obtained from a substantial group of patients, add new data to available literature by showing that these parameters are unassociated with distant metastasis. To our knowledge, there are no studies that have explored these parameters in the context of distant metastasis.

It is important to note that SUV_{max} reflects only the highest F-18 FDG uptake in the region of interest and does not represent the metabolic activity of the entire tumor. Glucose metabolism parameters, such as metabolic tumor volume and total lesion glycolysis, may have greater utility than other measurements in identifying malignancy or tumor characteristics (28). The primary limitation of our study, is the measurement of only SUV_{max} values for primary lesions and axillary LNs in F-18 FDG PET/CT, without considering additional parameters. Furthermore, the single-center, retrospective design, and the lack of significant differences regarding the majority of data are other limitations of the present study. Nonetheless, this study has examined patients with TNBC from various aspects, providing either provide additional evidence or new data for this field.

Conclusion

In TNBC patients, who have a worse prognosis and clinical course compared to other breast cancer subtypes, no relationship was found between the SUV_{max} value of the primary tumor obtained from staging F-18 FDG PET/CT and axillary LN metastasis or the Ki-67 proliferation index. Our data expand evidence in this regard and provide new data for distant metastasis, which also appears to be unassociated with the examined parameters.

Ethics

Ethics Committee Approval: This study received approval from the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (decision no: E-96317027-514.10-248478655, date: 10.07.2024). All diagnostic and therapeutic procedures were conducted in accordance with national guidelines and the Declaration of Helsinki.

Informed Consent: All patients provided informed consent for the procedures.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.V.T., E.A., G.U., Concept: Ö.V.T., E.A., Design: Ö.V.T., Data Collection or Processing: Ö.V.T., E.A., G.U., Analysis or Interpretation: Ö.V.T., Literature Search: Ö.V.T., Writing: Ö.V.T., G.U.

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ORIGINAL RESEARCH

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Effect of Vitamin D Deficiency on Fatigue in Systemic Sclerosis: A Cross-sectional Study

Sistemik Sklerozda D Vitamini Eksikliğinin Yorgunluk Üzerindeki Etkisi: Kesitsel Bir Çalışma

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Abstract

Objective: The purpose of this study was to explore the relationship between vitamin D deficiency (VDD) and fatigue severity, as well as its relationship with sleep quality, in subjects with systemic sclerosis (SSc).

Method: Our cross-sectional research included 98 subjects who were diagnosed with SSc according to EULAR/ACR 2013 classification criteria. Demographic, clinical, and laboratory data, including vitamin D (VitD) levels, were collected. Sleep quality was investigated with the Pittsburgh sleep quality index (PSQI) and fatigue severity with the multidimensional assessment of fatigue (MAF) scale.

Results: Subjects with VDD exhibited significantly poorer sleep quality as indicated by PSQI scores (12 vs. 8; p<0.001) and higher MAF scores (34.5 vs. 22.4; p<0.001). Multivariate analysis identified MAF score [odds ratio (OR): 1.204, 95% confidence interval (CI): 1.116-1.298, p<0.001] and disease symptom duration (OR: 1.009, 95% CI: 1.002-1.016, p=0.001) as independent predictors of VDD. ROC analysis demonstrated that an MAF score ≤27.7 and PSQI score ≤10.5 were optimal cut-off values for predicting VDD. Significant negative correlations were observed between VitD levels and MAF (r=-0.610, p<0.01) and PSQI (r=-0.346, p<0.01).

Conclusion: VDD is significantly associated with increased fatigue and poorer sleep quality in subjects with SSc. These signs indicate that addressing VDD through routine screening and supplementation may alleviate fatigue, enhance sleep quality, and raise the quality of life in SSc subjects.

Keywords: Multidimensional fatigue assessment (MAF) scale, Pittsburgh sleep quality index (PSQI), systemic sclerosis, vitamin D

Öz

Amaç: Bu çalışmanın amacı, sistemik skleroz (SSc) hastalarında D vitamini eksikliği ile yorgunluk şiddeti arasındaki ilişkinin yanı sıra uyku kalitesi ile ilişkisini değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya EULAR/ACR 2013 sınıflandırma kriterlerine göre SSc tanısı konan 98 hasta dahil edilmiştir. D vitamini düzeyleri de dahil olmak üzere demografik, klinik ve laboratuvar verileri toplanmıştır. Yorgunluk şiddeti çok boyutlu yorgunluk değerlendirme (MAF) ölçeği kullanılarak, uyku kalitesi ise Pittsburgh uyku kalitesi indeksi (PSQI) kullanılarak değerlendirilmiştir.

Bulgular: D vitamini eksikliği olan hastalar anlamlı derecede daha yüksek MAF skorları (34,5'e karşı 22,4; p<0,001) ve PSQI skorlarına göre daha düşük uyku kalitesi (12'ye karşı 8; p<0,001) sergilemiştir. Çok değişkenli analiz, MAF skorunu [olasılık oranı (OR): 1,204, %95 güven aralığı (GA): 1,116-1,298, p<0,001] ve hastalık semptom süresini (OR: 1,009, %95 GA: 1,002-1,016, p=0,001) D vitamini eksikliğinin bağımsız belirleyicileri olarak tanımlamıştır. ROC analizi, MAF skoru ≤27,7 ve PSQI skoru ≤10,5'in D vitamini eksikliğini öngörmek için en uygun kesme değerleri olduğunu göstermiştir. D vitamini düzeyleri ile hem MAF (r=-0,610, p<0,01) hem de PSQI (r=-0,346, p<0,01) arasında anlamlı bir negatif korelasyon tespit edilmiştir.

Sonuç: D vitamini eksikliği, SSc'li hastalarda artmış yorgunluk ve daha kötü uyku kalitesi ile önemli ölçüde ilişkilidir. Bu bulgular, rutin tarama ve takviye yoluyla D vitamini eksikliğinin giderilmesinin SSc hastalarında yorgunluğu hafifletebileceğini, uyku kalitesini iyileştirebileceğini ve yaşam kalitesini artırabileceğini düşündürmektedir.

Anahtar kelimeler: Çok boyutlu yorgunluk değerlendirme (MAF) ölçeği, D vitamini, Pittsburgh uyku kalitesi indeksi (PSQI), sistemik skleroz

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Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease involving immune dysregulation and vascular damage that is characterised by diffuse fibrosis of the skin and internal organs such as the lung and gastrointestinal tract (1). In SSc, systemic involvement and various clinical problems such as Raynaud's phenomenon, ischaemic digital ulcers, the thickening of inelastic skin due to tissue degradation, and joint contractures are associated. Fatigue is a common and debilitating symptom among various clinical manifestations of SSc, which significantly affects subjects' quality of life (2). Fatigue, which has multiple dimensions including social, physiological, and psychological, is a common presenting complaint in patients with various rheumatological conditions, including Sjögren's disease, ankylosing spondylitis, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (3,4). In spite of its prevalence, the underlying mechanisms contributing to fatigue in SSc are poorly understood and effective management strategies are limited.

Vitamin D (VitD), with well-documented roles in calcium homeostasis and bone metabolism, has immunomodulatory and anti-inflammatory activity, playing an important role in both innate and adaptive immunity. Several studies have described vitamin D deficiency (VDD) as a common comorbidity in autoimmune diseases, including SSc (5). The pathophysiological overlap between VDD and features of SSc, such as immune activation, chronic inflammation, and musculoskeletal involvement, raises the possibility that suboptimal VitD levels may contribute to fatigue in this patient population (6).

More recent evidence from other rheumatic diseases, such as RA and SLE, suggests a possible association between low VitD levels and increased fatigue (7). Nevertheless, studies specifically examining this association in SSc are rare. In view of the unique pathophysiology of SSc, characterised by vascular damage and fibrotic processes, it is essential to understand the role of VitD in fatigue in the context of this disorder.

The aim of this study was to evaluate the relationship between VitD concentrations and fatigue in subjects with systemic sclerosis. Through investigating this interaction, we aim to clarify an overlooked contribution of VDD to fatigue in SSc.

Materials and Methods

Study Design and Participants

We included in this cross-sectional study all consecutive subjects who were diagnosed with SSc according to EULAR/ACR 2013 classification criteria, and presented to our outpatient clinic between October 2024 and December 2024, who gave written informed consent after being fully informed about the aims of the study and evaluation methods (8). Patients with known malignancy, liver failure, chronic kidney disorder or other autoimmune diseases, endocrine or metabolic disorders affecting VitD metabolism; chronic infections; or comorbid conditions that may cause fatigue, such as recent surgery, trauma, or haemorrhagic events in the last three months, were excluded. We also excluded current VitD supplementation, pregnancy and breastfeeding, severe psychiatric or musculoskeletal disorders, and significant sunlight or ultraviole exposure in the past three months to minimise confounding factors. Additionally, we excluded patients who had a diagnosis of fibromyalgia according to the 1990 American College of Rheumatology fibromyalgia criteria from our study (9).

Ethics committee approval was obtained from the Research Ethics Committee of Marmara University Faculty of Medicine (approval no: 09.2024.1166, dated 18/10/2024). The study was conducted in accordance with the Declaration of Helsinki.

Data Collection

A combination of clinical assessments and patient-reported outcome measures was used for data elicitation. Demographic data (e.g. age, gender, disease duration) and clinical characteristics, including SSc-specific parameters (e.g., organ involvement, modified Rodnan skin score, serological markers), were collected from subjects' medical records and verified with a clinical examination. Additionally, acute phase values [such as erythrocyte sedimentation rate (ESR) (mm/h) and C-reactive protein (mg/L)] and VitD levels (ng/mL) were recorded from regular controls. 25-hydroxyvitamin D (25[OH]D) was used in measuring VitD levels. Since 25(OH)D <20 ng/mL is defined as VDD, and 25(OH)D 21-29 ng/mL is defined as insufficient, we included those with 25(OH)D <30 ng/mL in the VDD group and those with 25(OH)D ≥30 ng/mL in the non-VDD group (10).

Clinical Measurement

Active and inactive disease states were evaluated in detail using the indices of the European Scleroderma Study Group (EScSG) for disease activity. The calculation is made with a method consisting of ten elements, where each element is evaluated on a 10-point scale. Upon initial assessment, the index reflects activity levels in various organs or systems by assigning specific weights to each criterion. Subjects with a score of 2.5 or higher, based on the activity scoring and EScSG assessments conducted in accordance with the study's measurement protocol, were classified as having active disease (11).

The 17 regions of the modified Rodnan Skin Score (mRSS) include the feet, lower legs, upper arms, fingers, forearms, chest, hands, face, abdomen. All skin areas are palpated by squeezing or rolling between the thumbnail and pointer finger, respectively, but not excessively. The maximum mRSS score is 51, with 0 corresponding to normal thickness, 1 mild, 2 moderate, and 3 severe thickening, and the individual score is obtained by summing the scores obtained at 17 points (12).

Overall quality of life, general health, role-physical, vitality, social function, physical function, mental health, role-emotional, and bodily pain were assessed using the Turkish version of the 36-item short form (SF-36) covering these eight domains. The total score ranges from 0 to 100. Higher scores refer to a slightly better quality of life (13,14).

HADS is a self-report scale consisting of 14 questions measuring anxiety and depression. All questions are marked on a scale of 0 (no impairment) to 3 (severe impairment), with a mark of 0-7 considered normal, 8-10 considered borderline, and 11 and greater considered considered abnormal (15).

Patients' sleep quality was examined in the previous month with the Pittsburgh sleep quality index (PSQI), a 19-item questionnaire grouped into seven component scores, each with equal weight. When we look at the seven components of the PSQI: Sleep disorders, sleep medication use, daytime activity disorder and quality, onset, delay, duration, and efficiency of sleep, we can better understand overall sleep health. A global PSQI score (0-21) is calculated by summing the seven components, with higher scores indicating worse sleep quality and more sleep disturbances (16). The validity and reliability of the PSQI were confirmed in a study conducted in 1996 (17).

Multidimensional Fatigue Assessment (MAF) Scale

We evaluated fatigue utilizing the MAF scale, assessing various dimensions of fatigue, including its severity, frequency, timing, impact on daily activities, and overall quality of life. The MAF scale is a validated instrument that provides a comprehensive measurement of fatigue. It consists of 16 items covering four primary domains: Fatigue severity, timing, interference with activities, and global impact. The scores from each domain are summed to create a global fatigue index. The total score ranges from 1 to 50, with higher scores indicating greater fatigue. The MAF scale has demonstrated reliability and validity in assessing fatigue across various patient populations, including those with autoimmune diseases (18).

Statistical Analysis

Analysis of the data was performed using SPSS 26.0 statistical software (IBM, Chicago, USA). We assessed the normality of the data sets using the Shapiro-Wilk test. While categorical variables are presented as numbers and percentages, quantitative variables are summarised as mean ± standard deviation for normally distributed data, and for non-normally distributed data as median [25% (Q1) - 75% (Q3) quartiles]. For normally distributed parameters, independent t-tests were used to compare the two groups. Group comparisons were made using Mann-Whitney U tests for parameters not showing normal distribution. Categorical variables were analysed either using Fisher's exact test or the chi-square test. Spearman correlation tests were performed for parameters not showing normal distribution, and Pearson correlation tests were performed for parameters showing normal distribution to examine correlations between variables. Variables predicting VDD were primarily evaluated using binary logistic regression analysis, and those with significant p-values then included in multivariate analysis. The 95% confidence interval (CI) and odds ratio (OR) were estimated. Receiver operating characteristic (ROC) curve analyses were used to evaluate disease-related clinical variables for predicting VDD with the best specificity and sensitivity. The effect size (Cohen's d), power value (1-ß), and total sample size of MAF scale comparison between subjects with and without VDD were calculated using G*Power software (V3.1.9.2). The effect size, power value and total sample size were 1.07, 0.95 and 40, respectively. A statistically significant p-value of <0.05 was considered.

Results

A total of 98 subjects, 80.6% of whom were female, were evaluated. The average age was 49.99±13.15 years. The median EScSG activity index, MAF scale, and PSQI of all subjects were 2.0, 27.9, and 11, respectively. Baseline characteristics, clinical presentations, outcome measures, and treatment status of all subjects were presented in Table 1. The variables found to be significantly increased in the VDD group were disease symptom duration, number of digital ulcers, proximal muscle weakness, MAF scale (34.5 vs. 22.4), and PSQI (12 vs. 8). There was no difference between the groups in the drug treatments used. Autoantibodies and laboratory parameters are given in Table 2. ESR was significantly higher in the VDD group (33 vs. 16). In multivariate analysis, the independent predictors of VDD were MAF scale (OR: 1.204, 95% CI 1.116-1.298; p<0.001) and disease symptom duration (OR: 1.009, 95% CI 1.002-1.016; p=0.001). The results of the regression analysis are given in Table 3. The ROC analysis is given in Figure 1. The best cut-off value for predicting VDD using the MAF scale and PSQI obtained by the ROC curve analysis was ≤27.7 (sensitivity: 78.7%, specificity: 74.5%) and ≤10.5 (sensitivity: 70.2%, specificity: 66.7%), respectively. The correlation analysis between VitD level and admission characteristics, and SF-36 parameters is given in Table 4. There was a significant negative correlation between VitD level and the MAF scale (r=-0.610, p<0.01) and the PSQI (r=-0.346, p<0.01).

Table 1. Baseline characteristics, clinical manifestations and outcome measures of patients with systemic sclerosis according to the vitamin D deficiency

	All patients n=98	Non-vitamin D deficiency n=51	Vitamin D deficiency n=47	p-value
Age (years; mean SD)	49.99 SD 13.15	50.37 SD 12.29	49.57 SD 14.16	0.766
Female, gender, n (%)	79 (80.6%)	42 (82.4%)	37 (78.8%)	0.650
Disease symptoms duration (month)	**82 (38-168)**	**50 (31-125)**	**90 (50-170)**	**0.015**
EScSG activity indexes	2.0 (1.0-4.0)	1.5 (1.0-2.5)	2.0 (1.5-4.0)	0.160
Limited cutaneous SSc, n (%)	48 (49.0%)	27 (52.9%)	21 (44.7%)	0.414
Diffuse cutaneous SSc, n (%)	45 (45.9%)	22 (43.1%)	23 (48.9%)	0.565
The overlap of systemic sclerosis, n (%)	5 (5.1%)	2 (3.9%)	3 (6.4%)	0.669
Clinical manifestations				
Raynaud's phenomenon, n (%)	90 (91.8%)	46 (90.2%)	44 (93.6%)	0.717
Digital ulcers, n (%)	**38 (38.8%)**	**14 (27.5%)**	**24 (51.1%)**	**0.016**
Telangiectasias, n (%)	87 (88.8%)	44 (86.3%)	43 (91.5%)	0.411
Scleredema, n (%)	31 (31.6%)	17 (33.3%)	14 (29.8%)	0.706
Calcinosis cutis, n (%)	23 (23.5%)	10 (19.6%)	13 (27.7%)	0.347
Synovitis, n (%)	36 (36.7%)	17 (33.3%)	19 (40.4%)	0.467
Flexion contractures, n (%)	14 (14.3%)	5 (9.8%)	9 (19.1%)	0.185
Tendon friction rubs, n (%)	8 (8.2%)	3 (5.9%)	5 (10.6%)	0.475
Proximal muscle weakness, n (%)	**9 (9.2%)**	**1 (2.0%)**	**8 (17.0%)**	**0.013**
Upper GI symptoms, n (%)	68 (69.4%)	32 (62.7%)	36 (76.6%)	0.135
Lower GI symptoms, n (%)	34 (34.7%)	16 (31.4%)	18 (38.3%)	0.472
Pulmonary hypertension, n (%)	22 (22.4%)	8 (15.7%)	14 (29.8%)	0.093
Interstitial lung disease, n (%)	39 (39.8%)	21 (41.2%)	18 (38.3%)	0.771
Arrhythmia, n (%)	7 (7.1%)	2 (3.9%)	5 (10.6%)	0.255
Outcome measures				
Digital ulcers count	**0 (0-1)**	**0 (0-0)**	**0 (0-5)**	**0.001**
Pitting scars count	0 (0-3)	0 (0-3)	1 (0-3)	0.133
Modified Rodnan skin score	16 (8-26)	15 (9-26)	18 (8-30)	0.345
HAQ-DI	1.95 (0.85-7.00)	1.5 (0.70-7.0)	1.95 (1.40-9.0)	0.193

Table 1. Continued

	All patients n=98	Non-vitamin D deficiency n=51	Vitamin D deficiency n=47	p-value
MAF scale (mean SD)	**27.9 (19.3-35.1)**	**22.4 (15.5-28.0)**	**34.5 (28.1-38.6)**	**<0.001**
Pittsburgh sleep quality index	**11 (7-14)**	**8 (5-13)**	**12 (10-15)**	**0.001**
36-item short-form health survey (SF-36)				
Physical functioning	**50 (25-70)**	**55 (35-80)**	**35 (20-65)**	**0.015**
Role functioning/physical	**25 (0-50)**	**25 (0-75)**	**0 (0-50)**	**0.034**
Role functioning/emotional	33.3 (0-66.7)	33.3 (0-100)	0 (0-66.7)	0.073
Energy/fatigue	**50 (25-60)**	**55 (40-65)**	**45 (20-55)**	**0.010**
Emotional well-being	**52 (32-64)**	**56 (40-68)**	**48 (24-52)**	**0.010**
Social functioning	50 (25-62.5)	50 (25-75)	50 (25-62.5)	0.108
Pain	**45 (22.5-57.5)**	**45 (22.5-67.5)**	**45 (22.5-45)**	**0.036**
General health	36.3 SD 20.0	39.8 SD 19.6	32.5 SD 19.9	0.073
Health change	**50 (25–50)**	**50 (25 – 50)**	**50 (25 – 50)**	**0.037**

