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Determination of Optimum Imaging Numbers for ^{177}Lu-PSMA Radionuclide Treatment Dosimetric Calculation

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ABSTRACT

Introduction: Lutetium-177 (^{177}Lu) prostate-specific membrane antigen (PSMA) was first applied for treating castration-resistant prostate cancer (CRPC) in 2015, and PSA changes, low side effects, and good responses have been reported in the literature. Dosimetric calculations are required to determine the optimum number of treatments and prevent damage to critical organs. The aim of this study was to retrospectively investigate the feasibility of dosimetric calculations with fewer than four scans and to determine the most optimum imaging hours if dosimetric calculations can be performed with fewer than four scans.

Methods: Whole body and single-photon emission computed tomography/computed tomography scans (4th hour, 24th hour, 48th hour and 96th hour) were performed on the patients after ^{177}Lu-PSMA infusion. A comparison was made between doses calculated using four images, doses calculated using three images, and doses calculated using two images. The calculations were repeated with four images in nine configurations: 1st, 2nd, 3rd and 4th. Scan configurations were classified as C1-C9. C1 was accepted as the reference and evaluated statistically for significance research between other groups.

Results: For an amount of ^{177}Lu-PSMA activity of 3.7 GBq (100 mCi) per treatment, the mean kidney doses for C1, C2, C3, C4, C4, C5, C6, C7, C8, and C9 were calculated as 1.8±0.54 Gy, 1.83±0.57 Gy, 1.7±0.47 Gy, 1.91±0.57 Gy, 1.82±0.54 Gy, 1.59±0.47 Gy, 1.90±0.58 Gy, 1.82±0.57 Gy and 1.75±0.52 Gy, respectively. A significant difference was found in all groups among C2-C9 compared to C1.

Conclusion: Optimum dosimetric calculations for treating CRPC should be performed with C5 (three images taken at the 4th, 24th and 48th hours) after ^{177}Lu-PSMA injection. The error rate increases in calculations performed with a lower number of images.

Keywords: Castration-resistant prostate cancer, ^{177}Lu-PSMA, dosimetry, imaging time, imaging number

Introduction

Prostate cancer is one of the most common malignancies in the world and the third most common cause of cancer-related male death in the United States of America (USA) (1). Lutetium-177 (^{177}Lu) prostate-specific membrane antigen (PSMA) radioligand treatment has been applied in castration-resistant prostate cancer (CRPC) with high efficacy and low side effects (2-4). In line with these results, ^{177}Lu-PSMA treatment has been increasingly used. In radionuclide therapy, there are limiting organ radiation doses for treatment, depending on the retention and excretion mechanism of the radiopharmaceutical. The kidneys are among the most important radiation- limiting organs, especially in treatments performed through systemic circulation, called peptide receptor radionuclide therapy. The radiation-limiting organs for treating ^{177}Lu-PSMA are the kidneys, bone marrow, salivary glands, and lacrimal glands (5). Dosimetric calculation in radionuclide treatments is important to apply the therapeutic dose without damaging critical organs. Many dosimetry studies have suggested that dosimetric calculations should be performed for each patient individually after each treatment because the physiology of patients may differ (6,7). In addition, according to the European Atomic Energy Community guidelines, making dosimetric calculations for patients receiving radionuclide therapy have been required since February 2018 (8). The dosimetry formalism of Medical Internal Radiation Dose (MIRD), recommended in the dosimetry guidelines of the European Association of Nuclear Medicine, is used for dosimetric calculations in radionuclide treatments (5).

Accurate calculation of the activity in the organ is critical for the accuracy of the dosimetric calculation. For accurate dosimetric calculations in ^{177}Lu treatments, many scientific studies have been conducted and guidelines have been published (5,9-12). Factors affecting dosimetric accuracy include the calibration of the dose calibrator, determination of the calibration factor, imaging modality, attenuation correction, scatter correction, and imaging time (5,13). Current guidelines do not recommend specific time points but emphasize the need for imaging at different time points because of slow radiopharmaceutical excretion (5,9). Although dosimetric accuracy increases in direct proportion to the number of imaging scans after treatment, scientific studies have

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emphasized that dosimetric calculations should be performed by scanning at four different time points after treatment (14). Whole body (WB) and single photon emission tomography (SPECT)/computed tomography (CT) imaging for dosimetric calculation takes about 30 minutes. In clinics where treatment is frequent, this poses problems in terms of the number of patient views, patient comfort, and clinical density. Although obtaining the correct result of dosimetric calculations is the top priority for radionuclide treatments, applicability is also an important factor. Coming to the clinic for scanning emerges as a problem for both the patient and the clinic. Accordingly, dosimetric calculations for CRPC treatment dosimeters are usually performed with 4-5 images (15,16). In addition, recent scientific studies have declared that dosimetric calculations can be performed with one, two, and three images in CRPC treatments (17-19). However, it has been emphasized that as the number of scans decreases, the deviation also increases.

The aim of this study was to retrospectively investigate the feasibility of dosimetric calculations with fewer than four scans and to determine the most optimum imaging hours if dosimetric calculations can be performed with fewer than four scans.

Methods

The collection of human samples in this study was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (approval number: 2023/558, date: 06.04.2023).

^{177}Lu Radioisotope

The most commonly used radionuclide in CRPC fractional radionuclide treatments is ^{177}Lu. ^{177}Lu has a half-life of 6.64 days. The decayed ^{177}Lu turns into stable halfium-177 (^{177}Hf). During the decay of ^{177}Lu, while emitting beta particles with energy, which have an abundance of 78% ($E_{\beta max}$=497 keV), 9.8% ($E_{\beta max}$=384 keV), 12% ($E_{\beta max}$=176 keV), and 0.053% ($E_{\beta max}$=248 keV), it decays to ^{177}Hf, emitting photons at 6 different energies as well as two gamma rays with an abundance of 11% (208.4 keV) and 6.4%, 112.9 keV. While beta particles cause cancer cells to die, gamma photonsprovide imaging for dosimetric calculations.

Treatment Application

Clinical evaluations, biochemistry, and gallium-68 (^{68}Ga)-PSMA positron emission tomography/CT examinations of patients diagnosed with CRPC were performed. Patients with high ^{68}Ga-PSMA accumulation in tumor areas were considered suitable for radionuclide treatment and were treated. Patients received 7.55±0.3 GBq (204±8.34 mCi) ^{177}Lu-PSMA per treatment by intravenous infusion for 30 min. WB and SPECT/CT scans (4th, 24th, 48th, and 96th hours) were performed on patients after the infusion.

MIRD Formalism

Dosimetric calculations were performed using the MIRD method. In MIRD Formalism, Formula 1 is used to calculate the dose absorbed by the organs (20).

$$D_{Target \leftarrow Source} = \frac{k \times \tilde{A}_{Source} \sum_i n_i E_i \varphi_i}{m_i} \quad (1)$$

D: Dose absorbed in the target organ-gray (Gy)

Ã: Cumulative activity in a source organ-mega becquerel/second (MBq-s)

n: Ratio of radiation released at energy E per nuclear decay

E: Energy per radiation-mega electron volt (MeV)

ϕ: Absorption rate of the radiation energy released from the source at the target

m: Mass of the target organ (kg)

k: Proportion constant (Gy-kg/MBq-s-MeV)

For the isotopes of all radionuclides, the energy transferred from the source organ to the target organ was calculated using human-like phantoms, and nearby values called the S-factor were determined to calculate the dose absorbed by the target organ. After detecting the cumulative activity in the source organ, the dosage absorbed by the target organ is calculated using Formula 2 (20).

$$D_{Target \leftarrow Source} = S \times \tilde{A} \quad (2)$$

To determine the cumulative activity in the source organ, imaging is performed at different time points depending on the physical and biological half-life of the radionuclide. Based on the images acquired from the patient, the activity in the source organ was calculated. The cumulative activity in the source organ is calculated using Formula 3 for the activities in the source organs calculated at different time points.

$$\tilde{A} = \int_0^\infty A(t)dt \quad (3)$$

Imaging

The study included a total of 30 treatments of 30 patients (62±8 years) diagnosed with CRPC who received ^{177}Lu-PSMA treatment in our clinic. After each treatment, 4 images were analyzed (1st scanning: at 4th hour, 2nd scanning: at 24th hour, 3rd scanning: at 48th hour, and 4th scanning: at 96th hour), and a total of 120 images were analyzed. Imagines were performed using the General Electric brand Discovery NM/CT 670 model SPECT/CT (General Electric, Milwaukee, WI, USA) machine in our clinic. A Medium Energy General Purpose collimator was used for imaging. SPECT imaging was performed in the position in which the patient's abdomen and thorax region would enter the image field. SPECT imaging was performed with 360° imaging using a 128x128 matrix, 60 projections, and 20 s per projection parameter. In addition to the primary peak in the window range of 208 keV (±10%), the scattering peak in the window range of 178 keV (±5%) was used in the scatter correction process. An ordered-subset expectation maximization algorithm with 12 iterations, 5 subsets, and no postprocessing filter was used for image reconstruction. WB images were obtained at a scanning speed of 15 cm/min and with an energy window of 208 keV (±10%). From the acquired raw data, 3D scattering and reduction-corrected images were created.

Image Analysis

The software OXIRIX (Geneva, Switzerland) was used for image analysis. 3D volume of interest of organs holding activity were drawn from SPECT images, and organ counts were determined. For the rest of the body, counts were determined by drawing regions of interest from the

geometric means of the WB anterior and posterior images. The acquired counts were divided by the count/activity factor to determine the ^{177}Lu activities in the relevant organs and regions. These procedures were performed separately for the four post-treatment images of the patient.

Calculation of Organ Doses

Cumulative activities were calculated by entering the post-treatment organ activities and scan times using Formula 3. Radiation doses absorbed by the kidneys, liver, and WB were estimated using the calculated cumulative activities and Olinda/EXM 1.1 software. Calculations were repeated with four images in nine configurations as follows: 1., 2., 3., and 4. scans configuration 1 (C1); 2., 3., and 4. scans configuration 2 (C2); 1., 3., and 4. scans configuration 3 (C3); 1., 2., and 4. scans configuration 4 (C4); 1., 2., and 3. scan configuration 5 (C5); 1. and 4. scan configuration 6 (C6); 2. and 3. scan configuration 7 (C7); 2. and 4. scan configuration 8 (C8); and 3. and 4. scan configuration 9 (C9). The organ doses obtained were compared with the results of four imaging studies. A correlation test was performed between the values.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The pearson correlation test was used to analyze the relationship between C1 and C2-C9. The p-value was considered statistically significant when less than 0.05.