Values are presented as mean ± standard deviation (SD), number (%), or median (interquartile range). EScSG: The European systemic sclerosis study group, SSc: Systemic sclerosis, GI: Gastrointestinal, HAQ-DI: Health assessment questionnaire-disability index, MAF: Multidimensional assessment of fatigue

Table 2. Laboratory findings of patients with systemic sclerosis according to the vitamin D deficiency

	All patients n=98	Non-vitamin D deficiency n=51	Vitamin D deficiency n=47	p-value
Serum 25-hydroxyvitamin D levels, mg/L	30.9 (19-38)	37 (34-45)	19 (15-23)	<0.001
ESR, mm/h	23 (12-37)	16 (7-30)	33 (21-40)	<0.001
CRP, mg/L	2.96 (1.46-5.70)	3.10 (1.36-4.81)	2.96 (1.60-7.30)	0.408

Values are presented as mean ± standard deviation or median (interquartile range). ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3. The independent effects of some possible predictors in relation to vitamin D deficiency according to univariate/multivariate analysis

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	0.995 (0.966-1.026)	0.763		
EScSG activity indexes	1.270 (1.006-1.603)	0.044		
Disease symptoms duration (month)	1.006 (1.001-1.010)	0.016	1.009 (1.002-1.016)	0.001
Female, gender	1.261 (0.463-3.439)	0.650		
MAF scale	1.187 (1.106-1.274)	<0.001	1.204 (1.116-1.298)	<0.001
Pittsburgh sleep quality index	1.166 (1.060-1.281)	0.002		
Digital ulcers	2.758 (1.191-6.387)	0.018		
HAQ-DI	1.023 (0.978-1.070)	0.316		
36-item short-form health survey (SF-36)				
Physical functioning	0.982 (0.967-0.997)	0.022		
Role functioning/physical	0.987 (0.975-0.999)	0.030		
Role functioning/emotional	0.991 (0.982-1.001)	0.086		
Energy/fatigue	0.977 (0.958-0.997)	0.023		
Emotional well-being	0.973 (0.952-0.995)	0.016		
Social functioning	0.990 (0.976-1.004)	0.168		

Table 3. Continued

	Univariate	Multivariate
Pain	0.981 (0.963-1.000)	0.050
General health	0.981 (0.961-1.002)	0.075
Health change	0.980 (0.963-0.998)	0.025

OR: Odds ratio, CI: Confidence interval, EScSG: The European systemic sclerosis study group, MAF: Multidimensional assessment of fatigue, HAQ-DI: Health assessment questionnaire-disability index

Table 4. Correlation of clinical variables, MAF scale, Pittsburgh sleep quality index, 36-item short-form health survey and laboratory finding with serum 25-hydroxyvitamin D levels

	r/rho	
Age (years)	0.222*	r
EScSG activity indexes	-0.123	rho
Pittsburgh sleep quality index	-0.346**	rho
Modified Rodnan skin score	-0.108	rho
HAQ-DI	-0.057	rho
MAF scale	-0.610**	rho
ESR, mm/h	-0.312**	rho
36-item short-form health survey (SF-36)		
Physical functioning	0.238*	rho
Role functioning/physical	0.229*	rho
Role functioning/emotional	0.169	rho
Energy/fatigue	0.233*	rho
Emotional well-being	0.199*	rho
Social functioning	0.172	rho
Pain	0.182	rho
General health	0.086	r
Health change	0.241*	rho

MAF: Multidimensional assessment of fatigue, EScSG: The European systemic sclerosis study group, HAQ-DI: Health assessment questionnaire-disability index, ESR: Erythrocyte sedimentation rate, *: p<0.05, **: p<0.01, r: Pearson corelation /rho Spearman's corelation

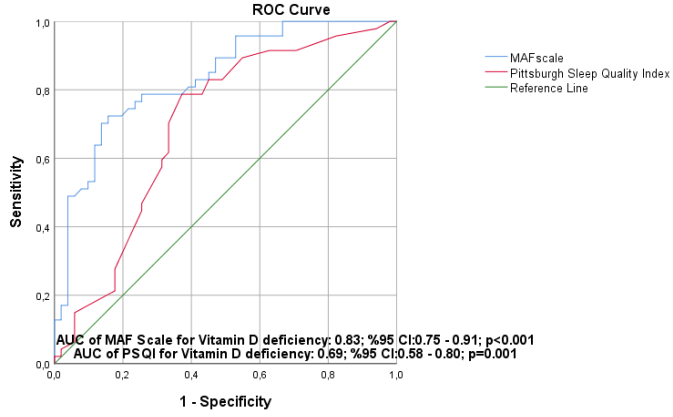

Figure 1. In ROC analysis, area under the ROC curve value of MAF scale and PSQI for vitamin D deficiency

ROC: Receiver operating characteristic, MAF: Multidimensional assessment of fatigue, PSQI: Pittsburgh sleep quality index, AUC: Area under the curve, CI: Confidence interval

Discussion

The present study demonstrates a significant association between VDD and fatigue severity as measured by the MAF scale in subjects with SSc. Subjects with VDD reported higher fatigue scores and worse sleep quality compared to those with adequate VitdD levels, emphasizing the potential role of VitD in the pathophysiology of fatigue in this population. Furthermore, MAF score and disease symptom duration were detected to be independent determinants of VDD among these subjects.

Fatigue is a widespread and debilitating sign in subjects with rheumatic diseases such as RA, SLE, SSc, and fibromyalgia (19). It significantly affects quality of life and often persists even when the underlying disease is controlled. The MAF is a revision of the original Piper fatigue scale, which was developed in the field of oncology but revised specifically for rheumatoid arthritis (20,21). The MAF scale has been used since then to assess fatigue in various rheumatological patient populations, such as SSc, ankylosing spondylitis, and chronic musculoskeletal physical therapy subjects, in many languages (22-24). In our study, subjects with VDD had higher MAF scale scores, indicating that these subjects experienced more advanced levels of fatigue. Yadav et al. (25) demonstrated that VDD is the strongest predictor of fatigue in subjects with rheumatoid arthritis. Another study has shown that VitD treatment helps alleviate fatigue even in healthy individuals (26). When the data are evaluated holistically, it becomes apparent that the results of our study are compatible with the results of other studies. Although the exact mechanism between VitD and fatigue is not yet fully understood, potential pathophysiological factors include oxidative stress, inflammation, cytokines, and neurotransmitters, as well as ion channel abnormalities (27).

In addition, a significant relationship was found between VDD and the PSQI. Higher PSQI scores were observed in subjects with VDD, which indicates poorer sleep quality.

VitD has significant effects on sleep metabolism. For example, the activation or degradation of enzymes in brain regions involved in sleep regulation, the metabolism of melatonin, and the influence on non-specific pain disorders are some of the underlying mechanisms by which VitD affects sleep (28). The positive effect of VitD on sleep has also been demonstrated that subjects receiving VitD supplementation have better sleep quality compared to the control group (29). These findings support the results of our study. It suggests that correcting VDD may improve both sleep and fatigue in SSc subjects.

Another finding of our study was that the ESR was significantly increased in the group with VDD. This can be explained by an inverse relationship between VitD and the inflammatory state (30). In addition, VitD regulates the expression of genes involved in immune reactions and encoding cytokines, promoting the synthesis of anti-inflammatory cytokines while regulating the production of pro-inflammatory cytokines. Both of these proven effects lead to a reduction in inflammation (31). MAF and symptom duration were identified as independent predictors of VDD. The independent relationship between the duration of symptoms, MAF, and VitD, may be explained by the contribution of VDD to the pro-inflammatory process. Besides, prolonged disease duration, limited mobility, reduced exposure to sunlight, or altered metabolism may also worsen the deficiency and exacerbate fatigue. As a result, the prolongation of the disease symptom duration and the more pronounced physical fatigue, which ultimately corresponds to higher MAF scale scores, may occur. The independent relationships identified between symptom duration, VitD levels, and fatigue severity suggest that VDD could act as both a consequence and a driver of disease burden in SSc.

Study Limitations

Limitations of this study include its cross-sectional design, which prevents drawing conclusions about causation and limits the ability to infer temporal relationships between VitD levels and fatigue. Additionally, small sample sizes may limit the generalisability of findings and reduce statistical power. The reliance on a single measurement of VitD levels and fatigue may not fully capture their dynamic relationship over time. Furthermore, potential confounding factors such as dietary intake of vitamin D, seasonal variations, and unmeasured comorbidities may have influenced the results. Future studies should address these limitations through longitudinal designs with larger and more diverse cohorts. Longitudinal studies are warranted to confirm these findings and explore the long-term effects of VitD supplementation on fatigue and overall quality of life in SSc subjects.

Conclusion

In conclusion, this study highlights a significant association between VDD and increased fatigue and sleep disturbances in subjects with SSc. These findings underscore the potential role of VitD in the multifactorial pathophysiology of fatigue and its impact on sleep quality in SSc. Addressing VDD through routine screening and targeted supplementation could offer a feasible strategy to alleviate fatigue, improve sleep quality, and enhance overall quality of life in this challenging disease.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Research Ethics Committee of Marmara University Faculty of Medicine (approval no: 09.2024.1166, dated 18/10/2024). The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained.

Information: This work has been submitted to the EULAR 2025 Congress.

Footnotes

Authorship Contributions

Concept: N.Ö., M.T.D., Design: N.Ö., M.T.D., Data Collection or Processing: N.Ö., M.T.D., Analysis or Interpretation: N.Ö., M.T.D., Literature Search: N.Ö., Writing: N.Ö., M.T.D.

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ORIGINAL RESEARCH

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The Positive Effect of Sacubitril-Valsartan Treatment on Frontal QRS-T Angle in Patients with Heart Failure

Kalp Yetmezliği Olan Hastalarda Sakubitril-Valsartan Tedavisinin Frontal QRS-T Açısı Üzerine Olumlu Etkisi

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Abstract

Objective: Introducing angiotensin receptor neprilysin inhibitors (ARNI) to daily clinical practice is one of the most important advances in the treatment of heart failure (HF). ARNI is associated with reduced mortality and hospitalization in HF patients due to structural and electrical remodelling. In this study, we investigated the effect of sacubitril/valsartan on the frontal QRS-T angle (f-QRS/Ta), which reflects abnormal ventricular repolarization, in patients with HF with reduced ejection fraction (HFrEF).

Method: The difference of f-QRS/Ta obtained from surface electrocardiograms (ECG) in patients with HF and systolic disfunction (EF ≤40%) before and after initiating ARNI treatment was evaluated retrospectively. Demographic, clinic and ECG characteristics of patients collected from hospital data and compared at one year follow-up.

Results: A total of 45 patients were enrolled in this study of whom 15 were female (33.3%). The mean NYHA class of the study population was class 2, and the mean left ventricle EF was 30%. ARNI treatment significantly reduced the QRS duration and f-QRS/Ta compared to the baseline ECG parameters. The mean QRS duration decreased from 106.9±10.3 msto 105±9.8 ms at 12 months follow-up, while the baseline f-QRS/Ta of 72.3±12° reduced to 67.4±12.6° after treatment and respectively p-values 0.008 and<0.001 were detected.

Conclusion: Our study has shown that in HFrEF patients, sacubitril/valsartan treatment led to a significant decrease in QRS duration and f-QRS/Ta values.

Keywords: ARNI, frontal QRS/Ta, heart failure

Öz

Amaç: Anjiyotensin reseptör neprisilin inhibitörlerinin (ARNI) günlük klinik uygulamaya dahil edilmesi, kalp yetmezliği (KY) tedavisinde yapısal ve elektriksel yeniden şekillenme yoluyla mortaliteyi ve hastaneye yatışları azaltması nedeniyle en önemli gelişmelerden biridir. Bu çalışmada, sacubitril/valsartanın azalmış ejeksiyon fraksiyonlu KY (HFrEF) olan hastalarda anormal ventriküler repolarizasyonu yansıtan frontal QRS-T açısı (f-QRS/Ta) üzerindeki etkisi araştırıldı.

Yöntem: Azalmış ejeksiyon fraksiyonlu KY olan hastalarda yüzey elektrokardiyogramlarından (EKG) elde edilen f-QRS/Ta farkı, ARNI tedavisinin başlatılmasından önce ve sonra retrospektif olarak değerlendirildi. Demografik, klinik ve EKG özellikler hastane verilerinden toplandı ve bir yıllık takipte karşılaştırıldı.

Bulgular: Çalışmaya toplam 45 hasta dahil edildi ve bunların 15'i kadın (%33,3) idi. Çalışma popülasyonunun ortalama NYHA sınıfı 2, sol ventrikül ejeksiyon fraksiyonu (EF) ise %30'du. ARNI tedavisi, QRS süresi ve f-QRS/Ta değerlerinde başlangıç EKG parametrelere kıyasla anlamlı bir azalmaya neden oldu. Ortalama QRS süresi, başlangıçta 106,9±10,3 ms'den 12 aylık takipte 105±9,8 ms'ye düştü. Başlangıç f-QRS/Ta değeri ise 72,3±12° iken tedavi sonrası 67,4±12,6°'ye düştü ve sırasıyla p-değerleri 0,008 ve <0,001 olarak tespit edildi.

Sonuç: Çalışmamız, HFrEF hastalarında sacubitril/valsartan tedavisinin QRS süresi ve f-QRS/Ta değerlerinde anlamlı bir azalmaya yol açtığını göstermiştir.

Anahtar kelimeler: ARNI, kalp yetmezliği, frontal QRS/Ta

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Introduction

Heart failure (HF) is a complex clinical syndrome that affects more than 64 million people worldwide (1). Long-term mortality rate remains over 50% despite contemporary advancements in treatment. In recent years, one of the most significant developments in HF treatment has been the demonstration of the favorable effects of angiotensin receptor neprilysin inhibitors (ARNI) on mortality and hospitalization (1,2). Therefore, in the current HF treatment guidelines of the European Society of Cardiology, ARNI is recommended as a first line treatmentoption (3). Sacubitril/valsartan (Sac/Val) is thecurrent ARNI used in HF treatment which consists valsartan, an angiotensin receptor blocker, and sacubitril, a molecule that inhibits the enzyme neprilysin, responsible for the degradation of endogenous vasoactive peptides like natriuretic peptides and bradykinin. In the prospective comparison of ARNI with angiotensin-converting enzyme inhibitor to determine impact on global mortality and morbidity in HF trial (PARADIGM-HF) study, it was observed that Sac/Val significantly reduced all-cause mortality, HF-related hospitalizations and cardiovascular mortality rates compared to enalapril. These results highlight the superiority of Sac/Val over traditional ACE inhibitors in improving outcomes in HF patients (2). The positive effect of Sac/Val on HF is classically attributed to the blockade of the renin-angiotensin-aldosterone system (RAAS) and the inhibition of natriuretic peptide breakdown, resulting in a reduction of myocyte injury, inflammation and fibrosis (4).

Electrocardiographic (ECG) changes are quite commonly encountered in patients with HF. These changes include conduction abnormalities, T-wave abnormalities, prolongation of QRS duration and QT interval, pathological Q waves, atrial fibrillation, and changes in the QRS-T angle (5,6). There is a significant association between a wide QRS-T angle, which is one of the markers of abnormal ventricular repolarization, and HF. It has been shown that a wide QRS-T angle increases the risk of developing HF by approximately threefold (7). Additionally, there is a significant association between a wide QRS-T angle and mortality. A wider QRS-T angle has also been linked to an increased risk of mortality in patients, particularly in those with HF (7,8).

Beyond its neurohormonal properities, the Sac/Val combination has also been observed to have electrophysiological effects, such as reduction in heart rate, QRS duration, and QTc interval as demonstrated in various studies. These electrophysiological effects may contribute to the overall improvement in ventricular function in HF patients (9,10). In this study, the effect of Sac/Val treatment on thefrontal QRS-T angle (f-QRS/Ta) changeswhichare known to be related with unfavourable eventsin patients HF with reduced ejection fraction (HFrEF) at long term follow-up was investigated.

Materials and Methods

Study Population

This study was designed retrospectively to evaluate patients with HF and a left ventricular ejection fraction (LVEF) ≤40% who were treated with ARNI and admitted to our cardiology outpatient clinic between January 2021 and February 2022. Patients with HFrEF older than 18 years and in New York Heart Association (NYHA) functional class 1-3, who were receiving guideline-directed medical therapy, were included in the study. Patients with NYHA functional class 4, chronic renal failure (GFR<60 mL/min/1.73 m²), atrial fibrillation, permanent pacemaker, left or right bundle branch block, or end-stage oncology were excluded from the study. Additionally, those unable to tolerate ARNI treatment or with difficulties in interpreting ECG were also excluded. The study was conducted in accordance with the ethical rules stated in the Declaration of Helsinki and the study protocols were approved by the Memorial Ataşehir Hospital Ethics Committee (decision no: 2024/15 date: 16.01.2025). Informed consent for this study was waived as it was a retrospective analysis. Informed consent for this study was waived because it was a retrospective analysis.

Data Collection

The baseline characteristics and laboratory data of all patients were obtained through retrospective screening of the hospital information system. The 12-lead surface ECGs were taken in the supine position at a paper speed of 25 mm/s, and recordings were obtained from patient files and were independently evaluated by two different cardiologists blinded to patients' data. All ECG records were scanned into electronic format using Adobe Photoshop (Adobe Inc., San Jose, CA, USA) and magnified by 400% to reduce errors. The P wave duration, PR interval, QRS duration, and QT duration on the ECG were measured using a digital millisecond timer. QTc was obtained by correction of QT duration for heart rate using the Bazett's formula (11). The f-QRS/Ta was determined as the absolute difference between the frontal QRS and T-wave axes, which were automatically derived from the ECG machine [Schiller, Cardiovit AT-102 G2 Switzerland)] as demonstrated in

Figure 1. The f-QRS/Ta values greater than 180° were subtracted from 360°. LVEF obtained by modified Simpson method using a Philips EPIQ 7 device (Philips Healthcare, Andover, USA) and a 2.5 MHz probe.

Statistical Analysis

Categorical data were expressed as frequencies and percentages and analyzed with Pearson's chi-square test, while continuous data were presented as mean ± standard deviation and analyzed with the Student's t-test. The Kolmogorov-Smirnov test was employed for variables with normal distribution. NT-proBNP levels, New York Heart Association functional class, and ECG indices (heart rate, QRS complex, QTc interval, T wave angle, QRS angle, f-QRS/Ta) were recorded both before and after ARNI treatment. A p-value of less than 0.05 was considered statistically significant. Statistical analyses and calculations were carried out using SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 63 patients with HFrEF who presented to the cardiologyoutpatient clinic were initially considered for the study. Following the application of the exclusion criteria, 18 patients were excluded, and 45 patients wererecruited in thisstudy. 71.1% of the patients (n=32) had an ischemic etiology. The mean NYHA class of the study population wasclass 2 and the meanleftventricle ejection fraction was 30%. The maximum tolerable ARNI doses for the patients were as follows: 8 patients (17.8%) received 100 mg/day, 16 patients (35.6%) received 200 mg/day, and 21 patients (46.7%) received 400 mg/day. Baseline characteristics, clinical, laboratory and echocardiographic variables are listed in Table 1.