Results

For an amount of ^{177}Lu-PSMA activity of 3.7 GBq (100 mCi) per treatment, the mean kidney doses for C1, C2, C3, C4, C4, C5, C6, C7, C8, and C9 were calculated as 1.8±0.54 Gy, 1.83±0.57 Gy, 1.7±0.47 Gy, 1.91±0.57 Gy, 1.82±0.54 Gy, 1.59±0.47 Gy, 1.90±0.58 Gy, 1.82±0.57 Gy and 1.75±0.52 Gy, respectively. A significant difference was found in all groups among C2-C9 compared to C1. The kidney dose per 3.7 GBq (100 mCi) ^{177}Lu-PSMA calculated in different configurations for the kidneys is given in Table 1.

Table 1. Results of kidney doses per 3.7 GBq (100 mCi) ^{177}Lu-PSMA in different configurations (Gy)

Treatment no	C1	C2	C3	C4	C5	C6	C7	C8	C9
1	1.59	2.13	1.42	2.09	1.83	1.27	2.12	2.14	1.52
2	1.95	1.97	1.92	2.15	1.78	1.97	2.14	1.69	0.80
3	1.70	1.19	2.08	1.62	1.70	1.04	1.22	1.19	2.73
4	1.33	1.39	1.13	1.39	1.24	0.85	1.39	1.43	1.34
5	1.83	1.86	1.67	1.86	1.93	1.84	1.86	1.86	1.52
6	2.63	2.63	2.47	2.71	2.74	2.49	2.71	2.59	2.41
7	2.59	2.72	2.28	2.73	2.64	1.74	2.75	2.73	2.35
8	2.12	2.13	1.98	2.26	2.16	1.92	2.26	2.06	1.92
9	1.46	1.46	1.38	1.57	1.44	1.31	1.57	1.40	1.49
10	1.49	1.48	1.43	1.48	1.59	1.46	1.50	1.48	1.38
11	1.94	1.94	1.99	1.95	1.91	1.92	1.98	1.94	2.04
12	1.55	1.55	1.45	1.65	1.52	1.36	1.65	1.50	1.75
13	1.65	1.67	1.59	1.76	1.65	1.50	1.77	1.65	1.71
14	3.10	3.09	2.70	3.23	3.00	2.57	3.22	3.01	2.82
15	3.11	3.11	2.67	3.36	3.03	2.50	3.29	3.16	2.84
16	1.99	2.13	1.95	2.26	2.11	1.84	2.26	2.13	2.08
17	1.40	1.40	1.36	1.51	1.35	1.27	1.51	1.34	1.50
18	1.31	1.30	1.21	1.34	1.44	1.25	1.34	1.27	1.15
19	1.70	1.71	1.57	1.82	1.74	1.52	1.82	1.67	1.61
20	1.38	1.38	1.38	1.45	1.35	1.29	1.45	1.34	1.51
21	1.75	1.75	1.76	1.58	1.95	2.09	1.49	2.21	1.48
22	1.39	1.39	1.33	1.50	1.37	1.21	1.50	1.38	1.47
23	1.07	1.08	0.99	1.16	1.06	1.00	1.15	1.07	1.07
24	0.93	0.94	0.90	1.02	0.91	0.76	1.04	0.94	1.09
25	1.84	1.87	1.67	1.87	1.94	1.85	1.87	1.87	1.53
26	1.45	1.47	1.39	1.58	1.45	1.32	1.58	1.42	1.50
27	1.53	1.53	1.43	1.63	1.50	1.34	1.63	1.48	1.73
28	2.01	2.15	1.97	2.28	2.13	1.86	2.28	2.15	2.10
29	2.58	2.71	2.27	2.72	2.64	1.73	2.74	2.72	2.34
30	1.66	1.68	1.60	1.77	1.66	1.51	1.78	1.66	1.72
Average ± SD	1.80±0.54	1.83±0.57	1.70±0.47	1.91±0.57	1.82±0.54	1.59±0.47	1.90±0.58	1.82±0.57	1.75±0.52

^{177}Lu: Lutetium, PSMA: Prostate-specific membrane antigen, Gy: Gray, SD: Standard deviation

In addition to Table 1, the mean and standard deviations (SD) of the patients' liver and WB doses were calculated as follows:

For an amount of ^{177}Lu-PSMA activity of 3.7 GBq (100 mCi) per treatment, the mean liver doses for C1, C2, C3, C4, C4, C5, C6, C7, C8 and C9 were calculated as 0.3±0.13 Gy, 0.31±0.14 Gy, 0.35±0.23 Gy, 0.32±0.16 Gy, 0.3±0.13 Gy, 0.23±0.12 Gy, 0.32±0.15 Gy, 0.31±0.14 Gy and 0.36±0.12 Gy respectively.

For an amount of ^{177}Lu-PSMA activity of 3.7 GBq (100 mCi) per treatment, the mean WB doses for C1, C2, C3, C4, C4, C5, C6, C7, C8 and C9 were calculated as 0.1±0.04 Gy, 0.1±0.04 Gy, 0.11±0.06 Gy, 0.09±0.04 Gy, 0.09±0.05 Gy, 0.1±0.04 Gy, 0.1±0.05 Gy, 0.1±0.05 Gy and 0.12±0.04 Gy respectively.

According to the pearson correlation test between C1 and other configurations, the averages of kidneys, liver, and WB were calculated as 0.936±0.06, 0.895±0.20, 0.909±0.21, respectively.

Discussion

Kidney doses were one of the main limiting factors for the cumulative treatment of ^{177}Lu-PSMA radioligands. Thus, we aimed to determine optimum imaging times with minimum scans for accurate kidney doses and compared different time points. Briefly, we found that three time points could give accurate dosimetric results, but dosimetric calculation with two time points may result in inaccurate results. We observed significant differences in patient kidney doses, and these differences were at a level that would affect the number of patient treatments. Because there are differences that will affect patient treatment, it is important to perform patient-specific dosimetric calculations in treatments. There are some difficulties in performing dosimetric calculations. Considering the burden that patient screening brings to the clinic, as well as the general condition of the patient population, transferring the patient to the clinic also poses a significant problem. Although these reasons are problematic aspects of dosimetric calculations, it is important to perform dosimetric calculations in terms of patient treatment effectiveness and patient safety. Although having less data to be used in dosimetric calculations is beneficial in terms of patient comfort and clinical intensity, it is more important to make the correct calculation. Although it is every clinic's dream to make accurate dosimetric calculations with low scanning, decreasing data may cause problems in calculations. When determining cumulative activity, the more measurement points considered in creating thetime activity curve, the closer the result is to reality. Therefore, the values obtained from the four images (4th, 24th, 48th, and 96th hour after treatment) were evaluated and compared with the results of the dosimetric calculation using different time configurations.

When it comes to kidney doses, which stand out as the critical organ in radioligand treatment due to the excretion mechanism; it was observed that there was a correlation between C1 configuration dose values and all configurations ($p<0.05$). Considering these results, it is seen that accurate dosimetric calculations can be made with three images taken from the patients. In the calculations made using three images, the highest correlation was calculated using the C5 (4th, 24th and 48th hour images). In this group, a difference of >10% was calculated in 2 patients, a difference between 5% and 10% in 8 patients, and the remaining values were calculated as <5%, also when looking at the SD values, the lowest deviation value was observed in the C5 configuration (Table 2). After C5, the highest correlation was found to be with C4. The reason for this is that both configurations have early post-injection images. When looking at other configurations, it was observed that the SD values increased. When looking at the two-image configurations, C8 was seen to have the highest correlation (0.961) and lowest SD (0.027). The reason why the highest correlation was with C5 was interpreted as the change in activity in the kidneys within 24 h after treatment was applied (21). Because the excretion rate was considered infinite in the period following the peak of activity retention, it was thought that measurements taken at a later time did not significantly affect our results.

The excretions of pharmaceuticals used in neuroendocrine tumor and CRPC treatments are different. Although many studies have investigated the dosimetric accuracy in neuroendocrine tumor treatments with ^{177}Lu compounds, there are few studies with low patient data in CRPC treatments (17-19). Although there are articles stating that two images are sufficient for kidney dosimetry, there are studies showing that two images have a high deviation rate and are not sufficient for other organ and tumor dosimetry. In their study of 20 treatments of 10 patients, Peters et al. (17) investigated the optimum imaging number for kidney and tumor dosimetry. They suggested that dosimetric calculations could be performed with two images in the first 24 h and the 168th hour. In the study conducted by Resch et al. (18) with the treatment of five patients, they suggested that lesion dosimetry should be performed on the 1st, 3rd, and 7th days, and that the most optimum imaging for kidney dosimetry should be performed on the 1st, 2nd, and 3rd days.

In their study with 13 patient treatments and the virtual patient lesion they created, Rinscheid et al. (19) suggested that three images were required for optimal tumor dosimetry. It has been emphasized in all studies that error rates increase as the number of images decreases. In the study conducted by Gleisner et al. (22) with 7 patients, they made calculations using images taken 1, 24, 96 and 168 hours after radionuclide application in ^{177}Lu/^{177m}Lu-DOTATATE treatment and taken between 33-70 days (5 images in total). They reported that there were 5-6% differences in the tumor dose and WB dose calculations made

Table 2. Pearson correlation test results for kidney dose calculation configurations

Kidneys correlations									
		C2	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
C1	Pearson correlation	0.967**	0.967**	0.980**	0.986**	0.806**	0.949**	0.961**	0.874**
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	30	30	30	30	30	30	30	30

**: Correlation is significant at the 0.01 level (2-tailed)

with and without the late image (33-70 day image), but there was no difference in the kidney dose (22). In this study, it was emphasized that late imaging was unnecessary for kidney dose calculation, but dose calculations with fewer images were not considered. As stated in the study, the limited number of patients may pose a statistical problem.