After 12 months of treatment with the maximum tolerable dose of ARNI, the ECG parameters were reassessed during the follow-up visit. Significant reduction was observed in the QRS duration and f-QRS/Ta compared to the ECG parameters obtained at the beginning of the treatment.

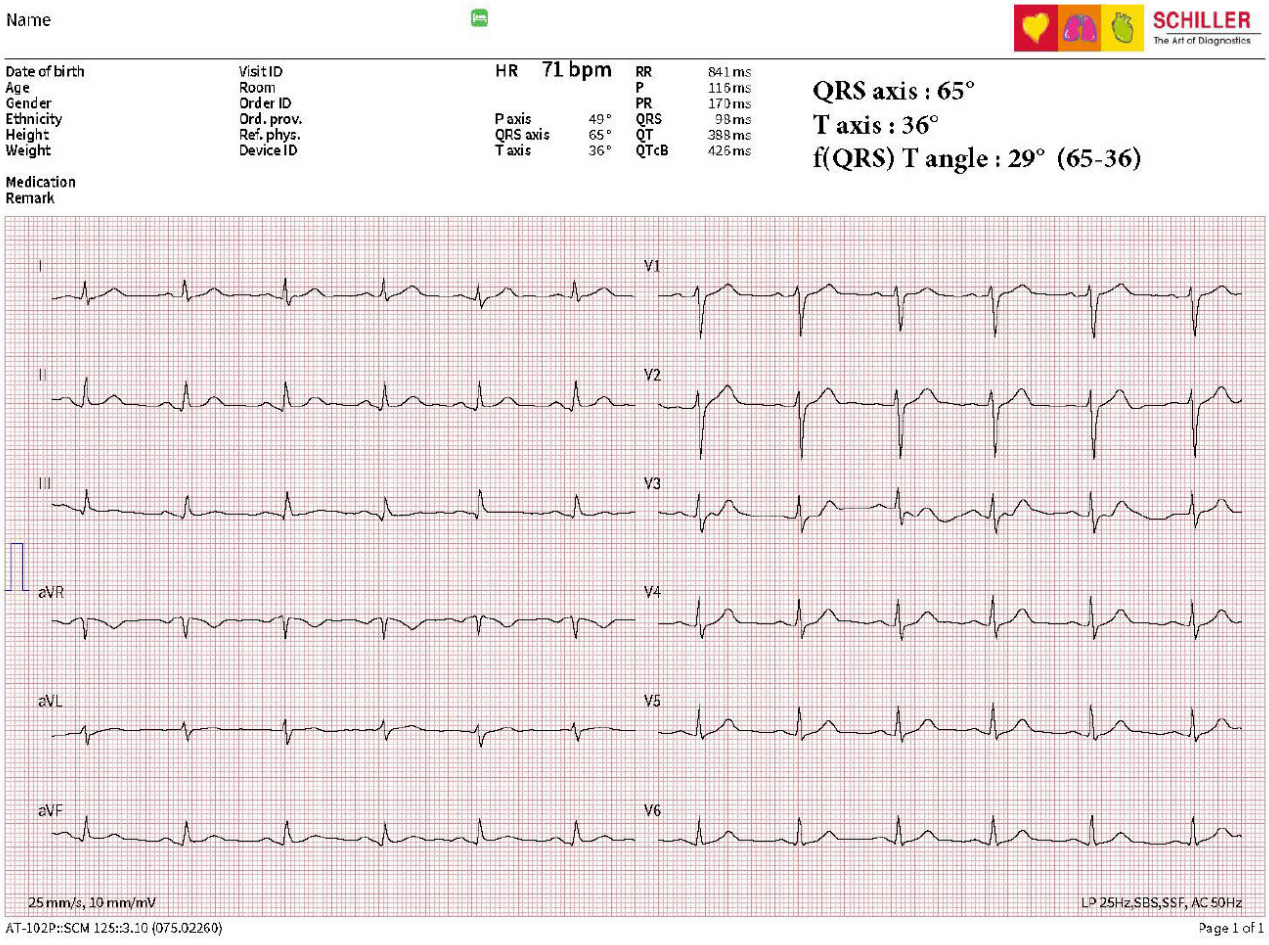

Figure 1. Example of f(QRS-T) angle calculation

The mean QRS duration decreased from 106.9±10.3 milliseconds to 105±9.8 milliseconds (p=0.008). Similarly, the baseline f-QRS/Ta of 72.3±12° was reduced to 67.4±12.6° after treatment, with p-values <0.001. Changes in ECG parameters observed during the treatment process are shown in Table 2.

Table 1. Demographic, clinical, laboratory and echocardiographic features

Variables	(n=45)
Demographic parameters	
Age, years	56.64±5.04
BMI, kg/m²	27.70±1.01
Female, n (%)	15 (33.3)
Hypertension, n (%)	16 (35.6)
Diabetes mellitus, n (%)	14 (34.1)
Smoking, n (%)	15 (33.3)
COPD, n (%)	9 (20)
Dyslipidemia, n (%)	13 (28.9)
Cerebrovascular disease, n (%)	4 (8.9)
Ischeamic etiology, n (%)	32 (71.1)
NHYA functional class	2.00±0.71
Laboratory parameters	
CRP mg/dL	4.04±2.03
Uric aside mg/dL	4.96±1.83
Albumin g/L	35.36±3.01
Sodium mEq/L	137.78±4.13
Potassium mEq/L	3.88±0.36
Haemoglobin g/dL	12.64±1.21
Glucose mg/dL	102.62±36.70
Glomerular filtration rate mL/dk/1.73 m²	85.20±8.19
Medications	
Beta-blocker therapy, n (%)	38 (84.4)
Thiazide diuretics, n (%)	14 (31.1)
Mineralocorticoid receptor antagonists, n (%)	33 (73.3)
Ivabradine, n (%)	12 (26.7)
Digoxin, n (%)	7 (15.6)
ARNI 100 mg, n (%)	8 (17.8)
ARNI 200 mg, n (%)	16 (35.6)
ARNI 400 mg, n (%)	21 (46.7)
Furosemide mg	33.29±10.23
Echocardiographic parameters	
LVH, n (%)	6 (13.3)
Severe mitral regurgitation, n (%)	3 (6.7)
Severe tricuspid regurgitation, n (%)	4 (8.9)
Severe aortic stenosis, n (%)	1 (2.2)
Atrial dilatation, n (%)	7 (15.6)
RV dysfunction, n (%)	7 (15.6)
LV ejection fraction %	30.26±3.91

ARNI: Angiotensin receptor neprilysin inhibitors, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, LV: Left ventricule, LVH: Left ventricular hypertrophy, RV: Right ventricule

Discussion

The main finding of our study was the significant decrease in the QRS duration and f-QRS/Ta compared to baseline ECG after treatment with ARNI in patients with HFrEF on long-term follow-up.

HF is a major public health concern with a long-term mortality rate exceeding 50% (1). Therefore, knowing the predictors of mortality and identifying high-risk patient groups are crucial for the management of HF. The f-QRS/Ta is a parameter that can be easily obtained from a standard ECG and represents an approximate value of the spatial angles of ventricular depolarization and repolarization. An increase in the angle indicates a greater heterogeneity of ventricular depolarization and repolarization. There is a significant relationship between the f-QRS/Ta and mortality in patients with HF. Scientific evidence indicates that a wide f-QRS/T has been identified to be a predictor of mortality in these patients (5,8,12).

The relationship between repolarization heterogeneity and malignant ventricular arrhythmia has been shown in human *in vivo* studies (13,14). Moreover, Ilkhanoff et al. (15) demonstratedthatthere is a significant association between interstitial fibrosis detected by cardiac magnetic resonance and an abnormal QRS/T angle (odds ratio 3.05, 95% confidence interval, 1.69-5.48). In our study, the reduction observed in the f-QRS/Ta with Sac/Val therapy may have been a result of the reverse remodeling effect of ARNI treatment, as demonstrated in prospective study of biomarkers, symptom improvement, and ventricular remodeling during Sac/Val therapy for HF (PROVE-HF) study (16). The reduction in fibrosis burden due to reverse remodeling, along with the decrease in repolarization

Table 2. Comparison of ECG parameters and NT-proBNP

Parameters	Before therapy	Follow-up	p-value
NT-proBNP, pg/mL	2765.29±1035.15	2652.33±1334.45	0.551
Heart rate, bpm	70.82±10.4	68.69±9.38	**0.011**
QRS, msn	106.96±10.37	105.09±9.81	**0.008**
QTc	379.47±25.72	382.71±20.58	0.173
QRS-angle	58.64±37.11	58.00±30.35	0.614
T-angle	-13.47±40.71	-7.78±34.07	**0.020**
f-QRS/T angle	72.33±12.09	67.44±12.67	**<0.001**

BNP: Brain natriuretic peptide, ECG: Electrocardiogram

heterogeneity, is consistent with the reduction in the f-QRS/Ta. In a rabbit model of ischemic HF, it has been shown that ARNI treatment can reduce ventricular arrhythmias due to its effects on negative electrical and structural remodeling, as well as its anti-inflammatory properties (17). Additionally, the QRS/T angle is an important parameter that can be used not only in patients with HF but also for various clinical conditions such as acute myocarditis, myocardial infarction, or acute pulmonary embolism (18-21).

There are compelling evidences about relationship between the duration of the QRS complex and HF. The Framingham heart study has shown that, in patients without a history of HF, a prolonged QRS duration increases the risk of developing HF. Left ventricular intraventricular conduction delay, which is consequently prolonged QRS duration, are associated with more advanced myocardial damage and poorer prognosis compared to a narrow QRS complex (22,23). Studies on the effect of Sac/Val treatment on QRS duration in HF patients have shown that after Sac/Val therapy, there is a reduction in QRS duration, a decline in left ventricular systolic and diastolic diameters, improvement in ejection fraction, and enhancement in global longitudinal strain, reflecting improvements electrophysiological and mechanical parameters (24,25). These results, which can primarily be explained by reverse cardiac remodeling, are consistent with the improvements observed in left ventricular mechanical parameters in the PROVE-HF study (16). The results of our study also show a statistically significant reduction in QRS duration, compared to baseline after treatment in HF patients treated with ARNI, which is consistent with this scientific evidence.

Study Limitations

Our study had several limitations. Firstly, a relatively significant limitation was the small sample size of the study. Secondly, our study was designed as a retrospective study. Thirdly, our study was a single-center study. Finally, we had ECG records both before ARNI treatment and after one year of the follow-up period and were not able to evaluate the temporal changes of f-QRS/Ta values. Due to these restrictions, our study may need to be validated with comprehensive studies.

Conclusion

In conclusion, our study has shown that in HFrEF patients, Sac/Val treatment led to a significant decrease in QRS duration and f-QRS/Ta values. This effect suggests that Sac/Val treatment may have a significant role in the favorable clinical outcomes of HFrEF through its impact on electrical and structural remodeling.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical rules stated in the Declaration of Helsinki and the study protocols were approved by the Memorial Ataşehir Hospital Ethics Committee (decision no: 2024/15 date: 16.01.2025).

Informed Consent: Informed consent for this study was waived because it was a retrospective analysis.

Footnotes

Authorship Contributions

Concept: M.K., Design: M.K., E.A., Data Collection or Processing: M.K., Analysis or Interpretation: M.K., E.A., Literature Search: M.K., E.A., Writing: M.K.

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

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ORIGINAL RESEARCH

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Our Six-year Wilms Tumor Results: A Single-center Experience

Altı Yıllık Wilms Tümör Sonuçlarımız: Tek Merkez Deneyimi

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Abstract

Objective: This study aimed to analyze the demographic, clinical, and pathological data of children diagnosed with Wilms tumor (WT) and operated on at a tertiary healthcare center.

Method: Our study is a retrospective, observational analysis of clinical records of patients diagnosed with WT at a tertiary pediatric center between May 2017 and June 2023. The patients were evaluated based on their age at diagnosis, gender, symptoms, associated anomalies, laboratory and radiological examinations, the affected kidney side, stage, postoperative treatment, and follow-up. Histopathological classifications and staging for all patients were performed according to the National Wilms Tumor Study Group (NWTSG). Chemotherapy treatment was determined based on the pathological stages and tumor histopathology. In cases with metastasis, if clinically appropriate, metastasectomy was performed and chemotherapy was administered. Treatment for recurrence included surgery, chemotherapy, and radiotherapy.

Results: The average age of these patients was 3.8 years, with an equal distribution of male and female patients. The most common symptoms were abdominal mass, hematuria, and fever. Right kidney involvement was found in 50% of patients, left kidney involvement in 40%, and bilateral involvement in 10%. Treatment protocols were determined according to the NWTSG guidelines, with unilateral radical nephrectomy performed on all patients except two, who received preoperative chemotherapy. Pathological evaluation revealed that all patients had nephroblastoma (triphasic type), with anaplastic features found in three patients. Two patients presented with pulmonary metastases. With an average follow-up of 2.15 years, no recurrences were observed during the study.

Öz

Amaç: Bu çalışmanın amacı, Wilms tümörü (WT) tanısı konulan ve üçüncü basamak bir sağlık merkezinde ameliyat edilen çocukların demografik, klinik ve patolojik verilerini analiz etmektir.

Yöntem: Çalışmamız, Mayıs 2017 ile Haziran 2023 arasında üçüncü basamak bir çocuk hastanesinde WT tanısı konulan hastaların klinik kayıtlarının retrospektif, gözlemsel olarak analiz edilmiştir. Hastalar, tanı anındaki yaşlarına, cinsiyetlerine, semptomlarına, ilişkili anomalilere, laboratuvar ve radyolojik muayenelerine, etkilenen böbrek tarafına, evresine, ameliyat sonrası tedavisine ve takibine göre değerlendirildi. Tüm hastalar için histopatolojik sınıflandırmalar ve evrelemeler Ulusal Wilms Tümörü Çalışma Grubu'na (NWTSG) göre yapıldı. Kemoterapi tedavisi, patolojik evrelere ve tümör histopatolojisine göre belirlendi. Metastazı olan olgularda, klinik olarak uygunsa metastazektomi yapıldı ve kemoterapi uygulandı. Tekrarlama tedavisi cerrahi, kemoterapi ve radyoterapiyi içeriyordu.

Bulgular: Bu hastaların ortalama yaşı 3,8 yıldı ve erkek ve kız hastalar arasında eşit dağılım vardı. En sık görülen semptomlar abdominal kitle, hematüri ve ateşti. Hastaların %50'sinde sağ böbrek tutulumu, %40'ında sol böbrek tutulumu ve %10'unda bilateral tutulum bulundu. Tedavi protokolleri NWTSG kılavuzlarına göre belirlendi ve preoperatif kemoterapi alan iki hasta hariç tüm hastalara unilateral radikal nefrektomi uygulandı. Patolojik değerlendirme tüm hastalarda nefroblastoma (trifazik tip) olduğunu ve üç hastada anaplastik özellikler bulunduğu görüldü. İki hastada pulmoner metastazlar görüldü. Ortalama 2,15 yıllık takip süresiyle çalışma sırasında hiçbir nüks gözlenmedi.

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Conclusion: WT treatment should be approached with a multidisciplinary strategy and executed with careful surgical techniques. This study supports the effectiveness of current methods in the treatment of WT and highlights their positive impact on survival rates.

Keywords: Child, experience, tumor, Wilms

Sonuç: WT tedavisi multidisipliner bir strateji ile ele alınmalı ve dikkatli cerrahi tekniklerle uygulanmalıdır. Bu çalışma WT tedavisindeki mevcut yöntemlerin etkinliğini ve sağkalım oranlarını desteklemektedir.

Anahtar kelimeler: Çocuk, deneyim, tümör, Wilms

Introductıon

Wilms tumor (WT) is the most common renal tumor, accounting for approximately 6% of malignancies in infants and children (1). It is estimated that a germ cell mutation is responsible for about 10-15% of WTs (2). The most common clinical symptoms include abdominal mass, abdominal pain, hematuria, fever, and hypertension. The lungs are the most common site of metastasis (3). Evaluation of a child with suspected WT includes physical examination, complete blood count, blood biochemistry, urinalysis, and appropriate imaging, such as abdominal ultrasound (USG) or computed tomography (CT). However, a definitive diagnosis of WT can be made through a biopsy or surgical resection. Treatment protocols included surgical excision, chemotherapy, and radiotherapy in selected patients. Advancements in surgical techniques, anesthesia, and intensive care procedures, along with the chemotherapy and radiotherapy, have increased survival rates to over 90% (4).

This study aimed to examine the demographic characteristics, clinical and pathological findings, treatment processes, and follow-up outcomes of patients diagnosed with WT who underwent surgery at our tertiary pediatric hospital.

Materials and Methods

This retrospective observational study included the clinical records of patients diagnosed with WT at a tertiary pediatric hospital between May 2017 and June 2023. The study was approved by the Ethics Committee of the University of Health Sciences Turkey, Ümraniye Training and Research (protocol number B.10.1.TKH.4.34.H.GP.0.01/453) on 23.11.2023 and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who underwent surgery and were pathologically diagnosed with WT were included in the study and evaluated in terms of age at diagnosis, sex, symptoms, accompanying anomalies, laboratory, and radiological findings, affected side of the kidney, stage, postoperative treatment, and follow-up. Histopathological classification and staging of all patients were performed according to the National Wilms Tumor Study Group (NWTSG) guidelines. The NWTSG-5 protocol has also been used for treatment (5).

Patients were evaluated by a multidisciplinary pediatric oncology board (comprising pediatric surgery, pediatric urology, pediatric hemato-oncology, radiation oncology, pediatric radiology, and pathology departments) based on their clinical findings, laboratory tests, and radiological imaging results. The treatment plan was determined. Chemotherapy was customized according to the pathological stage and tumor histopathology. In cases of metastasis, metastasectomy was performed, and chemotherapy was administered if the patient's clinical condition was acceptable. Recurrence treatment included surgery, chemotherapy, and radiotherapy. Preoperative chemotherapy was administered in cases in which surgery was deemed highly risky, the tumor could not be completely resected, or the presence of a thrombus in the inferior vena cava.

Statistical Analyses

In our study, simple statistics were used, and the mean ± standard deviation (SD) and % values of the groups were calculated using Microsoft Excel.

In our study, basic statistical analyses were performed using Microsoft Excel. The results are presented as mean ± SD and percentage values for each group. As the study did not involve any group comparisons, p-values were not reported.

Results

Ten patients were included in this study. Of the children, five were male and five were female: (M/F =1/1). The mean age at diagnosis was 3.8 years (46 months), with a range of 8-101 months. One patient (10%) exhibited an associated anomaly: Left undescended testis and right inguinal hernia. The most prevalent symptoms at diagnosis were intra-abdominal mass, hematuria, fever, burning sensation, abdominal pain, and fatigue. The findings are summarized in Table 1. The right kidney was affected in 5 patients (50%), the left kidney in 4 patients (40%), and the tumor was bilateral in 1 patient (10%) (Table 2).