The main purpose of our study was to determine whether we can obtain the most accurate radiation dose with the least amount of imaging. In the statistical analysis, it was determined that the post-treatment C1 configuration for kidney doses was highly correlated with the values of C7 and C8 configurations calculated from two images. The difference between the C1 and C8 configurations was >10% in 6 patients, 5-10% difference in 15 patients, and the remaining values were <5%. The difference between the C1 and C7 configurations was calculated as >10% in 4 patients, and the difference between 5% and 10% in 6 patients, and the remaining values were <5%. The average percentage difference between the C1 and C7 configurations was calculated to be 5.86% (8.82). Similar to our study, Maaß et al. (23), based on the results of their study with 15 patients, reported that kidney doses could be calculated with scans performed at the 4th and 48th h. Although it has been seen in both studies that dosimetric calculations can be made using two images, there are differences between the scanning times of the studies. While their patient group comprised patients who received ^{111}In-labeled-diethylenetriaminopentaacetic acid-octreotide for the treatment of neuroendocrine tumors, our patient group comprised patients diagnosed with CRPC who received ^{177}Lu-PSMA. The different retention and excretion mechanisms of both radiopharmaceuticals may affect the pharmacokinetics in organs and therefore the scanning times. In a study conducted by Guerriero et al. (24) with a method similar to ours, with 28 patients receiving ^{177}Lu/90 Y-DOTATATE treatment, early post-treatment imaging significantly affected the dose results. They stated that the first four days of data for ^{177}Lu are important for the accuracy of the results. They calculated that late image data changes the results by 5%. Although different pharmaceuticals are used, renal retention appears to be similar (24).

When looking at WB values; it was determined that there were differences between the C1 configuration dose values and the C4 configuration dose values (p=0.267). There was a high correlation between C1 configuration and C2 (0.999), C5 (0.997), C7 (0.997), and C8 (0.991) had the value respectively (Table 3).

When looking at liver values; it was determined that there was a difference between the C1 configuration dose values and the C4 configuration dose values (p=0.232). There was a high correlation between C1 configuration and C2 (0.999), C3 (0.994), C5 (0.991), and C7 (0.996) had the value, respectively (Table 4). Although the liver is not a critical organ in terms of radiation toxicity, it affects the results when the liver is considered as the source organ.

In dosimetric calculations, the dose absorbed by an organ, the activity within the organ itself, and the dose absorption due to activity in other organs are considered. Maaß et al. (23) In his study, only the activity change in the kidney was examined, and the contribution of the activity change in other organs to the kidney was not considered. In the present study, we determined the scanning time, and the effect of activity in other organs, as well as activity in the kidney, was also included in the calculation. Therefore, in our study, the total dose absorbed by the kidney was calculated. The main purpose in determining effective scanning hours for dosimetric calculation is the total dose absorbed by the kidney.

Considering these values, results closest to the values obtained with four scans can be obtained for kidney doses with scans performed at the 4th, 24th, and 48th h after treatment. Although current guidance for ^{177}Lu-PSMA treatment recommends that the late time point should be performed at least 4-7 days later, in our study, we found the 4th, 24th, and 48th scan times to be the optimum scan times.

Study Limitations

Conducting this study with more frequent patient data and imaging at the 240th hour after treatment for clearer detection of excretion may enable error rates to be determined more clearly. Since the study was retrospective, it was conducted with four images up to the 96th hour.

Table 3. Pearson correlation test statistical analysis results of whole body dose calculation configurations

Whole body correlations

		C2	C3	C4	C5	C6	C7	C8	C9
C1	Pearson correlation	0.999**	0.909**	0.389	0.997**	0.996**	0.997**	0.991**	0.972**
	Sig. (2-tailed)	<0.001	<0.001	0.267	<0.001	<0.001	<0.001	<0.001	<0.001
	n	30	30	30	30	30	30	30	30

**: Correlation is significant at the 0.01 level (2-tailed)

Table 4. Pearson correlation test statistical analysis results of liver dose calculation configurations

Liver correlations

		C2	C3	C4	C5	C6	C7	C8	C9
C1	Pearson correlation	0.993**	0.994**	0.416	0.991**	0.944**	0.996**	0.922**	0.906**
	Sig. (2-tailed)	<0.001	<0.001	0.232	<0.001	<0.001	<0.001	<0.001	<0.001
	n	30	30	30	30	30	30	30	30

**: Correlation is significant at the 0.01 level (2-tailed)

Conclusion

It was observed that three imaging sessions after CRPC treatment would be sufficient for optimal dosimetric calculation. Taking the images at the 4th, 24th, and 48th hours or 4th, 24th, and 96th hours after the injection showed that the deviation would be at the lowest rate compared to four scans.

Ethics Committee Approval: The collection of human samples in this study was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (approval number: 2023/558, date: 06.04.2023).

Informed Consent: Retrospective study.

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The Association of Vitamin B12 and Folic Acid Levels with the Effects of Induction Chemotherapy in Acute Leukemia Patients

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ABSTRACT

Introduction: It is essential to achieve remission with induction chemotherapy and then to provide normal hematopoiesis as fast as possible in acute leukemia (AL) patients in order to minimize treatment-related problems. Both vitamin B12 (vitB12) and folic acid (FA), which are both essential vitamins in the process of cell proliferation, affect the process of reestablishing normal hematopoiesis. In patients who have AL, the purpose of this study is to explore the connection between vitB12 and FA and the accomplishment of hematological remission and bone marrow recovery following induction chemotherapy, as well as infection during induction.

Methods: A retrospective study was conducted on the collected information of 71 AL patients who were diagnosed and monitored at the department of hematology between February 2012 and May 2017. The patients' ages ranged from 21 to 67 years, with 47 being the median age. There were 37 male and 34 female patients.

Results: The median level of vitB12 was 386 pg/mL, with a range of 71-2000, while the median level of FA was 5.57 ng/mL, with a range of 2-19. A total of 57 patients (80.3%) reacted favorably to the induction chemotherapy, whereas 14 patients or 19.7%, did not. There were 67 individuals who had febrile neutropenia (94.4%) and 20 patients who developed a fungal infection (28.6%). The correlation between vitB12 and FA levels with remission, bone marrow recovery, duration of febrile neutropenia, and fungal infection was investigated, and the results showed that there was no statistical significance ($p>0.05$).

Conclusion: It was not possible to establish a connection between vitB12 and FA and the accomplishment of hematological remission and bone marrow recovery, as well as infections during induction chemotherapy in AL patients.

Keywords: Vitamin B12, folic acid, acute leukemia

Introduction

Acute leukemias (ALs), both acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL), are hematological malignancies characterized by the accumulation of blasts in the bone marrow, leading to the impairment of normal hematopoiesis (1-4). The treatment of ALs comprises induction and consolidation phases, and morbidity and mortality related to the treatment are the major concerns (2-4). During the induction phase, patients are at a fairly high-risk of complications such as infections due to neutropenia and bleeding due to thrombocytopenia. The risk of complications decreases once hematological remission and subsequently bone marrow recovery are achieved after induction chemotherapy (2,4-6).

Both vitamin B12 (vitB12) (7,8) and folic acid (FA) (9-11) are the cofactors of reactions involved in DNA biosynthesis. Thus, both vitamins play an important role in the proliferation of cells, especially highly proliferating cells such as those in the hematopoietic system. Therefore, their deficiencies cause reduced cell proliferation in the hematopoietic system, leading to mostly anemia and less frequently leukopenia and thrombocytopenia (7,10,11).

Regarding the role of vitB12 and FA in the cell proliferation of the hematopoietic system, the level of both vitamins could be important in the achievement of bone marrow remission and recovery after induction chemotherapy, and furthermore in the prevention of complications with the improvement of cytopenias. The objective of this study was to examine the correlation between vitB12 and FA levels and the achievement of hematological remission and bone marrow recovery following induction chemotherapy, as well as the incidence of infection during the induction phase, in patients with AL.

Methods

A retrospective analysis was conducted on the data of 71 patients with AL who received diagnosis and treatment at the Department of Hematology, University of Health Sciences Turkey, İstanbul Training and Research Hospital, from February 2012 to May 2017. The study was approved by

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the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 1086, date: 22/09/2017). The data collected covered several parameters, including vitB12, FA, lactate dehydrogenase, transferrin saturation, and ferritin levels at the time of diagnosis, as well as diagnostic and follow-up hemograms. As exclusion criteria, the use of drugs affecting vitb12 and FA absorption, diagnosis of malnutrition, and diagnosis of malabsorption were accepted. In addition, the study documented the patients' remission status following chemotherapy, and the occurrence of febrile neutropenia and fungal infection. The duration of febrile neutropenia and the number of days required for bone marrow recovery were also recorded. Hematological remission was assessed between the 21st and 28th days of treatment and defined as a bone marrow blast percentage <5% by morphological examination. The bone marrow recovery day was evaluated according to the peripheral blood counts at two values; days 1) neutrophil count >500x10^6/L and platelet count was >20000x10^6/L and 2) neutrophil count >1000x10^6/L and platelet count >50000x10^6/L.

The induction chemotherapies utilized for the patients were 3+7 (idarubicin 12 mg/m^2/day iv for 3 days and cytarabin 100 mg/m^2/day iv continous infusion for 7 days), 3+5 (idarubicin 12 mg/m^2/day iv for 3 days and cytarabin 100 mg/m^2/day iv continous infusion for 5 days), all trans retinoic acid (ATRA) + idarubicin (tretinoin 45 mg/m^2/day po till hematological remission was obtained, idarubicin 12 mg/m^2/day iv for 4 days at 2, 4, 6, 8 days), and hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD) (cyclophosphamide 300 mg/m^2 bid iv for 3 days, dexamethasone 40 mg/day iv for 4 days and on days 11-14, vincristine 2 mg/day iv on day 4 and 11, doxorubicin 50 mg/m^2/day iv on day 4).

Statistical Analysis

The data was analyzed with SPSS 24 statistical program, and was presented as numbers and percentages or median and ranges when appropriate. For evaluation of categorical values, the chi-square test and for continuous values Mann-Whitney U test were used. Spearman correlation test was used for the evaluation of correlation between vitamin levels and bone marrow recovery days, duration of febrile neutropenia. All p-values 2-sided with statistical significance of at the 0.05 alpha level.