Laboratory tests revealed normal alpha fetoprotein, human chorionic gonadotropin, lactate dehydrogenase, and ferritin levels. Doppler USG and CT imaging was performed to evaluate tumor invasion following the detection of a renal mass in patients undergoing abdominal USG. All patients exhibited normal echocardiographic findings.

A unilateral radical nephrectomy was performed in 9 patients with unilateral WT, and 2 of these received preoperative chemotherapy. One of these patients was a 7-year-old girl with lung metastasis at the time of diagnosis for whom chemotherapy was initiated at an external facility. The other patient was a 4-year-old girl with a thrombus in the renal vein and inferior vena cava (Figure 1).

In cases where preoperative CT or magnetic resonance imaging was performed, contralateral exploration was conducted even in the absence of evidence of pathology in the contralateral kidney. A minimum of 5-7 samples was obtained from hilar and ipsilateral para-aortic or caval lymph nodes. A patient with bilateral WT underwent a left-sided nephrectomy and a right-sided biopsy. Given the pathological compatibility of the biopsied side with a WT, subsequent surgical procedures were performed, which entailed a nephrectomy and mass excision on the right side.

Variables such as age, sex, tumor side, tumor size, stage, presence of anaplasia, presence of nephrogenic rest, histology, and follow-up results are presented in Table 2. Postoperative bleeding requiring transfusion was not observed. One patient with bilateral tumors died postoperatively.

The pathology of all patients was reported as nephroblastoma (triphasic type). Anaplasia was identified in 3 patients, representing 30% of the study sample. Two patients exhibited evidence of lung metastasis (Figure 2). One of the 4 patients underwent chemotherapy and the others received radiotherapy. Eight children are currently being monitored for metastasis. The mean follow-up period was 2.15 years (range, 5 months-6 years).

Table 1. Clinical presentation

Symptoms	Number of patients (n)
Abdominal mass	7
Hematuria	3
Fever	2
Loss of weight	1
Fatigue	1
Abdominal pain	1

Table 2. Clinical and histopathological features

Patient	Age (month)	Sex	Side	Tumor size (cm)	Stage (COG)	Anaplasia	Nephrogenic rest	Histology	Follow-up
1	40	M	Right	8.7x7.5x7.3	III	Diffuse	Absent	Unfavorable	Disease free (3 years)
2	24	M	Right	14.5x12x9.8	II	Absent	Present	Favorable	Disease free (3 years)
3	36	M	Left	5x4.2x3.7	I	Absent	Absent	Favorable	Disease free (6 years)
4	58	F	Left	9x6x5	I	Absent	Absent	Favorable	Disease free (5 years)
5	8	M	Right	13x11.5x11	I	Absent	Absent	Favorable	Disease free (2 years)
6	32	F	Left	4.7x3x2.8	III	Absent	Present	Favorable Thrombus in renal vein and vena cava	Disease free (1 year)
7	45	F	Bilateral	Left 15x10x9 Right 10.5x5.5x4	III	Diffuse	Absent	Unfavorable	Exitus
8	84	F	Right	11.5x6x5	I	Absent	Absent	Favorable	Disease free (6 months)
9	30	M	Left	5.5x5x4.8	III	Focal	Absent	Unfavorable	Disease free (4 years)
10	101	F	Right	17x13x9	II	Absent	Absent	Favorable	Disease free (8 months)

COG: Children's oncology group

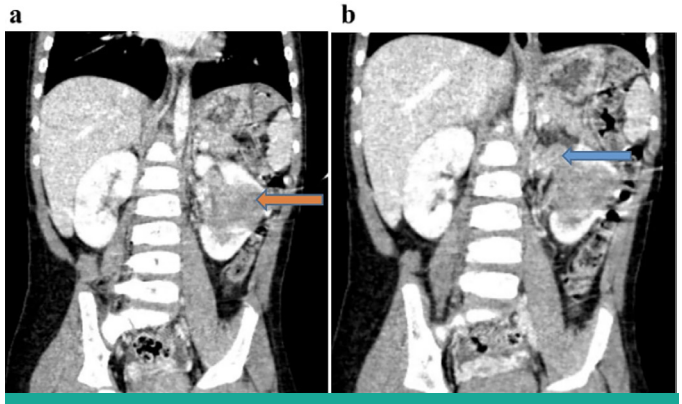

Figure 1. Coronal section CT image of the patient; a) CT image of a coronal section demonstrating a mass originating from the mid-pole of the left kidney (orange arrow), b) Left renal vein invasion (blue arrow)

CT: Computed tomography

Discussion

WT is the most prevalent renal tumor in children, affecting 1 in 10,000 children (6). According to the data, the age of onset of the tumor is 1-5 years in 78% of cases (7). The mean age of our patients was found to be 3.8 years, which is similar to that reported in the literature. Two patients (20%) were less than 5 years of age. The female-to-male ratio of the patients was 1:1. Analysis of the symptoms presented at the initial evaluation revealed that the most common finding was an abdominal mass (70%). The most common complaints were hematuria and fever. Abdominal mass is the most common presenting symptom of WT (8). In our series, abdominal mass was similarly identified as the most common presenting symptom.

Monophasic WTs may be difficult to distinguish from other tumors, in which case immunohistochemistry is helpful. WT1 was nuclear positive in 90% of cases. The blastemal component was positive for WT1, PAX8, and vimentin. The epithelial component was positive for cytokeratin, EMA, and CD56 expression. The stromal component is positive for vimentin, shows variable positivity for BCL2 and CD34, with weak expression or negativity for WT1(9). WT1 was negative in 2 of our patients. Although WT1 is specific and sensitive, it may be negative in 10% of the cases.

The diagnosis of WT is usually straightforward; however, monophasic WTs are difficult to distinguish from other histologically similar renal tumors. The pure blastemal type of WT must be differentiated from tumors such as neuroblastoma, primitive neuroectodermal tumor or Ewing sarcoma, desmoplastic small round cell tumor, and synovial sarcoma. Therefore, immunohistochemical and molecular

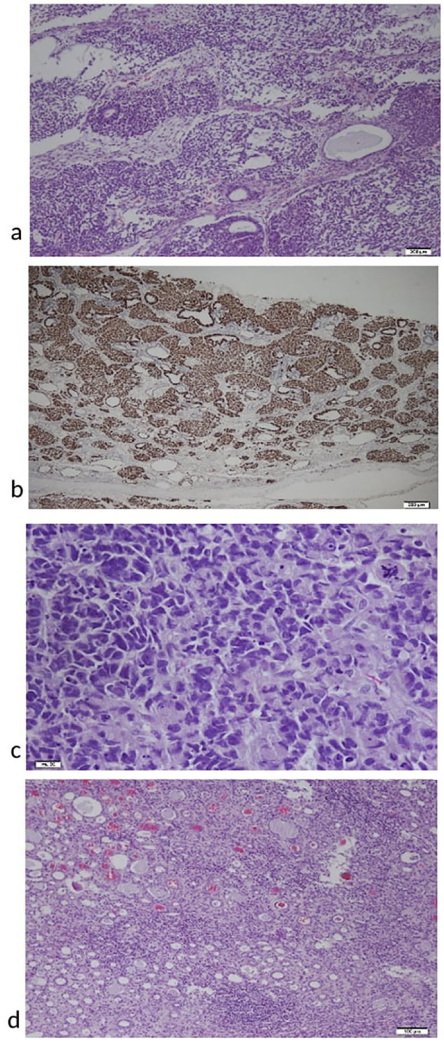

Figure 2. Triphasic Wilms tumor, staining in tumor cells with WT-1, anaplasia area, presence of nephrogenic rest

a) Triphasic Wilms tumor; stromal, blastemal and epithelial components (H&E, x4),

b) Staining of tumor cells with WT-1 (x4-WT-1),

c) Anaplasia area showing marked pleomorphism with numerous mitotic figures (H&E, x40),

d) Presence of nephrogenic rest in the renal parenchyma (H&E, x10)

WT: Wilms tumor, H&E: Hematoxylin and eosin

techniques are important. Blastemal components may show focal CD99 positivity, but this is not diffuse and membranous, as in Ewing sarcoma. Desmoplastic small round cell tumor is immunohistochemically similar to WT. The diagnosis should be made based on the EWS-WT1 t(11;22)(q13;q12) translocation. Neuroblastoma is characterized by high catecholamine levels and histological salt and pepper chromatin. Both tumors were positive for NSE and CD56; however, WT1, which is a marker

used in the characterization of tumors, was negative for indicating neuroblastoma. Pure epithelial WT should be differentiated from metanephric adenoma, renal cell carcinoma, and hyperplastic perilobar nephrogenic rest. The combination of CK7-, AMACR-, WT1+, and CD57+ favors metanephric adenomas. In the differential diagnosis of a pure stromal type WT, clear cell renal sarcoma and mesoblastic nephroma should be considered. Cystic WT should be distinguished from cystic nephroma (CN) and cystic partially differentiated nephroblastoma (CPDN). CN contains DICER1 mutations, whereas these mutations are absent in CPDN and WT. Since none of our patients had a monophasic histology, differential diagnosis was not necessary nor difficult. Triphasic components were found in all patients (10).

WT is similar to the histology of the developing kidney, and originates from the nephrogenic blastema. Histopathologically, it comprises blastemal, epithelial, and stromal components. The blastema component consists of undifferentiated cells with small and regular nuclei. The epithelial component contains differentiated elements, such as tubules and papillary structures. The stromal component may contain heterologous elements, such as adipose tissue and cartilage. Anaplasia, seen in 7-10% of WTs, is characterized by atypical multipolar mitotic figures, marked nuclear enlargement (at least 3-fold), and hyperchromasia. Anaplasia is divided into focal anaplasia, which is confined to the primary intrarenal tumor, and diffuse anaplasia, which extends beyond the tumor capsule. Focal anaplasia is defined as a clearly demarcated focus within the primary intrarenal tumor, but, in rare cases, multiple foci are allowed for diagnosis: up to 4 foci in the children's oncology group definition and up to 2 foci ≤15 mm according to the International Society of Paediatric Oncology (SIOP) definition.

In our series, focal anaplasia was found in 1 patient and diffuse anaplasia in 2 patients. One of the patients with diffuse anaplasia was also a patient with bilateral WT who died. In the patient with focal anaplasia, no recurrence was observed during 4 years of follow-up (11).

It has been reported that genitourinary abnormalities are common in patients with WT (12). In our series, the incidence of concomitant anomalies was 10%, occurring in 1 out of 10 patients. This is a low rate compared with data reported by some authors, who indicated a rate of 26%. In another study, the prevalence of all genitourinary malformations in patients with WT was found to be 5% (13).

In one patient, the incidence of WT on both sides was observed to be 10%. Right kidney involvement was found in 5 (50%) patients and left kidney involvement in 4 (40%) patients. According to some sources, left kidney involvement is more common (14); however, in our study, right-sided involvement was higher.

The most important prognostic factors in WT treatment are tumor stage, histopathological anaplasia, absence of preoperative rupture, and positivity for some biological markers (15). Regarding clinical staging, 4 (40%) of our patients were stage 3, 4 (40%) were stage 1, and 2 (20%) were stage 2. Favorable histology was observed in 3 (30%) patients. In a study by Breslow et al. (7), the rate of unfavorable histology was 11%, which was lower than that in our study. The remaining 7 (70%) had a favorable histology.

Nephrogenic rest is a precursor lesion of WT originating from various sites, such as blastemal, stromal, and embryonal nephroblastic tissue, and may be confused with other malignant tumors (16). Nephrogenic rests were found in 2 patients with favorable histology and without anaplasia.

In our 2 patients with lung metastasis, the survival rate 2-year follow-up period with treatment was quite high. However, the survival rate in WT cases is reported to be 75% in metastatic patients and over 90% in non-metastatic patients (17). With the current multidisciplinary treatment, chemotherapeutic drugs, and improvements in radiotherapy, significant progress have been achieved for WT (18). We agree with this view, and our results support this hypothesis.

In cases of horseshoe kidney, bilateral WT, thrombus in the hepatic vein or vena cava, solitary kidney, or respiratory distress due to lung metastases, NWTSG recommends preoperative chemotherapy (19). In our series, two patients with lung metastases and thrombus in the renal vein and inferior vena cava received preoperative chemotherapy.

The mean follow-up period of our patients was 2.15 years, and no mortality was observed during this period. Increased surgical experience, development of radiologic imaging techniques, and shrinkage of masses with chemotherapy have decreased the morbidity and mortality associated with WT.

In another study conducted in Turkey, the frequency of vascular invasion was 8% (20). In our study, the frequency of vascular invasion was 10%. There are reports that intravascular invasion of WT occurs in 20-35% of cases (21).

The most important aspect of WT surgery is to prevent tumor rupture and shedding intraoperatively (22). The surgical team was careful not to rupture the tumor capsule. We believe that this care was one of the reasons for the success of our follow-up.

In the present study, no recurrence was observed during the follow-up period. A recurrence rate of 4.3% for favorable histology and 42% for unfavorable histology has been reported in the literature (23).

When reviewing studies conducted in recent years, the outcomes of patients with focal anaplastic WT are comparable to those of identically treated patients with non-anaplastic intermediate-risk WT in SIOP studies. The outcomes for patients with high-stage diffuse anaplastic WT remain poor, presenting challenges for treatment and management. Recent studies have shown improvements in effectiveness with increased treatment, but also an increase in toxicity (24).

There are authors who argue that patients with stage I and II focal anaplastic WT have remarkably good survival rates when treated with doxorubicin and radiation. In their studies, they reported that intensification of therapy could improve survival in stage IV focal anaplastic WT, albeit with an increased risk of toxicity (25).

In a noteworthy recent study, the aim was to investigate prognostic factors for WT through peripheral blood cell profiling. It was found that overall survival and event-free survival were worse in patients with an absolute monocyte count below $0.325\times10^3/\mu L$ and those with stage IV disease (26).

It is well known that clinicians' evaluation of a patient's eligibility for postoperative radiation is crucial. Postoperative radiation has been shown to be associated with poor prognosis in patients with WT (27).

Moreover, some authors suggest that the rapid advancements in molecular biology, imaging, and radiotherapy will lead to better outcomes and reduced toxicity in WT patients. Advances in radiation techniques such as intensity-modulated radiation therapy have made it possible to explore heart protection strategies when delivering whole lung radiation (28).

A computer-aided prediction system was developed in a study to predict the response of WT to preoperative chemotherapy, using contrast-enhanced CT before treatment. It was reported that the designed program helped accurately identify WT cases, less likely to respond to preoperative chemotherapy. Consequently, they argued that surgery could be recommended for these tumors in advance, thereby avoiding the drawbacks of preoperative chemotherapy (29).

Our primary goal is to ensure the best possible survival for these patients. In addition to all of this, recent studies have indicated that survival rates may vary according to race, ethnicity, metropolitan status, and age (30).

Study Limitations

One of the limitations of this study was the relatively small number of patients. However, the fact that the study was single-center and that all surgeons who performed the surgeries were experienced in tumor surgery is important and meaningful in terms of preventing inconsistencies in staging and pathology evaluation. Another one is, in the statistical analysis, p values were not reported because there was no comparison group. Because it does not possible to perform statistical analysis in a study group consisting of ten patients.

Conclusion

Patients with WT should be managed with a multidisciplinary approach, planned treatment, and close follow-up. Increased surgical experience, development of radiological imaging techniques, and shrinkage of masses due to chemotherapy have decreased morbidity and mortality in WT. As observed in our series, the number of patients detected in stage 1 was equal to the number of patients detected in stage 3. This finding supports our conclusions.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Turkey, Ümraniye Training and Research (protocol number B.10.1.TKH.4.34.H.GP.0.01/453) on 23.11.2023 and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Y., F.T.G., Z.İ., Concept: S.Y., Z.İ., Design: S.Y., F.T.G., F.T., Data Collection or Processing: S.Y., İ.T., F.T., Analysis or Interpretation: S.Y., İ.T., O.Ş., Z.İ., Literature Search: S.Y., F.T.G., F.T., O.Ş., Writing: S.Y., İ.T., O.Ş.

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

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ORIGINAL RESEARCH

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Feasibility and Efficacy of Carotid Stenting in Patients with Contralateral ICA Occlusion

Kontralateral ICA Oklüzyonu Olan Hastalarda Karotis Stentlemenin Uygulanabilirliği ve Etkinliği

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Abstract

Objective: This study was conducted to assess the feasibility, safety, and efficacy of carotid artery stenting (CAS) in patients with severe ipsilateral carotid artery stenosis and contralateral internal carotid artery occlusion (CCO) and compare the outcomes with a matched control group without contralateral occlusion.

Method: A retrospective study was conducted on 247 patients treated with CAS between April 2020 and July 2024. Of these, 21 patients with CCO were matched 1:1 to a control group without CCO based on age and sex. Procedural success, periprocedural complications, and short- to mid-term follow-up outcomes (median follow-up: 24 months) were analyzed.

Results: Technical success was accomplished in every case. Two periprocedural complications were identified in each group. Three patients in the CCO group and two in the control group died during the follow-up, with myocardial infarction determined to be the cause of death in one patient from each group. No new ischemic cerebrovascular events were recorded in either group during the follow-up period.

Conclusion: CAS is a feasible and effective treatment for patients with severe carotid stenosis and CCO, yielding outcomes comparable to patients without contralateral occlusion.

Keywords: Angioplasty, carotid stenosis, cerebrovascular stroke

Öz

Amaç: Çalışmanın amacı kontralateral internal karotis arter oklüzyonu (KKO) olan ve ciddi ipsilateral karotis arter stenozu bulunan hastalarda karotis arter stentleme (KAS) işleminin uygulanabilirliğini, güvenliğini ve etkinliğini değerlendirmek; bu sonuçları kontralateral karotis arter oklüzyonu olmayan eşleştirilmiş kontrol grubu ile karşılaştırmaktır.

Yöntem: Nisan 2020 ile Temmuz 2024 tarihleri arasında KAS uygulanan 247 hasta ile retrospektif bir çalışma yapıldı. Bu hastalardan KKO'ya sahip 21 hasta, yaş ve cinsiyet açısından 1:1 oranında eşleştirilmiş kontrol grubu ile karşılaştırıldı. Prosedürel başarı, periprosedürel komplikasyonlar ve kısa-orta dönem takip sonuçları (medyan takip süresi: 24 ay) analiz edildi.

Bulgular: Hastaların tamamında teknik başarı sağlandı. Periprosedürel komplikasyonlar her iki grupta da ikişer hastada gözlendi. Takip süresi boyunca KKO grubunda 3 hasta, kontrol grubunda ise 2 hasta hayatını kaybetti; her iki grupta da birer hastada miyokard enfarktüsü ölüm nedeni olarak belirlendi. Takip süresi boyunca hiçbir hastada yeni iskemik serebrovasküler olay saptanmadı.

Sonuç: KAS, ciddi karotis stenozu ve KKO'su olan hastalar için uygulanabilir ve etkili bir tedavi seçeneğidir. Bu hasta grubundaki sonuçlar, kontralateral oklüzyonu olmayan hastalarla karşılaştırılabilir düzeydedir.

Anahtar kelimeler: Anjiyoplasti, karotis stenozu, serebrovasküler inme

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Introduction

Stroke stands as the third major cause of mortality, preceded by coronary artery disease and cancer, with ischemic events associated with over 80% of all strokes (1,2). Among these, 15-20% of ischemic strokes result from carotid artery stenosis, and approximately 10% of patients with carotid artery stenosis also present with contralateral internal carotid artery (ICA) occlusion (CCO) (3). Revascularization methods, including carotid endarterectomy (CEA) and carotid artery stenting (CAS), are available for long-term stroke risk mitigation in individuals with severe carotid stenosis, regardless of symptom status. The North American symptomatic CEA trial demonstrated a heightened perioperative stroke risk in patients with CCO undergoing CEA relative to those without (4). Similarly, findings from the asymptomatic carotid atherosclerosis study trial indicated an increased risk of perioperative stroke, as well as higher rates of periprocedural mortality and non-fatal myocardial infarction in patients with CCO undergoing CEA (5). While CEA remains the standard treatment for stroke prevention, CAS has gained increasing acceptance in carotid revascularization due to technological advancements and expanding clinical expertise in managing carotid stenosis (6). Patients with carotid stenosis and CCO have traditionally been regarded as high-risk candidates for CEA or CAS (7). In recent years, however, some high-risk patients have been deemed suitable for CAS when the procedure is carried out by an experienced operator with careful selection criteria applied to optimize outcomes (8).

The aim of the current study was to compare the technical success, efficacy, and safety of CAS, as well as periprocedural complications and follow-up outcomes in patients with CCO versus those without CCO, serving as confirmatory research that reinforces existing findings while focusing on patient data within the CCO group.

Materials and Methods

Ethical committee approval was received from the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2024-72). The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of in 2000. Following this, a retrospective study was conducted on patients with atherosclerotic stenosis of the extracranial ICA who underwent CAS at a single institution between April 2020 and July 2024. In the study group, inclusion criteria encompassed patients with contralateral ICA occlusion and ≥70% stenosis in the ipsilateral ICA, while exclusion criteria included non-elective cases, acute stroke, intracranial tumors, and hemorrhage. In the control group, patients with ≥70% ICA stenosis and a patent contralateral ICA were included, whereas those with contralateral ICA occlusion or near-occlusion, as well as non-elective cases, acute stroke, intracranial tumors, and hemorrhage were excluded. All patients initially referred for stent placement due to carotid stenosis underwent Doppler ultrasound imaging followed by either computed tomography angiography or contrast-enhanced magnetic resonance angiography of the head and neck. Patients confirmed to have ≥70% stenosis via non-invasive imaging were subsequently scheduled for cerebral digital subtraction angiography (DSA) with the intent to perform CAS. However, in 11 cases, stenting was not carried out due to the absence of significant hemodynamic stenosis on DSA, and in three cases, anatomical constraints precluded stent placement. As a result, 247 subjects who had CAS performed during the course of the study were retrospectively analyzed, and 23 patients with CCO were identified. Two of these patients were excluded due to insufficient follow-up data. Ultimately, 21 patients with CCO who underwent CAS were included in the analysis.

Propensity score matching (1:1 nearest-neighbor) was applied to form the control group, using propensity scores derived from logistic regression with standardized "age" and "sex" used as predictors. During the matching process, patients with contralateral ICA occlusion or near-occlusion were excluded. Propensity scores were utilized to select the most comparable control group patients from a cohort of 182 participants. This created a demographically and clinically similar control group, while minimizing bias and ensuring unique pairings. Next, a comparative evaluation was carried out between patients who underwent CAS for severe carotid stenosis with CCO and patients without CCO or near-occlusion. The outcomes analyzed included technical success, safety, procedural efficacy, peri-procedural complications, and short- to mid-term follow-up. The study comprehensively assessed demographic characteristics, comorbidities, procedural access, plaque composition, collateral circulation patterns in the study group, technical success, and periprocedural complications, alongside short- to mid-term outcomes such as restenosis, ischemic events, and all-cause mortality. Additionally, procedural data encompassed intraprocedural thromboembolic events, periprocedural stroke, and access site complications, while clinical outcomes were evaluated hyperperfusion-related complications, myocardial

infarction, major and minor ischemic strokes, and mortality over the follow-up period. Angiographic findings were also recorded specifically for patients in the CCO group.

The procedures were performed by interventional radiologists with a minimum of four years of experience in carotid stenting. All CAS procedures were conducted electively, and all patients gave their written informed consent for participation prior to the procedure. To ensure adequate antiplatelet activity, dual antiplatelet therapy was administered to the patients (aspirin 100 mg/day and clopidogrel 75 mg/day) for at least seven days before the procedure, with efficacy confirmed via resistance testing. Continuous monitoring of oxygen saturation, ECG, and blood pressure was started at the initiation of the procedure. After local site preparation and anesthesia, an 8-French femoral sheath was inserted into the femoral artery under ultrasound guidance. An intra-arterial heparin dose of 70-100 U/kg was administered via the sheath to prevent thrombotic complications. Four-vessel angiography was subsequently carried out, and a long sheath (Fubuki XF, Asahi Intecc, USA) was advanced into the targeted common carotid artery (CCA) to facilitate the procedure. A micro guidewire was used to traverse the stenotic segment, enabling the deployment of a distal embolic protection device. In cases where the protection device or stent could not cross the lesion, a 3-mm balloon catheter (Simpass, Simeks, Turkey) was employed for pre-dilation over a 0.014-inch guidewire.

A distal protection device (Spider FX, Covidien, MN, USA, or FilterWire EZ, Boston Scientific, MA, USA) was placed in the distal cervical ICA. The stents were sized to match the diameter of the distal CCA and were deployed from the unaffected ICA segment across the stenosis to the CCA to ensure complete plaque coverage. A secondary telescoping stent was positioned if additional coverage was needed. In all cases, post-stent balloon angioplasty using a 5-mm balloon (Simpass, Simeks, Turkey) was carried out to optimize luminal expansion. Intravenous atropine was administered as needed to manage hemodynamic instability, including bradycardia, asystole, or hypotension during balloon inflation. At the conclusion of the procedure, a final cerebral angiography was carried out after removing the distal embolic filter.

The patients were continuously monitored for their cardiac and neurological status for 24 hours postoperatively, with hourly neurological evaluations. Discharge typically occurred on postoperative day 1 or 2. Follow-up evaluations, including neurological assessments and duplex ultrasonography, were carried out on the day after the procedure and at 1, 6, and 12 months in the first year, followed by annual reviews to assess vessel patency, restenosis, or other complications. Postoperatively, the patients were advised to continue a combination of aspirin (100 mg/day) and clopidogrel (75 mg/day) as antiplatelet treatment for a minimum of six months, with aspirin therapy continued indefinitely.

Statistical Analysis

Data entry and statistical analyses were carried out using the SPSS for Windows version 18.0 software package (SPSS Inc., Chicago, IL, USA). The normality of data distribution was evaluated using both visual methods (histograms and probability plots) and analytical methods (Shapiro-Wilk test). The numerical data were presented as the median (1^{st}-3^{rd} quartile), while categorical variables were summarized using frequency distributions and percentages. Comparisons of non-normally distributed numerical data and categorical variables were carried out using the Mann-Whitney U test. The chi-square test was employed for categorical variable assessment, with statistical significance established at $p<0.05$.

Results

The study included a total of 42 participants, with 21 patients in the study group and 21 in the control group. The mean age of the cohort was 69.5 years (interquartile range: 67.0-71.5); among the participants, 32 were males and 10 were females. The age and gender distribution, as well as smoking history, were similar between both groups (p=0.850, p=0.999, and p=0.525, respectively). No statistically significant differences were identified regarding the prevalence of hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, or peripheral arterial disease between the two groups (p>0.05). However, cerebrovascular disease was significantly more prevalent in the study group (66.7%), compared to the control group (23.8%) (p=0.005). Further details are presented in Table 1.

Procedural access was obtained from the right side in 57.1% of the cases in both groups (p=0.999). Balloon pre-dilatation before stent deployment was carried out in 23.8% of the study group and 14.3% of the control group; this difference did not reach statistical significance (p=0.348). Post-dilatation was carried out in all cases in both groups. Symptomatic presentations were observed in 57.1% of the study group and 52.4% of the control group, with no significant difference between the two groups (p=0.500).

The overall complication rate was 9.5% in both groups (p=0.999). Evaluation of the plaque composition indicated that 28.6% of plaques in the study group could be classified as soft, while 71.4% were mixed. In the control group, 33.3% of plaques were soft, 9.5% were calcified, and 57.1% were mixed. The follow-up periods were comparable between the two groups (p=0.371). A summary of these findings is provided in Table 2.

Among the patients in the control group, 85.7% (n=18) had normal-to-mild contralateral ICA stenosis, while 14.3% (n=3) exhibited moderate contralateral ICA stenosis. Angiographic evaluation of the occluded ICA in the study group revealed cerebral arterial filling through the anterior communicating artery (ACoA) alone in 9.5% (n=2) of the cases, through the posterior communicating artery (PCoA) alone in 19% (n=4) of the cases, through both the ACoA

Table 1. Comparison of age, gender, smoking status, and comorbidities between the study and control groups

Feature	All subjects (n=42) n (%)	Study group (n=21) n (%)	Control group (n=21) n (%)	p
Age (years)/median (1st-3rd quartile)	69.5 (67.0-71.5)	70.0 (65.5-75.5)	69.0 (67.5-71.0)	0.850[a]
Gender				
Male	32 (76.2)	16 (76.2)	16 (76.2)	0.999[b]
Female	10 (23.8)	5 (23.8)	5 (23.8)	
Smoking status				
No	16 (38.1)	9 (42.9)	7 (33.3)	0.525[b]
Yes	26 (61.9)	12 (57.1)	14 (66.7)	
Comorbidities				
Hypertension	36 (85.7)	17 (81.0)	19 (90.5)	0.331[b]
Diabetes mellitus	19 (45.2)	11 (52.4)	8 (38.1)	0.352[b]
Coronary artery disease	25 (59.5)	15 (71.4)	10 (47.6)	0.116[b]
Hyperlipidemia	8 (19.0)	2 (9.5)	6 (28.6)	0.116[b]
Peripheral artery disease	7 (16.7)	4 (19.0)	3 (14.3)	0.500[b]
Cerebrovascular disease	19 (45.2)	14 (66.7)	5 (23.8)	**0.005**[b]

[a]: Mann-Whitney U test, [b]: Chi-square test

Table 2. Comparison of procedural characteristics between the study and control groups

Variables	All subjects (n=42) n (%)	Study group (n=21) n (%)	Control group (n=21) n (%)	p
The side of stent angioplasty				
Right	18 (42.9)	9 (42.9)	9 (42.9)	0.999[a]
Left	24 (57.1)	12 (57.1)	12 (57.1)	
Predilatation				
No	34 (81.0)	16 (76.2)	18 (85.7)	0.348[a]
Yes	8 (19.0)	5 (23.8)	3 (14.3)	
Presence of symptoms				
No	19 (45.2)	9 (42.9)	10 (47.6)	0.500[a]
Yes	23 (54.8)	12 (57.1)	11 (52.4)	
Complications				
No	38 (90.5)	19 (90.5)	19 (90.5)	0.999[a]
Yes	4 (9.5)	2 (9.5)	2 (9.5)	
Plaque composition				
Soft	13 (31.0)	6 (28.6)	7 (33.3)	-
Calcific	2 (4.8)	-	2 (9.5)	
Mixed	27 (64.3)	15 (71.4)	12 (57.1)	
Follow-up duration (months)/median (1st-3rd quartile)	24.0 (11.0-36.0)	24.0 (10.0-43.0)	20.0 (11.0-31.5)	0.371[b]

[a]: Chi-square test, [b]: Mann-Whitney U test

and PCoA in 57.1% (n=12) of the cases, and through the ACoA, PCoA, retrograde flow via the ipsilateral ophthalmic artery, or leptomeningeal collaterals in 14.3% (n=3) of the cases (Figures 1, 2). A subgroup analysis using the chi-square test assessed the impact of plaque composition, cerebral collateral circulation, and comorbidities, on CAS outcomes in both the study and control groups, revealing no statistically significant differences.

The technical success rate, defined as the effective resolution of stenosis after stent placement, was 100% in both groups. During the periprocedural period, one patient in the occlusion (study) group experienced hypotension requiring adrenergic medication. One patient in the control group developed hypotension requiring medical treatment, another experienced bradycardia lasting 24 hours, and a third had concurrent hypotension and bradycardia requiring intervention. Transient hypotension occurred in both groups but was excluded as a periprocedural complication since it resolved spontaneously or with short-term isotonic saline infusion without adrenergic support.

Two complications were documented in the occlusion (study) group. One patient experienced an ipsilateral

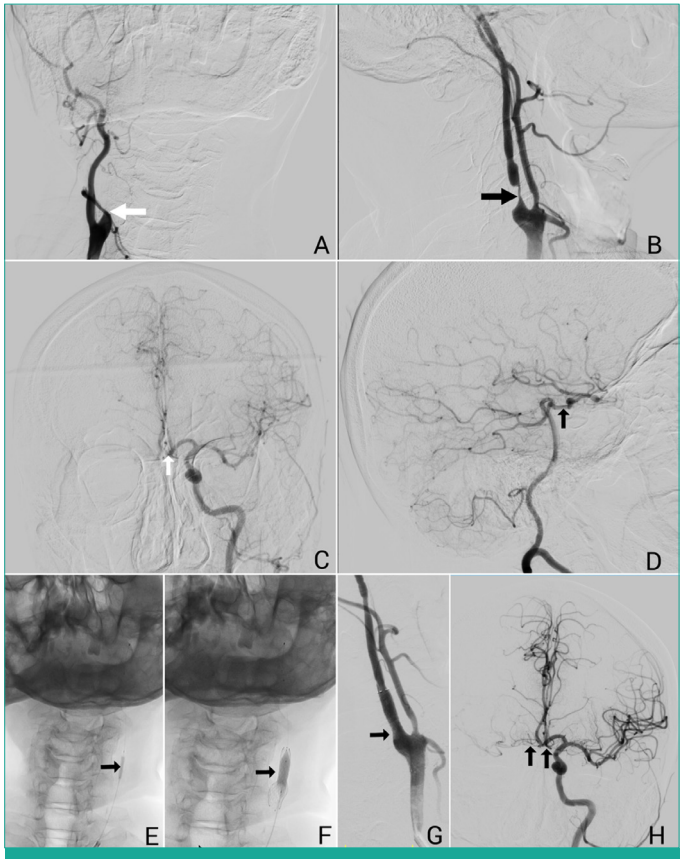

Figure 1. A. Anteroposterior digital subtraction angiography (DSA) of the cervical region demonstrating occlusion of the right internal carotid artery (ICA) (white arrow). B. Left lateral projection of the cervical DSA demonstrating severe stenosis of the proximal left ICA (black arrow). C. Anteroposterior cranial DSA obtained from the left ICA demonstrating that, except for the right anterior cerebral artery territory, the right cerebral hemisphere is not opacified via the anterior communicating artery (white arrow). D. DSA of the circle of Willis, performed prior to stent angioplasty, confirming good collateral flow from the left vertebral artery via the posterior communicating artery (black arrow). E, F. Balloon angioplasty carried out prior to stent placement to treat the stenosis, followed by in-stent balloon dilatation (black arrows). G, H. Post-procedural lateral cervical and anteroposterior cranial angiograms demonstrating an increased ICA diameter and the restoration of intracranial blood flow, respectively (black arrows)

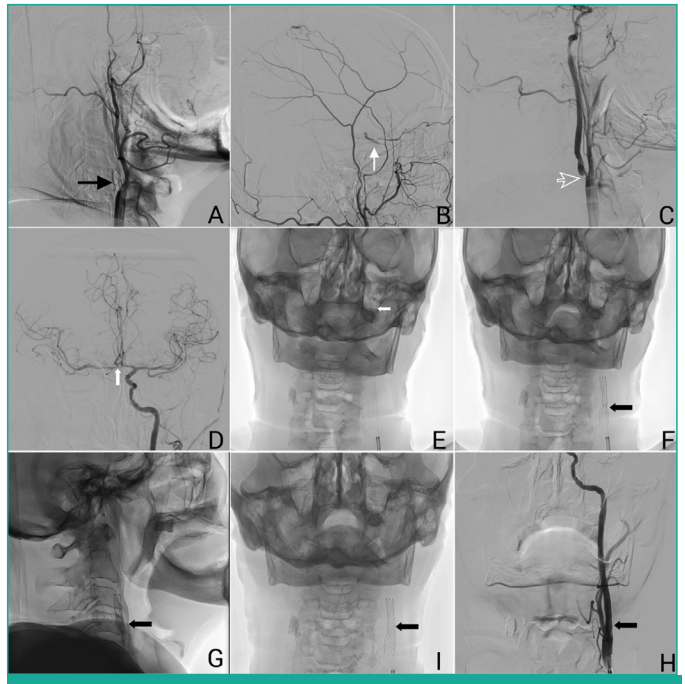

Figure 2. A. Lateral digital subtraction angiography (DSA) of the cervical region, obtained via the right common carotid artery, revealing complete occlusion of the right internal carotid artery (ICA) (black arrow). B. Cranial lateral view images obtained from the right common carotid artery demonstrating collateral flow through the ipsilateral ophthalmic artery on the occluded side (white arrow). C. The left lateral projection of the cervical region DSA revealing severe narrowing of the proximal segment of the left ICA (white arrow). D. Anteroposterior cranial DSA of the circle of Willis demonstrating effective flow to the right cerebral hemisphere from the left ICA through the anterior communicating artery (white arrow). E-G. AP cervical images demonstrating the placement of a distal protection device, lateral cervical view showing stent angioplasty extending from the ICA to the CCA to cover the stenotic segment, followed by in-stent balloon angioplasty, respectively (arrows). I, H. Anteroposterior cervical image following in-stent balloon angioplasty demonstrates optimal stent diameter. Post-procedure AP cervical angiogram shows improvement in the diameter of the ICA (black arrows)

cerebral embolism, with complete clinical recovery during the follow-up. Another patient developed a minimal ipsilateral frontal subarachnoid hemorrhage four days after stent placement, followed by ipsilateral frontal lobar hemorrhage one day later, leading to a fatal outcome (Figure 3). Two complications were also reported in the control group. One patient experienced transient contralateral hand weakness, which was resolved within a few days, while another patient had ipsilateral cerebral embolism, presenting with dysarthria and weakness in the contralateral upper and lower extremities. This patient was discharged with a modified Rankin score of 3 following rehabilitation. No statistically significant difference was noted in the overall complication rates between the two groups (p=0.999).