Results

A total of 71 AL patients (60 AML, 11 ALL patients) were included in the study. The study population had a median age of 47 years, ranging from 21 to 67. Of the whole sample, 37 individuals were male, accounting for 52% of the population, whereas 34 individuals were female, representing 48% of the population. Twenty patients (28%) had lymphadenopathy, 14 (20%) had splenomegaly, and 28 (40%) had hepatomegaly. The study observed a median white blood cell count (WBC) of 16.4x10^9/L. The median hemoglobin level was found to be 8.9 g/dL. The median platelet count was measured at 41.5x10^9/L. The median mean corpuscular volume level was determined to be 91.5 fL. The median lactate dehydrogenase level was recorded as 437 U/L. The median transferrin saturation was calculated to be 39%, while the median ferritin level was measured at 470 ng/dL. The study found that the median vitB12 level was 386 pg/mL, with a range of 71-2000 pg/mL. Additionally, it was observed that 7 out of the total patients, accounting for 10% of the sample, had a vitB12 level below 126 pg/mL, indicating a low level. The study observed a median FA level of 5.57 ng/mL, with a range of 2-19. A total of 10 patients, accounting for 14% of the sample, had a low FA level of 3.1 ng/mL. Patient characteristics are presented in Table 1.

The induction chemotherapy regimens used for the patients were 3+7 in 53 (74.6%) patients, 3+5 in 3 (4.2%) patients, ATRA + idarubicin in 4 (5.6%) patients, and HCVAD in 11 (11.6%) patients. Hematological

Table 1. Patient characteristics

Characteristic	**(n=71)**
Median age, years, (range)	47 (21-67)
Gender, n (%)	
Male	37 (52%)
Female	34 (48%)
Subtype of acute leukemia, n (%)	
AML	60 (85%)
ALL	11 (15%)
Lymphadenopathy, n (%)	
Present	20 (28%)
Absent	51 (72%)
Splenomegaly, n (%)	
Present	14 (20%)
Absent	57 (80%)
Hepatomegaly, n (%)	
Present	28 (40%)
Absent	43 (60%)
Median WBC, x10^9/L, (range)	16.45 (0.81-279.84)
Median hemoglobin level, g/dL, (range)	8.9 (4.6-13.1)
Median platelet count, x10^9/L, (range)	41.5 (2-238)
Median MCV level, fL, (range)	91.5 (75.1-147.1)
Median LDH level, U/L, (range)	437 (114-3859)
Median vitamin B12 level, pg/mL, (range)	386 (71-2000)
Vitamin B12, n, (%)	
Low (<126 pg/mL)	7 (10%)
Normal (>126 pg/mL)	62 (90%)
Median folic acid level, ng/mL, (range)	5.57 (2-19)
Folic acid, n, (%)	
Low (<3.1 ng/mL)	10 (14%)
Normal (>3.1 ng/mL)	60 (86%)
Median tranferrin saturation, (%) (range)	39 (5-95)
Median ferritin level, ng/dL, (range)	470 (8-1702)
Types of chemotherapies, n (%)	
3+7	53 (74.6%)
3+5	3 (4.2%)
ATRA + idarubicin	4 (5.6%)
HCVAD	11 (11.6%)

Table 1. Continued

Characteristic	(n=71)
Response to induction chemotherapy, n (%)	
Present	57 (80.3%)
Absent	14 (19.7%)
Neutrophil count >500x10^6/L and platelet count >20000x10^6/L, day, median (range)	23 (11-40)
Neutrophil count >1000x10^6/L and platelet count >50000x10^6/L, day, median (range)	25 (13-40)
Febrile neutropenia, n, (%)	
Present	67 (94.4%)
Absent	4 (5.6%)
Duration of febrile neutropenia, days, median (range)	4 (1-16)
Fungal infection, n, (%)	
Present	20 (28.6%)
Absent	50 (71.4%)

ALL: Acute lymphocytic leukemia, AML: Acute myeloid leukemia, LDH: Lactate dehydrogenase, MCV: Mean corpuscular volume, WBC: White blood cell count, ATRA: All trans retinoic acid, HCVAD (hyper-CVAD): Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone

remission was achieved in 57 (80.3%) patients. In those patients, regarding bone marrow recovery, the median day of neutrophil count >500x10^6/L and platelet count >20000x10^6/L was 23 days (range, 11-40) and the median day of neutrophil count >1000x10^6/L and platelet count >50000x10^6/L was 25 days (range, 13-40). Febrile neutropenia occurred in 67 (94.4%) patients, and the median duration of febrile neutropenia was median 4 days (range, 1-16). Twenty (28.6%) patients had fungal infections (Table 1).

The median vitB12 level was 438 pg/mL (range, 71-2000) in responders and 257 pg/mL (range, 111-2000) in non-responders (p=0.151). The median FA level was 5.57 ng/mL (range, 2-18.99) in responders and 5.71 ng/mL (range, 3.07-10.42) in non-responders (p=0.765). The median vitB12 level was 306 pg/mL (range, 111-927) in patients with a fungal infection and 416 pg/mL (range, 71-2000) in patients without a fungal infection (p=0.425). The median FA level was 5.73 pg/mL (range, 2.55-14.35) in patients with a fungal infection and 5.41 pg/mL (range, 2-18.99) in patients without a fungal infection (p=0.732).

vitB12 level was not correlated with neutrophil count >500x10^6/L and platelet count >20000x10^6/L (p=0.142, r=0.200) and with neutrophil count >1000x10^6/L and platelet count >50000x10^6/L (p=0.092, r=0.231). FA level was not correlated with days of neutrophil count >500x10^6/L and platelet count >20000x10^6/L (p=0.523, r=-0.087) and with days of neutrophil count >1000x10^6/L and platelet count >50000x10^6/L (p=0.677, r=-0.058). vitB12 level was not correlated with the duration of febrile neutropenia (p=0.104, r=-0.210) and also FA level was not correlated with the duration of febrile neutropenia (p=0.138, r=-0.190) (Table 2).