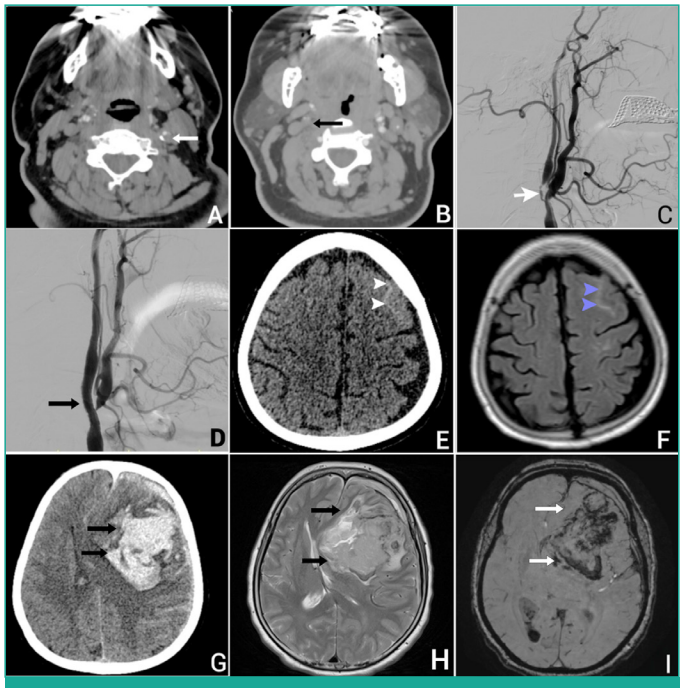

Figure 3. A. Preprocedural computed tomography angiography (CTA) demonstrating a high-grade stenosis of the left internal carotid artery (ICA) caused by a mixed-type plaque (white arrow). B. Preprocedural CTA shows occlusion of the right ICA (black arrow). C. The left lateral projection of cervical digital subtraction angiography (DSA) demonstrating significant stenosis in the proximal segment of the left ICA (white arrow). D. The stenosis was effectively managed with the placement of a stent spanning the carotid bifurcation (black arrow). E. Non-contrast axial brain computed tomography demonstrating hyperdensity in the left frontal cerebral sulcus, suggestive of subarachnoid hemorrhage (arrowheads). F. Brain magnetic resonance imaging (MRI) FLAIR sequence demonstrating hyperintensity in the left frontal cerebral sulcus, consistent with subarachnoid hemorrhage (arrowheads). G-I. Axial non-contrast brain CT, T2 weighted MRI, and susceptibility weighted imaging demonstrating a large parenchymal hematoma in the left frontal lobe, causing midline shift and compressing the lateral ventricles, respectively (arrows)

No new ischemic cerebrovascular events were observed in either group during the follow-up. The study group reported three patient deaths, one due to early postoperative intracranial hemorrhage secondary to hyperperfusion syndrome, one from pulmonary infection, and another from myocardial infarction. Two deaths were recorded in the control group, one resulting from heart failure-related volume overload and the other from myocardial infarction, which was unrelated to the vascular interventions.

Discussion

Severe stenosis of the carotid artery, when accompanied by CCO, can further compromise cerebral hemodynamics and elevate the risk of ischemic events in the brain (9). CEA is widely recognized as the superior treatment for symptomatic stenosis, whereas most studies have demonstrated that CAS is not inferior to CEA in managing asymptomatic stenosis (10-12). CCO is believed to heighten the risk of stroke during CEA, primarily because clamping the target artery can further compromise cerebral blood flow. This effect is considered to be unrelated to the embolic risk associated with the procedure. Consequently, there is a growing consensus that CAS may offer a safer alternative in patients who also have CCO, because it eliminates the requirement for arterial clamping.

The current study confirmed that CAS represents a feasible and effective treatment choice for patients with severe carotid stenosis, regardless of the presence or absence of CCO. The technical success rate was 100% in both groups, underscoring the procedural reliability of CAS in this high-risk population. No significant differences were observed in periprocedural complication rates or short- to mid-term outcomes between the two groups, with the overall complication rate at 9.5% in both cohorts. Importantly, although cerebrovascular disease was significantly more prevalent in the CCO group, this did not translate into a higher incidence of new ischemic events during follow-up.

In a previous study, neurological events, including both TIA and stroke, were recorded in 60% of the patients (n=82) with contralateral ICA, in whom the progression of asymptomatic carotid stenosis was being followed (13). The incidence of neurological events was comparable in the current study and was 66.7% among the 21 patients with contralateral ICA occlusion, showing these complications. Despite the smaller sample size in the current study, the

similarity in the outcomes suggests that the results are reliable, could be applicable to a broader population, and highlight the potential clinical relevance of our study in this specific cohort.

We analyzed the patterns of cerebral arterial collateral circulation in patients with contralateral ICA occlusion and severe ipsilateral ICA stenosis (≥70%) (Figure 1). We observed collateral flow through the ACoA alone in 9.5% (n=2), PCoA alone in 19% (n=4), both ACoA and PCoA in 57.1% (n=12), and ACoA, PCoA, and retrograde flow via the ipsilateral ophthalmic artery; or leptomeningeal collaterals in 14.3% (n=3) of the cases. A previous study conducted in a larger cohort of 38 patients reported collateral pathways via ACoA alone in 15.8%, PCoA alone in 7.9%, and both ACoA and PCoA in 13.2% of the cases (14). The methodological differences between the two studies must be considered when analyzing these findings. The published study excluded patients with ipsilateral ICA stenosis greater than 50%, whereas we specifically included patients with contralateral ICA occlusion and severe ipsilateral stenosis ≥70%. This difference in inclusion criteria most likely accounts for the variations in collateral distribution and rates observed between the two studies. In our cohort, the higher hemodynamic burden caused by severe ipsilateral stenosis most likely promoted the recruitment of multiple collateral pathways, particularly the combined utilization of ACoA and PCoA, which we observed in 57.1% of the cases. In contrast, the exclusion of patients with significant ipsilateral stenosis in the published study may explain the lower prevalence of multi-pathway collaterals and, the relatively higher proportion of single-pathway collateral flow. Our findings underscore the critical impact of the severity of ipsilateral stenosis on the development and recruitment of cerebral collateral circulation in patients with contralateral ICA occlusion. The greater demand for alternative perfusion routes in the setting of advanced stenosis likely drives the activation of more extensive collateral pathways. Further studies involving larger patient populations with standardized inclusion criteria are required for a more thorough understanding of the impact of stenosis severity on collateral flow patterns and their clinical implications.

Previous studies have reported periprocedural complication rates of 3.6% in a cohort of 416 patients undergoing CAS over a 10-year period and 3.95% in a group of 152 high-risk patients (15,16). We observed a periprocedural complication rate of 9.5% (n=2), in the current study, which is notably higher than previous reports. This discrepancy may be attributed to the relatively smaller size of the sample in our study, as a limited number of patients can amplify the impact of individual complications.

Cerebral hyperperfusion syndrome (CHS) presents with a spectrum of clinical symptoms resulting from cerebral damage caused by vasogenic edema or intracerebral hemorrhage. Given its non-specific and variable presentation, CHS can be easily misdiagnosed, potentially leading to a life-threatening progression of the condition. Headache has been identified as the most common presenting symptom in CAS, and is reported in approximately 35% of all cases (17). However, it is noteworthy that nearly two-thirds of the patients do not report a prior history of headache, indicating that the absence of headache is not sufficient to exclude CHS (17). The underlying pathophysiology of CHS is not yet fully understood, but is thought to involve a combination of elevated cerebral blood flow and associated clinical symptoms. Pre-perioperative blood pressure control is essential to reduce the risk of CHS (18). A meta-analysis involving 8,731 patients undergoing CAS reported an overall incidence of CHS at 4.6%, aligning with findings of the current study where 4.8% (n=1) of patients developed CHS (17). In previous studies, patients with and without CCO exhibited no differences in the occurrence of in-hospital composite events, such as non-fatal myocardial infarction and stroke, after CAS, corroborating the findings of the current study (19,20).

Previous studies with longer follow-up durations (56 months and 4 years) reported stroke rates of 3.7% to 5.3%, myocardial infarction rates of 9.3% to 15.4%, and mortality rates of 22.2% to 31.4% (21,22). We observed a lower rate of such events, although the median follow-up period in the current study was also shorter at 24 months. We observed mortality in 14.3% of the patients in the occlusion (study) group and 9.5% of the patients in the control group. MI was observed in 4.8% of the patients in each group, and no ischemic cerebrovascular events were recorded in either group. The lower incidence in our findings may be attributed to the shorter follow-up period, highlighting the need for extended follow-up to better evaluate long-term outcomes in this patient population.

The findings of this study indicate that CAS may be a viable treatment option for patients with CCO, especially those at high risk for CEA. Although no significant differences were observed in complications or short- to mid-term outcomes between patients with and without CCO, these results should be interpreted cautiously due to certain

limitations. Contralateral occlusion may not necessarily be a contraindication for CAS if thorough pre-procedural planning and careful intra-procedural techniques are applied. Additionally, the assessment of collateral flow during the planning phase may help identify patients who could benefit most from CAS.

Study Limitations

The primary strength of the current study lies in its matched cohort design, which minimizes potential confounders and enhances the validity of all comparisons between the CCO and control groups. Additionally, the inclusion of long-term follow-up data provides valuable insights into the durability of CAS outcomes in these populations. However, the study is subject to certain limitations, most notably the inherent biases resulting from its retrospective design and the sample size, which limits the generalizability of the findings. Furthermore, the single-center design may not fully account for variations in procedural techniques, operator expertise, or experience of the interventionalist across different institutions. Additionally, differences in stent type and design, as well as patient age, may have influenced the outcomes of CAS and should be considered among the study's limitations. Moreover, the absence of a CEA or medical management control group limits direct comparison of outcomes across different treatment strategies, which could provide further clinical insight.

Conclusion

This study indicates that CAS may be a safe and viable treatment option for patients with CCO, with outcomes comparable to those without CCO. While these findings contribute to the growing body of evidence, they should be interpreted cautiously due to certain limitations. Further research with larger patient groups and extended follow-up is needed to validate these results and better define the role of CAS in this population.

Ethics

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (approval number: 2024-72). The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of in 2000.

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

Footnotes

Authorship Contributions

Concept: M.C., M.F.A., Ç.E., T.G., Design: M.C., A.D., O.T., T.G., Data Collection or Processing: M.B., Ç.E., O.T., Analysis or Interpretation: M.B., A.D., M.F.A., O.T., Literature Search: M.C., M.B., Ç.E., Writing: M.C., A.D., M.F.A., T.G.

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

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REVIEW

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Anesthesia and Drug Addicted Patients

Uyuşturucu Madde Kullanan Hastalarda Anestezi

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Abstract

In recent years, drug use has been increasing worldwide and in our country. This article aimed to raise awareness about the difficulties that clinicians may encounter in patients with substance addiction during anesthesia and the management of these difficulties. Drug use has short-term and long-term effects on all organs and systems. In addition, these substances interact with many drugs and can lead to unpredictable results. This situation is more complicated for anesthesiologists; many drugs from the barbiturate, narcotic, and hypnotic groups are used to provide amnesia, analgesia, and anesthesia, which are the basis of anesthesia practice. Patients who are addicted to drugs usually hesitate to share their substance use information with the clinician in the preoperative period. As a result, different clinical states occur due to possible drug interactions. Inferences about substance use are made by evaluating the clinical status of drug interactions in patients who underwent anesthesia without information about substance addiction. In patients with learned substance addiction; in order to prevent unexpected effects, it is necessary to know the interactions of the substance used with anesthetic drugs. In patients with drug addiction, it is important for clinicians to understand the interactions of anesthetic drugs with these substances. As a result; patients who use drugs are now more frequently encountered in anesthesia practice. Understanding the current drugs and their effects on the body may provide advantages in the follow-up and treatment of patients.

Keywords: Anesthesiology, anesthetic effects, cocaine, drug abuse, drug addiction, drug dependence, hallucinogens, LSD, methamphetamine

Öz

Son yıllarda, dünyada ve ülkemizde uyuşturucu madde kullanımı giderek artmaktadır. Bu yazıda, anestezi uygulamasında madde bağımlılığı olan hastalarda klinisyenin karşılaşabileceği zorluklar ve bu zorlukların yönetimi hakkında bir farkındalık yaratılması amaçlandı. Uyuşturucu madde kullanımının tüm organ ve sistemlere kısa ve uzun dönemde etkileri bulunmaktadır. Ayrıca bu maddeler birçok ilaçla etkileşmekte ve öngörülemeyen sonuçlara sebep olabilmektedir. Anestezistler için bu durum daha karmaşıktır; anestezi pratiğinin temeli olan amnezi, analjezi ve anesteziyi sağlamak için barbitürat, narkotik ve hipnotik grubu birçok ilaç kullanılmaktadır. Madde bağımlısı olan hastalar genellikle preoperatif dönemde madde kullanımı bilgisini klinisyenle paylaşmaktan çekinmektedir. Bunun sonucunda karşılaşılabilen ilaç etkileşimleri nedeni ile farklı klinik tablolar oluşmaktadır. Madde bağımlılığı hakkında bilgi sahibi olunmadan anestezi uygulaması yapılan hastada oluşan ilaç etkileşimleri ile oluşan klinik tablo değerlendirilerek madde kullanımı hakkında çıkarım yapılmaktadır. Madde bağımlılığı öğrenilen hastalarda ise; beklenmeyen etkilerin önlenmesi amacıyla kullanılan maddenin anestezik ilaçlarla etkileşimlerinin bilinmesi gerekmektedir. Uyuşturucu bağımlısı olan hastalarda anestezi yönetimi, anestezik ilaçların bu maddelerle etkileşimlerinin bilinmesi önemlidir. Sonuç olarak; günümüzde uyuşturucu madde kullanan hastalarla anestezi pratiğinde daha sık karşılaşılmaktadır. Güncel uyuşturucu maddeleri ve bu maddelerin vücuttaki etkilerini bilmek, hastaların takip ve tedavilerinde avantaj sağlayabilir.

Anahtar kelimeler: Anestezik etkiler, anesteziyoloji, halusinojenler, kokain, LSD, madde bağımlılığı, metamfetamin, uyuşturucu bağımlılığı

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Introduction

In recent years, drug use and its variety have been increasing. For this reason, the importance of knowing the effects of drugs on the systems and the points to be considered in anesthesia applications has increased in the follow-up of patients with drug addiction. Patients who use drugs often hide the drug they are addicted to, which puts anesthetists in a difficult situation and causes them to face various complications during the preoperative, intraoperative, and postoperative periods. Therefore, knowing the narcotic substances and the effects of these substances on the body in anesthesia applications will be advantageous for clinicians during follow-up and treatment of patients. This article aimed to raise awareness about the difficulties that clinicians may encounter in patients with substance addiction detected during anesthesia evaluation and the management of these difficulties.

Narcotic substances or drugs are chemical compounds and drugs that have pleasurable, calming, or stimulating effects and create a constant desire for higher doses, leading to withdrawal symptoms when discontinued (1).

Substance/drug addiction, on the other hand, is the state of not being able to overcome the constant desire to use the substance, even though its harmful effects are known.

Narcotic drug users experience relaxation and euphoria after drug use. Effects such as pleasure, satisfaction, a feeling of power, forgetting one's problems, and the disappearance of sexual problems make it difficult for the individual to quit the drug (2).

When the effect of the drug wears off, a feeling of hopelessness, unhappiness, loneliness, and guilt starts to take over. The other potential harms of narcotic drugs to the body are as follows (3-5):

- Psychological
  - Detachment from the social environment, inability to do work, reluctance, introversion, loneliness, apathy, excessive excitement, selfishness, loss of appetite, confidence, temperament changes, increased suicidal tendencies
- Central nervous system
  - Memory loss, insomnia, speech disorders, inappropriate behavior, decreased intelligence, and hallucinations consisting of sound and light.
- Digestive system
  - Nausea, vomiting, abdominal pain, diarrhea, constipation, stomach and bowel spasms
- Kidney and liver
  - Kidney and liver dysfunctions or failure
- Musculoskeletal system
  - Septic arthritis, rhabdomyolysis, osteomyelitis, and abscess
- Eyes
  - The drug user may feel discomfort with light, and night blindness may occur.
- Respiratory system
  - Shortness of breath and cough
- The use of common syringes or poor hygiene
  - Acquired immune deficiency syndrome (AIDS), hepatitis B and C infections.

Approach to Anesthesia

There are many narcotic drugs that we do not encounter in practical applications. We should be aware of the effects of these drugs even if we do not use them in practice. As anesthesiologists, it is important for us to have a thorough understanding of both narcotic drugs and their effects on the body. This knowledge will facilitate our management of patients during preoperative, postoperative, and emergency situations for those who use these drugs. Patients who use narcotic substances usually do not share this information with physicians during preoperative evaluation, which leaves physicians with various complications of these substances during the intraoperative period. The feeling of trust that can be established with the patient during the preoperative evaluation can encourage the patient to share information about their addiction.

Knowing the substance used by the patient will save the anesthesiologists time and enable them to take appropriate precautions against complications. These complications may be directly related to the effects of the substance or may be caused by the conditions of the addicts themselves. AIDS, hepatitis B, and C-like diseases can be observed among intravenous drug abusers, as well as local abscess formation and infective endocarditis. Tuberculosis-like infections are more common among malnourished addicts because of their relatively weak immune systems (3,5).

In addition to the type of surgical intervention to be performed in substance addicts, a detailed physical examination and necessary examinations for differential diagnosis should be requested. Electrocardiogram, posteroanterior chest X-ray, blood tests for liver enzymes, creatinine, creatinine kinase, and troponin are among those.

Venous thrombosis is common in intravenous substance addicts (6). In chronic drug addicts, inhalation anesthesia can be used as the method for anesthetic induction because it is difficult to find vascular access due to thrombosis. The use of a central venous catheter may also be another reason for preference. Because these patients may potentially abuse the central venous catheter, its removal at the end of the operation should be carefully considered.

Various additives are added to narcotic substances to increase their production, reduce their cost, and thus increase their profit. Cocaine is mixed with lidocaine to take advantage of its similar effect on the nasal mucosa. Due to the addition of talcum powder as a cost-cutting additive, ventilation perfusion incompatibility and pulmonary hypertension can occur in the lungs (7).

Sedative substances reduce the minimum alveolar concentration (MAC) of inhaled anesthetics, whereas stimulant substances have the opposite effect (3). MAC adjustment should be made taking into account the substance used by the patient. Risk of substance abuse should be considered in patients who require intravenous and inhalational anesthetic drugs.

Cocaine causes coronary vasospasms and increases cardiac oxygen demand (8). Cocaine addiction should be investigated in young patients with chest pain.

Ecstasy is a serotonergic substance. Other sympathomimetic drugs should be avoided in such patients. Serotonin can cause severe serotonin syndrome. Death may occur as a result of rhabdomyolysis, hyperthermia, and dehydration (9). Thus, dandrolene and cooling measures should be prepared. In these patients, dehydration and excessive water consumption may cause hyponatremia. Cerebral edema and death may occur due to rapid changes in blood sodium levels. Because of its quick impact, sodium levels can be quickly restored to normal using hypertonic saline solutions (10).

Withdrawal syndrome may occur due to preoperative withdrawal from drugs such as heroin, alcohol, and tobacco. In the babies of addicted pregnant women, withdrawal syndrome-like effects can be observed at rates as high as 60% at birth. Milder symptoms are observed in alcohol and tobacco addicts. These symptoms can include a variety of symptoms, such as a strong desire for a particular substance, anxiety, depression, insomnia, agitation, tendency toward violence, hallucinations, tachycardia, hypertension, sweating, nausea, vomiting, abdominal pain, and diarrhea. Symptoms regress with preintake of the substance (11-13).

It should be remembered that there may be adjustment disorders in patients with substance abuse scheduled for local anesthesia, and caution should be exercised during the procedure.

Choosing patient-controlled analgesia for postoperative analgesia can prevent pain-related agitation and reduce the possibility of withdrawal syndrome.

Due to late complications and withdrawal syndrome that may occur in the postoperative period, patients should be transferred to postoperative care units (PACU) or intensive care units where follow-up and treatment can be carried out by monitoring.

Below, we will provide some information about frequently used narcotic drugs, their effects on the body, and the issues that should be considered by anesthesiologists.

Classification of Narcotic Substances

- **Narcotics**
  - Morphine
  - Heroin
  - Methadone
  - Codeine
- **Stimulants**
  - Amphetamines
  - Cocaine
  - Caffeine
  - Nicotine
- **Depressants**
  - Barbiturates
  - Alcohol
  - Methaqualone
  - Meprobamate
  - Diazepam
  - Chlordiazepoxide
- **Hallucinogens**
  - Marijuana

Lysergic acid diethylamide (LSD)

Phencyclidine

Ecstasy

- **Solvents**

  Thinners and alike

Lately, the increasing use of narcotics and the variety of narcotic substances have gained attention regarding the effects of substances on organ systems and the issues that we need to pay attention to in our anesthesia applications for drug addicts. Here we will talk about the drugs that we often encounter and their effects.

Marijuana and Cannabis

Marijuana, as commonly called, is a plant and drugs that are made from that plant that induce intoxication and pleasure among the users (Figures 1, 2). Other names include "weed," "joint," "rip," "powder," "geezer," and "hemp". It is the most common narcotic substance found worldwide and in our country as well (14,15). Cannabis is prepared from the flowering bud area, leaves, and stems of the marijuana plant in powder or liquid form. The active ingredient is "tetrahydrocannabinol".

For medical purposes, cannabis can be used during chemotherapy or radiotherapy sessions for psychiatric diseases, neurological diseases, AIDS, and various eating disorders (16).

The use of marijuana in low doses induces sympathetic activation. Its parasympathetic effect decreases. Heart rate and cardiac output increase (17). The effect of the anesthetic agent is potentiated. Drugs that increase heart rate, such as ketamine, pancuronium, atropine, and epinephrine, should be avoided. Strong inhalation agents can also cause deep myocardial depression if used. The use of moderate- and high doses cause a sympathetic block. There is no parasympathetic effect. It can perform relative parasympathetic dominance. It may cause bradycardia and hypotension. It can also cause supraventricular or ventricular arrhythmias. ST segment and T-wave abnormalities can be observed (3,8).

Cross-tolerance may develop between marijuana and alcohol, barbiturates, opioids, benzodiazepines, and phenothiazines (3). When used in the form of inhalation, upper airway irritation, lung epithelial dysfunction, bronchial damage, chronic cough, bronchitis, emphysema, and bronchospasm can be observed. It should be considered that oropharyngitis and acute upper airway edema may occur in patients undergoing general anesthesia. The use of prophylactic dexamethasone may be beneficial in such patients (18).

Although it has no proven teratogenic effects among pregnant women, in cases of chronic use, it may cause uteroplacental circulatory disorders, intrauterine growth

Figure 1. Marijuana plant. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

Figure 2. Indian hemp plant and powdered version. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

retardation, low neonatal birth weight, and mental retardation (19).

Cocaine

Cocaine is an alkaloid extracted from the leaves of the Erythroxylum coca plant (Figure 3). In the 1100s, the Incas used their cocaine-filled saliva as local anesthesia in their trepanation (drilling a hole in the skull) rituals.

It was first isolated from coca leaves in Germany in 1859 by Albert Niemann. Its use in surgery was realized by William Steaward Halsted in 1880. In 1884, it was used as a local anesthetic for eye operations. Then, it was put on the market by pharmaceutical companies for medical use in the treatment of toothaches (Figure 4). It was allowed to be used for recreational purposes in the United States until it was restricted by medical authorities in 1914. It has no medical use as of today (20).

Due to its low molecular weight and high lipid solubility, cocaine diffuses easily between lipid membranes. Because it cannot be metabolized, its damage is permanent. A type of enzyme that metabolizes cocaine is present in bacteria that live in the vicinity of cocaine source plants that use cocaine as its only source of carbon and nitrogen. Cocaine esterase is only slightly stable at body temperature. Derivatives have been produced that have been modified to remain stable at body temperature (21-23).

It has stimulating and addictive properties in the central nervous system. It prevents the reuptake of dopamine, norepinephrine, and serotonin. Severe hypertension may occur during laryngoscopy. To reduce this complication, nitroprusside, nitroglycerin, and calcium channel blockers, hydralazine, can be used. Because esmolol and similar β-blockers increase cocaine-induced coronary vasoconstriction, the use of β-blockers such as propranolol, is contraindicated (21). Hypertension, hypotension, and arrhythmias may be observed among cocaine users during general anesthesia (24). Cocaine-associated myocardial ischemia is due to coronary artery vasoconstriction and/or increased platelet aggregation leading to thrombus formation. For prevention, phentolamines, nitroglycerin, verapamil, benzodiazepines, thrombolytic therapy, and aspirin can be used (25).

Platelet count changes associated with cocaine use may be associated with platelet activation due to vasospasm and autoimmune response. These factors may cause thrombus formation (3). Even after a long period of non-use of cocaine, its negative effects on the cardiovascular system persist. Cocaine use is an important cardiac risk factor.

Infections (tuberculosis, AIDS, *Staphylococcus aereus*), aspiration pneumonia, lung abscess, septic embolism, pulmonary edema, barotrauma, pneumonic lung infiltrates, vasculitis, pulmonary infarction, pulmonary hypertension, and gas exchange disorders may occur in the respiratory system due to cocaine use (26).

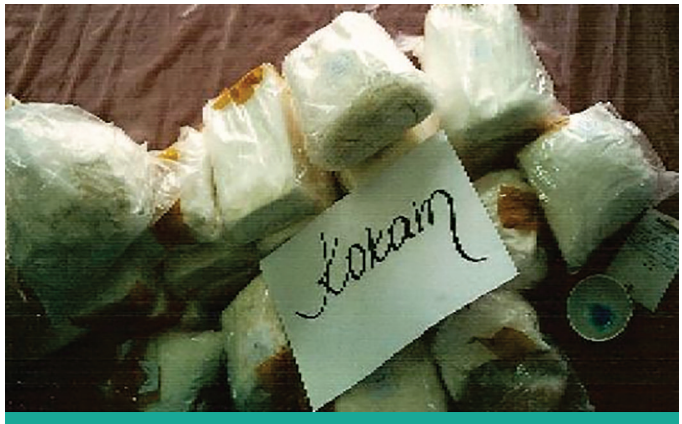

Figure 3. Sample of cocaine in powder form. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

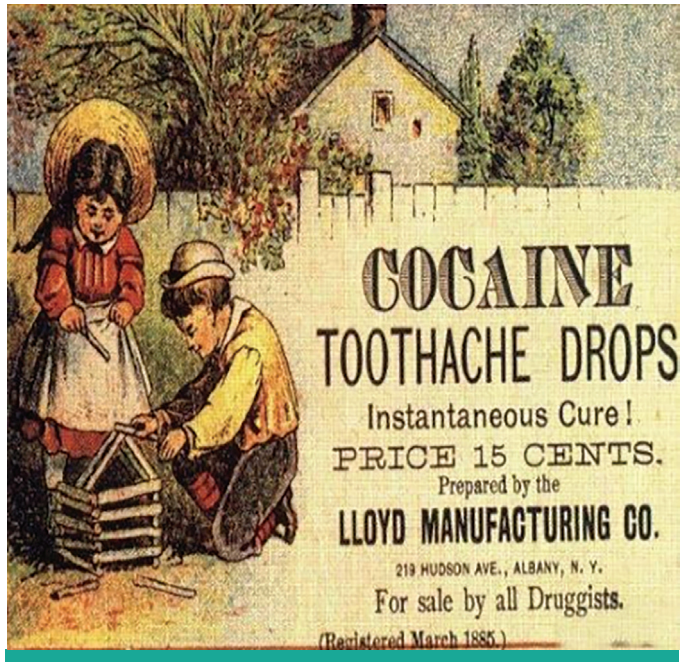

Figure 4. Cocaine drip advertisement aimed at reducing toothache. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

Acute renal failure may also develop due to vasospasm induced by cocaine or rhabdomyolysis (27).

Emergency childbirth is seen 4 times more among patients using cocaine (3). The negative effects of cocaine on the cardiovascular system increase over time. Increased oxygen demand and limited or decreased oxygen delivery are observed due to increased heart rate, blood pressure, and left ventricular contraction. As a result of decreased uteroplacental blood flow after rapid uteroplacental diffusion, uteroplacental insufficiency, acidosis, and hypoxia may occur. As a result of these effects, placental separation, premature birth, hypertension, and death in the womb can occur. Chronic cocaine addiction can cause permanent biochemical and functional changes in the fetus (28).

Changes in pain perception and aggressive behaviors may be encountered among cocaine addicts under local anesthesia because of changes in μ and K opioid receptor density and abnormal endorphin levels (29).

Ketamine should be used with caution or not used at all, as it can stimulate the central nervous system and amplify cardiac effects.

Amphetamine-methamphetamine (alpha-methylphenethylamine)

They are sympathomimetic substances of a synthetic nature and are most commonly found in oral intake form. When methamphetamine use is evaluated globally, it is seen that its use has spread and seriously threatens global health (30). In the 1930s, they were used medically to improve physical and mental performance (31). Due to their use in the treatment of attention-deficiency disorder and hyperactivity disorder, they are substances that are easy to access illegally. They are frequently used as stimulants among long-haul drivers, athletes, and students. As a result of its long-term use, people may develop physical and psychological dependence. In pregnant women, hypertension and proteinuria, which may be accompanied by epilepsy-like seizures, may result from acute intake of amphetamine (32). This condition can be confused with pre-eclampsia or eclampsia.

Ecstasy

Its chemical name is 3,4-methylenedioxy-N-methylamphetamine (MDMA). It is similar to both stimulants (amphetamines) and hallucinogens. MDMA was developed in 1912 by a German pharmaceutical company with the purpose of creating a hemostatic drug. It was first reported as a narcotic by the Drug Enforcement Administration in 1985 (33). Tablet or capsule forms are available (Figure 5). It is an effective serotonergic agent. Its effect starts 20-60 minutes after intake and lasts for an average of 4-6 hours. This period can last up to several days. It can cause increased mobility, interest in the opposite sex, increased energy, confidence, and perception changes in users. The side effects of ecstasy include increased blood pressure, tachycardia, intravascular coagulopathy, liver failure, impaired coordination, and fluid and electrolyte disruption. Sudden death may also develop because of the added substances. When used at high doses, it can trigger malignant hyperthermia. Severe hyponatremia and cerebral edema may occur due to excessive sweating and increased water consumption (9).

Opioids

The attractive features of this type of substance are its analgesic and euphoric effects. Rapid tolerance to these substances develops quickly. With the ever-increasing use of drugs, physical dependence, psychological dependence, and acute withdrawal syndrome may develop. During acute withdrawal syndrome, various symptoms, such as restlessness, insomnia, tachycardia, tachypnea, and hypertension, may be observed (9). These substances can be taken orally, subcutaneously, or intravenously (Figure 6).

Morphine, codeine, meperidine, fentanyl, methadone, and heroin are some of the opioids that are commonly

Figure 5. Various samples of ecstasy. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

abused. Morphine is the most well-known among them. It is produced from opium. Heroin, also known as diamorphine, is a semi-synthetic opiate alkaloid produced from morphine (34).

It is a substance with a very high addictive potential. Even a single intake over a short period is enough to experience severe withdrawal syndrome. The metabolite of heroin crosses the blood–brain barrier faster than morphine. Pain tolerance may decrease because of decreased endogenous opioid production. These patients may experience exaggerated pain after surgery. Methadone is a synthetic opioid that prevents effects such as euphoria and depression in acute withdrawal syndrome. Reduced desire for the substance allows the addict to be re-introduced into society (35).

Opioid addicts should not receive opioid antagonists or agonist antagonists. They can manifest an acute withdrawal syndrome. Symptoms of acute withdrawal syndrome may emerge seconds after naloxone administration. Diphenhydramine, doxepin, and clonidine can relieve these symptoms (3).

Hemodynamic instability is observed in addicts. Vascular access can be difficult to establish. After acute opioid use, the MAC and required doses of anesthetics can decrease. However, after chronic opioid use, cross-tolerance to

Figure 6. Heroin hydrochloride, which was released to the market by the Bayer pharmaceutical company in the 1900s. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

antidepressants and barbiturates may develop. Propofol may be preferred because the thiopental dose may increase. In such patients, local anesthesia may be preferred for postoperative pain control. Hypotension and discitis may be more common in patients receiving local anesthesia than in normal patients.

Many diseases such as tetanus, botulism, human immunodeficiency virus (HIV)/AIDS, hepatitis B, hepatitis C, pneumonia, endocarditis, osteomyelitis, peptic ulcer, and skin infections can be diagnosed among heroin users. These diseases can occur due to the effects of the substance itself, poor hygiene conditions, and use of common syringes with other addicts. HIV is a neurotropic virus. In the presence of HIV-induced central nervous system infection, progressive demyelinating disease, and neurological deficits, local anesthesia may be contraindicated (36-39).

In substance users, due to malnutrition and decreased intravenous fluid, fluid replacement and drug dose adjustment may be required for patients under anesthesia.

Barbiturates

It has sedative and hypnotic effects as a central nervous system sedative. The first barbiturate was produced in Germany by Emil Fischer in 1902 (40). They can lead to physical and psychological dependence. They can cause personality disorders and brain damage.

Benzodiazepine

It is a central nervous system depressant. The first benzodiazepine chlordiazepoxide was discovered by chance in 1955. It was made available as diazepam in 1960 (41). It has sedative, hypnotic, anxiolytic, and anticonvulsant effects. Because they can cause anterograde amnesia, they can be used for sexual assault purposes (39).

Its effect starts within 30 minutes after intake. Reaches its peak level within 1-2 hours and its effects can last up to 10 hours. They potentiate the effects of alcohol and opioids. When taken together with these substances or in the presence of excessive use, they can cause death.

Hallucinogens

These substances cause visual and tactile sensations of living or inanimate objects that do not actually exist. LSD, phencyclidine, mescaline, ecstasy, and magic mushroom are the most well-known (Figures 7, 8). LSD was synthesized by Dr. Albert Hofmann in the late 1930s from ergotamine,

which is found in the fungus Claviceps purpurea (42). They can be found on the market in liquid, impregnated on paper, gel, powder, or powder forms. They are colorless, odorless, and tasteless.

The acute effects begin within 20 to 60 minutes of intake and can last up to 6-12 hours. They activate the sympathetic nervous system. They can cause hypertension and tachycardia, leading to increased body temperature. They can cause sudden mood swings. Users of such substances may suddenly start crying immediately after laughing. They can cause increased mobility, interest in the opposite sex, increased energy, confidence, and perception changes in users (43).

Figure 7. Various examples of hallucinogens used on the market. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

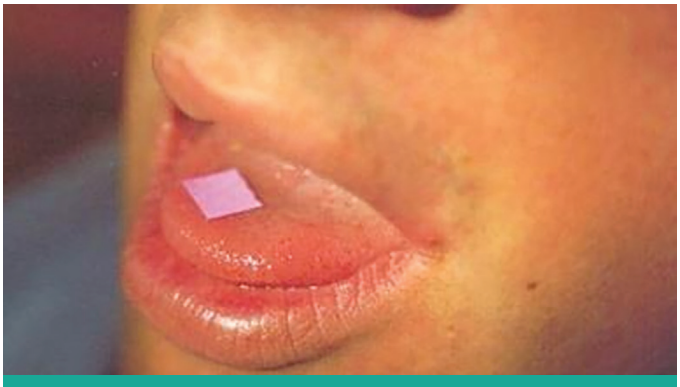

Figure 8. LSD (Lysergic acid diethylamide) sample. (quated from Salihoğlu Z, Anesthesiain the Drug-Using Patient. İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and ReanimationResidents' Traning Seminar 2013)

Anesthesia is extremely risky due to autonomic dysregulation, cardiomyopathy, large changes in blood pressure, and tachycardia caused by these substances. The risk of cerebral and coronary vasospasm is high. Arterial vasospasm, arrhythmia, myocardial ischemia, myocardial infarction, and non-hemorrhagic cerebral vascular events may be observed among users of these substances (44). Vasopressors such as ephedrine should be used with caution due to their exaggerated response to sympathomimetics.

Severe hyponatremia and cerebral edema may occur due to excessive water consumption by ecstasy users. Therefore, the fluid and electrolyte balances should be carefully evaluated. The reduced plasma cholinesterase activity prolongs the effect of succinylcholine. The effect of anesthetic substances metabolized in the liver and kidney may be prolonged due to fat accumulation in the liver and acute renal failure. Sudden death may also develop due to the presence of additives (45).

Solvents

Solvents are cheap, readily available, and legal substances that can affect the central nervous system. Thinner, acetone, household paints, glues, rubber, lighter gas, cement, and cleaning agents may contain solvents.

Dizziness, temporary euphoria, and hallucinations may be experienced after use. Due to its euphoria-inducing property and easy accessibility, it is used more frequently by adolescents. Cardiac arrhythmias, myocardial ischemia and infarction, blood pressure changes, bronchial damage, liver toxicity, methemoglobinemia, acute respiratory distress syndrome, pulmonary hypertension, acidosis, cerebral or pulmonary edema, and consequential death may occur in solvent abusers (46). Chronic use may cause permanent changes in the central nervous system. Degeneration and widespread brain atrophy are observed (47). Local anesthesia may be risky due to altered perception and aggressive behavior.

Bonsai

It is a synthetic drug. It is a psychoactive substance with marijuana-like effects. Bonsai, which was introduced for sale in 2004 as an alternative to marijuana, is also known as synthetic marijuana. Their effects may constantly change because their content is constantly changing to enable users to evade drug tests. More than 100 substances, including rat poisoning and fluorescent powder, were detected. The most common effects are dry mouth, tachycardia, hypertension,

heart attack, restlessness, impaired perception, vomiting, hallucinations, convulsions, paranoia and anxiety (48). The condition can cause sudden cardiac arrest (49).

Because tolerance develops rapidly, addiction can be formed within a short period of time. The fact that it is cheap and easily accessible has caused its widespread use, especially among adolescents.

In 2014, a study by Mutlu et al. (50) conducted on 1877 healthcare workers, titled "the perspective of healthcare workers about addiction", it was revealed that the most frequently used substance was cannabis (1%). Benzodiazepines, meperidine, and methylphenidate were the other preferred substances.

According to the 2021 Report of the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), which includes Turkey, 28.9% (83 million) of adults (aged 15-64) have used illicit drugs at least once in their lifetime. Substance use experience is more common among men (50.6 million) than among women (32.8 million). The most commonly experimented narcotic substance is cannabis. Opioids have been detected in 76% of fatal overdoses. 5.5% of new HIV diagnoses were attributed to intravenous drug use. The most commonly used stimulant is cocaine. The second stimulant that comes in second is amphetamine. 90% of the reported patients treated for methamphetamine addiction were citizens of Germany, Slovakia, Turkey, and the Czech Republic. Amphetamine-related deaths were reported by Germany (124), Finland (48), Slovakia (13), Austria (13), Czech Republic (12), and Turkey (55) in 2019. Deaths from synthetic cannabinoids continue to decrease in Turkey. In 2019, over 400 new psychoactive substances were found in the European drug market. In 2020, the EMCDDA monitored approximately 830 new psychoactive substances in Europe, of which 46 were reported for the first time (51).

Conclusion

As a result; due to the increasing variety of narcotics and their easier accessibility, the frequency of encounters between anesthesiologists and patients using narcotics is increasing. The interactions between addictive and anesthetic drugs can lead to critical clinical conditions in all organs and systems. In the coming years, with the development of technology, more varieties of synthetic narcotics will be on the market. More comprehensive studies on the interactions of new or commercially available addictive substances with various drugs. In addition; during the preoperative period in anesthesia practice, it is important to increase the awareness of anesthesiologists about addiction and to perform anamnesis without prejudice. In this way, both anesthesiologists will provide safer and easier perioperative patient care, follow-up, and treatment, and the patient will have a more comfortable perioperative process.

Ethics

Footnotes

Authorship Contributions

Concept: S.B.B., G.A., A.E., Y.Ö., K.E., Z.S., Design: S.B.B., G.A., A.E., Y.Ö., K.E., Z.S., Data Collection or Processing: S.B.B., G.A., A.E., Y.Ö., K.E., Z.S., Analysis or Interpretation: S.B.B., G.A., A.E., Y.Ö., K.E., Z.S., Literature Search: S.B.B., G.A., A.E., Y.Ö., K.E., Z.S., Writing: S.B.B., G.A., A.E., Y.Ö., K.E., Z.S.

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REVIEW

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Breastfeeding in Mothers with Chronic Illnesses

Kronik Hastalığı Olan Annelerde Emzirme

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Abstract

The growing number of women who wish to have children with chronic diseases has resulted in a lack of knowledge regarding the management of the process during breastfeeding. The difficulties experienced by mothers with chronic diseases during the breastfeeding period have a negative impact on the success of breastfeeding. If healthcare personnel adopt a proactive approach and are equipped to manage breastfeeding issues, it will facilitate the achievement of breastfeeding goals by mothers with chronic diseases. The aim of this systematic review is to evaluate the current literature on breastfeeding issues, experiences, medication use, and management in mothers with chronic disease.

Keywords: Breastfeeding, chronic diseases, mother

Öz

Kronik hastalıklara sahip çocuk sahibi olmak isteyen kadınların sayısındaki artış, emzirme dönemindeki sürecin yönetimine ilişkin bilgi eksikliğine yol açmıştır. Kronik hastalığı olan annelerin emzirme döneminde yaşadığı zorluklar, emzirmenin başarısını olumsuz etkilemektedir. Sağlık personelinin proaktif bir yaklaşım benimsemesi ve emzirme sorunlarını yönetebilecek donanıma sahip olması, kronik hastalığı olan annelerin emzirme hedeflerine ulaşmasını kolaylaştıracaktır. Bu sistematik derlemenin amacı, kronik hastalığı olan annelerde emzirme problemleri, deneyimleri, ilaç kullanımı ve yönetimi ile ilgili mevcut literatürü değerlendirmektir.

Anahtar kelimeler: Anne, emzirme, kronik hastalıklar

Introduction

Breast milk is a unique biofluid that contains all the nutrients necessary for the optimal growth and development of infants. The World Health Organization, UNICEF, and the American Academy of Pediatrics recommend initiating breastfeeding within the first hour after birth, exclusive breastfeeding for the first six months of life, and continuing breastfeeding for two years or longer (1,2). A meta-analysis of 14 studies found that children who were breastfed for at least six months experienced a lower incidence of obesity, diabetes, asthma, sudden infant death syndrome, otitis media, lower respiratory tract illnesses, and gastrointestinal infections (3,4). It is estimated that approximately 10-20% of pregnant women have one or more chronic diseases (5). Lack of information on medication use during pregnancy and postpartum leads women with chronic illnesses, such as lupus and polycystic ovary syndrome, to start formula feeding earlier and breastfeed for shorter periods (6). In this review, the management of breastfeeding in mothers with chronic diseases is discussed, focusing on the drugs and approaches that can be used during the relevant period.

Method

This review included original research articles (either observational or experimental), clinical guidelines, and systematic reviews published in English. The focus was

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on the breastfeeding experiences of mothers with chronic conditions. Case reports, conference abstracts and commentaries were excluded from the review. The term "breastfeeding" is defined as any method by which the infant consumes breast milk, including methods other than direct breastfeeding such as bottle-fed expressed breast milk. The search strategy was conducted using a keywords, including "chronic diseases", "mother", "breastfeeding", "woman", "diabetes mellitus", "multiple sclerosis", "myasthenia gravis", "rheumatic diseases", "bipolar disorder", "attention deficit hyperactivity disorder", "depression", and "autism spectrum disorder", across databases, including PubMed, Google Scholar, and Scopus. Furthermore, manual search strategies were employed including the scanning of reference lists and cited articles within each database. The search is limited to publications published between January 2014 and March 2024. The review included 36 original research articles, along with 25 systematic reviews, 2 meta-analysis reviews, and 3 guidelines (note: There is a numerical inconsistency in the original input; please verify for accuracy). Articles were extracted by one author and verified by a second, and discrepancies were resolved by discussion and consensus.

Diabetes

Diabetes is one of the most prevalent chronic diseases among pregnant women and mothers (7). Among women who were not previously diagnosed with diabetes, 6% developed gestational diabetes mellitus (GDM), which was first diagnosed during pregnancy and is characterised by glucose intolerance (8). GDM alters maternal metabolism, gut flora, and placental structure, leading to changes in breast milk composition, including immune factors, proteins, lipids, hormones, and nutrients (9). The colostrum of mothers with GDM has a higher concentration of human milk oligosaccharides, which promote growth, support intestinal microbiota balance, strengthen the immune system, and reduce infection rates (10). Some studies have found that women with GDM are generally less likely to initiate and continue breastfeeding than non-diabetic mothers (11). One-third of mothers with GDM experience delayed stage 2 lactogenesis due to obesity, insulin resistance, and inadequate support; this constitutes the most significant barrier to successful breastfeeding (12). However, recent studies comparing mothers with GDM who manage their condition through diet with those who use medication have shown no difference in breastfeeding rates at hospital discharge and three months postpartum (13). It is therefore important to provide support to these mothers from the pregnancy period onward in order to initiate and sustain breastfeeding (14). Infants of mothers with GDM are at an increased risk of complications, including hypoglycaemia, preeclampsia, preterm birth, fetal macrosomia, polyhydramnios, shoulder dystocia, caesarean delivery, neonatal respiratory distress, and delayed lactogenesis II. These complications frequently result in the separation of the mother-infant pair, leading to the initiation of formula supplementation and a reduction in breastfeeding duration. In such cases, it is recommended that mothers express and store breast milk during the final weeks of pregnancy for use postpartum (15). In the management of GDM, oral hypoglycaemic agents and insulin are employed to regulate glucose levels. Insulin, a large molecule that is not expected to pass into breast milk through diffusion, is considered to be compatible with breastfeeding. Glyburide is an oral hypoglycaemic agent used in the treatment of GDM and pregestational type 2 diabetes. It is a low-molecular-weight compound that is not expected to pass into breast milk through diffusion, rendering it compatible with breastfeeding. Nevertheless, infants should be monitored for hypoglycaemic symptoms (16). Metformin, which reduces insulin resistance, is considered safe during lactation. However, caution should be exercised in premature infants or infants with impaired kidney function (17).

Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune inflammatory disease characterised by the formation of sclerotic plaques in the central nervous system, leading to neuronal demyelination and damage. Approximately two-thirds of all MS cases occur in women of childbearing age. Given that many women diagnosed with MS may still desire to have children at the time of diagnosis, it is crucial to engage in a proactive discussion of the impact of treatment options on pregnancy and breastfeeding. In general, there is a reduction in the risk of relapse during pregnancy in MS. However, an increase in the risk of relapse is observed following childbirth (18). The following medications were employed: interferon beta (IFN-B), glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, cladribine, monoclonal antibodies (natalizumab, ofatumumab, ocrelizumab, and alemtuzumab), and disease-modifying antirheumatic drugs (DMARDs) such as rituximab. It has been demonstrated that breastfeeding protects against relapse in women with MS following childbirth (19). It is reported that the rate of postpartum relapse in breastfeeding women is 37% lower than in women who do not breastfeed or give both breast

milk and formula after birth (20). The British Association of Neurology recommends encouraging breastfeeding of mothers with MS during the postpartum period. It was stated that if the disease relapses, methylprednisolone can be used, and breastfeeding can continue during this process. Among the medications used in MS treatment, glatiramer acetate, IFN-B, and natalizumab can be used during breastfeeding (21). Another study published in 2023 showed that ocrelizumab and ofatumumab are considered safe during breastfeeding and are present in very low concentrations in breast milk (22-24). Despite all of this, the available data on the use of monoclonal antibodies and DMARDs during pregnancy and breastfeeding is limited. Although the European Medicines Agency (EMA) asserts that IFN-B is safe during breastfeeding, the Food and Drug Administration has not provided reliable data for any medication (25). A case-by-case evaluation should be conducted. In conclusion, breastfeeding should be encouraged for mothers with MS, as it confers both physical and psychological benefits. Nevertheless, the potential effects of treatments administered during this process on the health of both the mother and the infant should be discussed with the family, and a joint decision should be made regarding the continuation of breastfeeding.

Myasthenia Gravis

Myasthenia Gravis (MG) is an autoimmune disease characterized by the formation of muscle antibodies against the acetylcholine receptor, MuSK, or LRP4 at the neuromuscular junction, resulting in weakness. Neonatal myasthenia occurs in 5-15% of babies born to mothers with MG. Weak sucking, swallowing difficulties, and hypotonia are observed in infants due to decreased muscle strength. The condition usually persists for several days or weeks before gradually improving lasting no more than three months. It is important to provide help and support regarding breastfeeding during this period (26). Many of the drugs used in the treatment of MG are compatible with breastfeeding. Pyridostigmine, low to moderate doses of corticosteroids, azathioprine, tacrolimus, cyclosporine, and their metabolites have very low concentrations in breast milk; therefore, they can be used during breastfeeding (27-30). Breastfeeding should be encouraged to mothers with MG (31). However, breastfeeding is not recommended for mothers with MG who use mycophenolate mofetil, methotrexate, and cyclophosphamide (32-34).

Rheumatic Diseases

Rheumatic Diseases (RDs), including systemic lupus erythematosus, inflammatory arthritis (rheumatoid, psoriatic, juvenile, spondyloarthropathies,), and other rare rheumatic diseases (vasculitis, scleroderma, and sarcoidosis), are frequently observed in women of reproductive age. The advent of more efficacious treatments for rheumatic diseases has enabled women to live longer and healthier lives, thereby enhancing their reproductive capacity (35).

A prospective study conducted in Norway involving women with lupus revealed that breastfeeding rates were 78% at 6 weeks postpartum, 54% at 6 months, and 30% at 12 months postpartum. The study observed that multiparous women breastfed for a longer duration than primiparous women, and that disease activity did not affect breastfeeding (36). Women with autoimmune RDs encounter difficulties in making informed decisions about infant feeding and long-term management due to a lack of information and support. Some women reported feeling pressured to breastfeed and expressed feelings of guilt when they were unable to breastfeed successfully or chose not to breastfeed. Consequently, it is imperative to implement targeted interventions to assist women with rheumatic diseases in their infant feeding decisions. These interventions should adopt a non-judgmental and person-centered approach, including the education of healthcare professionals (37). The 2023 guidelines published by the British Society for Rheumatology regarding the use of anti-rheumatic drugs during pregnancy and breastfeeding indicate that prednisolone, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, intravenous immunoglobulin, and anti-TNF drugs (infliximab, etanercept, adalimumab, certolizumab, and golimumab) are considered safe during breastfeeding. The safety of biological DMARDs (rituximab, IL-6 inhibitors, IL-1 inhibitors, abatacept, belimumab, IL-17 inhibitors, and IL-12/23 inhibitors) during breastfeeding is based on the limited evidence available (38).

Bipolar Disorder

The postpartum period represents a high-risk period for mothers with bipolar disorder, particularly during the initial month following delivery. This is due to an increased risk of developing psychosis (39). In a study published by the French Neuropsychopharmacology Society in 2023, mood stabilizers were classified using Hale's system for the safety of antipsychotic drugs during breastfeeding. This classification was based on the potential for adverse effects on the infant, with the drugs classified as L2 (safer) and L4 (possibly hazardous) in the risk assessment categories. Mood stabilisers, including carbamazepine, lamotrigine,

olanzapine, quetiapine, and risperidone which have been classified in the L2 group, have been the subject of limited studies in breastfeeding women. No evidence of adverse effects on breastfed infants has been reported in the literature (40-45). Studies concerning lithium and valproate, classified as L4, indicate a potential risk for breastfed infants. However, it is reported that breastfeeding can continue on a case-by-case basis, with the decision to continue breastfeeding (40,46,47). Lithium represents a first-line treatment option for postpartum psychosis. The excretion of lithium into breast milk and its concentration in the infant's serum are highly variable. However, it has been observed that lithium does not accumulate in the infant despite being excreted into breast milk (48). It is recommended that lithium serum levels in infants, thyroid function tests, and blood urea and creatinine values be monitored on the second day and first week postpartum. Furthermore, clinical follow-up should be continued in the first and second months postpartum (48). The lithium dosage may increase during pregnancy, so the mother's serum levels should be frequently monitored postpartum, and the dose adjusted to prevent excessive exposure to the baby through breast milk (49). Furthermore, it is important to monitor any changes in the infant's movements, including hypotonia, restlessness, or feeding difficulties (50). In conclusion, given the relatively high exposure of breastfed infants to lithium and the limited short- and long-term safety data, lithium should be considered in situations where alternative treatments are not available (51). For mothers with bipolar disorder, insomnia has been demonstrated to increase the risk of manic episodes, while four hours of uninterrupted sleep has been shown to reduce this risk. Therefore, feeding can be continued with expressed breast milk provided by another adult in order to ensure that the infant remains nourished with breast milk (52). It is of great importance that mothers in this patient group are followed carefully when breastfeeding is stopped. It has been postulated that an increase in dopaminergic discharge resulting from a reduction in prolactin and oxytocin levels may be a contributing factor in the onset of manic episodes (8).

Depresif Disorders

Depressive symptoms are a common occurrence during the postpartum period, with an estimated prevalence of 7-20% among mothers (53). Mothers diagnosed with depression prior to pregnancy who continued breastfeeding until the third month postpartum exhibited a reduction in depressive symptoms (54). Furthermore, maternal depression has been demonstrated to have a detrimental impact on the infant's microbiota. However, breastfeeding has also been shown to mitigate this effect (55). The French Neuropsychopharmacology Society has classified antidepressants that can be used during the postpartum period as L2 (safer) and L3 (moderately safe). Antidepressants classified as L2 included amitriptyline, citalopram, clomipramine, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine. A limited number of studies have been conducted on breastfeeding women, and no evidence of adverse effects on breastfed infants has been found (40). Among the drugs classified as L3, bupropion, duloxetine, esketamine, milnacipran, mirtazapine, and vortioxetine have been reported to cause mild side effects during the breastfeeding period (40). At present, there is no medication in the L1 category widely used by breastfeeding women that has shown any evidence of adverse effects on infants. In conclusion, a complex relationship between breastfeeding and maternal depression indicates that supporting the mental health of mothers during the peripartum period would enhance the likelihood of successful breastfeeding.

Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral disorder that affects 2-5% of adults. It has been documented that mothers with ADHD, due to their experiences of needing to focus their attention, may perceive breastfeeding as a challenging and complex process (56). It was demonstrated that the intention to breastfeed and the duration of breastfeeding were both negatively affected as a consequence (57). Dopaminergic, noradrenergic, and serotonergic drugs are employed to treat ADHD and are increasingly prescribed to women of childbearing age. The use of methylphenidate during breastfeeding is considered safe, as it is present at undetectable levels in breast milk, and no adverse effects on the infant have been reported (58). Nevertheless, amphetamine and clonidine are contraindicated during breastfeeding due to their high concentrations in breast milk, which can result in sleep disturbances, aggression, and seizures in breastfed infants (59). The use of atomoxetine, guanfacine, and modafinil during breastfeeding is not recommended due to a lack of data on their effects during this period (60,61).

Autism Spectrum Disorder

Autism is a neurodevelopmental condition that typically begins in childhood and is characterised by difficulties in verbal and non-verbal communication, restricted and

repetitive behaviours, and an altered perception of the world in terms of visual and sensory perception (62). A significant proportion of autistic mothers express a desire to breastfeed, yet breastfeeding rates are reported to be low due to a lack of adequate support from healthcare professionals and social networks, fatigue, disruption of routine, and sensory challenges such as intolerable sensations during breastfeeding, including "touch" and "pain" (63). In a study, it was stated that 10% of mothers with autism were uncomfortable with direct contact during the breastfeeding process; this led them to feed their babies with expressed milk. However, it has also been observed that when mothers receive breastfeeding support, their unpleasant feelings tend to decrease (64). On the other hand, it was found that some mothers with autism perceived the ritual of preparing formula milk as a source of peace of mind, which was the reason for their moderate approach to giving formula milk (65). Furthermore, healthcare professionals should be aware of the need to respect the privacy of autistic mothers and to obtain their permission before touching them. They should provide assistance to the mother without physical contact. Thus, continued collaboration between autistic mothers and healthcare professionals can ensure breastfeeding success (66).

Conclusion

The decision-making process of mothers with chronic diseases about breastfeeding is affected by many factors. It is necessary for these mothers to be informed about breastfeeding from the beginning of their pregnancy, to be provided with breastfeeding counseling after birth, and to have the mother-baby couple closely monitored. In this process, which is different for each mother, it will be effective for health professionals to know the risks that mothers with chronic diseases may experience, to support mothers' self-confidence, and to be informed about the effects of the medications used on breastfeeding. In addition, pediatricians should cooperate with doctors managing the mothers' chronic diseases to ensure that the health of both the mother and the baby is maintained during breastfeeding. Treatment plans for these mothers should be tailored and managed on an individual basis, taking into consideration the specific needs of each patient. As a result, since pediatricians play a critical role in managing the breastfeeding process of mothers with chronic diseases, their knowledge of this issue and their close monitoring of breastfeeding will positively affect the breastfeeding outcomes of mothers.

Ethics

Footnotes

Authorship Contributions

Concept: N.K., Design: N.K., Data Collection or Processing: I.Ç.H., Analysis or Interpretation: N.K., Literature Search: I.Ç.H., Writing: I.Ç.H.

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