All analysis for vitB12 was done after exclusion of patients with WBC of >1x10^9/L, and results were not different regarding statistical significance.

Table 2. Correlation of vitamin B12 and folic acid levels with bone marrow recovery and duration of febrile neutropenia

(n=71)	Vitamin B12		Folic acid	
	r-value	p-value	r-value	p-value
Neutrophil count >500x10^6/L and Platelet count >20000x10^6/L, day	0.200	0.142	-0.087	0.523
Neutrophil count >1000x10^6/L and platelet count >50000x10^6/L, day	0.231	0.092	-0.058	0.677
Duration of febrile neutropenia (day)	-0.210	0.104	-0.190	0.138

Discussion

vitB12 ve FA are two important vitamins whose deficiencies cause megaloblastic anemia, leukopenia and thrombocytopenia in normal subjects (7,10,11). From this point of view, their levels might have an impact on the achievement of hematological remission and bone marrow recovery after induction chemotherapy, as well as the occurrence of complications such as infections in AL patients. In this study, the levels of both vitB12 and FA were similar in responders and non-responders; in patients with and without a fungal infection during induction phase. In addition, there was no correlation between both vitamins and the bone marrow recovery day and duration of febrile neutropenia.

In recent years, age, performance status of patients, and genetic risk factors have formed the basis for evaluating prognosis in AL patients (2,12). Therefore, there are inadequate data about the effects of vitB12 and FA on attainment of hematological remission after induction chemotherapy. On the other hand, the influence of vitB12 and FA on bone marrow recovery has been investigated in children with ALL. Tandon et al. (13) demonstrated that FA deficiency was associated with late bone marrow recovery in 58 children with ALL. In the same study, vitB12 deficiency was associated with only toxic deaths during induction, but not with bone marrow recovery. Roy Moulik et al. (14) showed that the incidence of thrombocytopenia and neutropenia was higher during induction chemotherapy in FA-deficient patients, in a slightly higher number of children with ALL (n=150). In fact, we have insufficient knowledge about the factors affecting bone marrow recovery after induction chemotherapy. However, Gerbing et al. (15) recently investigated the effect of telomere length on bone marrow recovery in 97 AL patients. They indicated that patients with decreased telomere content had delayed recovery of neutrophils. In contrast to previous studies, we could not exhibit an association of vitB12 and FA with bone marrow recovery.

Another important issue is the development of infections during treatment in patients with AL (2,4,5,6). vitB12 and FA deficiencies have been associated with immune system dysfunction, leading to opportunistic infections in normal people (16,17). Besides the normal population, the association of FA with infections has been studied in AL patients by Roy Moulik et al. (14). They found that FA-deficient children with ALL had an increased incidence of febrile neutropenia during induction. However, we could not demonstrate an association between

vitB12 and FA levels and fungal infection and duration of febrile neutropenia. Because most of the patients had febrile neutropenia attacks, we did not perform any analysis regarding the presence of febrile neutropenia. Our results were not surprising, considering that vitB12 and FA levels were not associated with bone marrow recovery.

Study Limitations

The retrospective nature of the study and the small number of vitamin-deficient patients is the limitations of this study. Although invalid for FA, vitB12 levels have been found to be higher in some hematological diseases such as chronic myeloid leukemia, polycythemia vera, and myelofibrosis (18). In addition, nearly 30 % of AML patients could have elevated levels of vitB12 (18). However, how vitB12 levels change in ALL patients is conflicting (19,20). Another issue regarding vitB12 is that to determine the true vit B12 deficiency, homosistein or methyl malonic acid levels are required. However, our patients did not have, which could have masked the true incidence of vitB12 deficiency. Furthermore, as this was a retrospective study, post-treatment vitB12 and FA data of the patients could not be evaluated because they could not be accessed.

Conclusion

The association of vitB12 and FA with the attainment of hematological remission and bone marrow recovery and infections during induction chemotherapy could not be established in AL patients. However, further research with extensive cohorts of patients is necessary to examine the impact of vitamin inadequacies on treatment results and consequences in individuals with AL.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 1086, date: 22/09/2017).

Informed Consent: Retrospective study.

Authorship Contributions: Concept - S.E.; Design - S.E., E.S.; Data Collection or Processing - S.E.; Analysis or Interpretation - S.E., E.S.; Literature Search - S.E.; Writing - S.E., E.S.

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

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Bioresonance Therapy for Smoking Cessation

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ABSTRACT

Introduction: The World Health Organization reports that cigarette smoking is responsible for over 8 million deaths yearly. There is increasing evidence in the literature that alternative therapies such as bioresonance, acupuncture, and hypnosis are effective in smoking cessation. The aim of this study was to evaluate the effectiveness and results of bioresonance therapy for smoking cessation.

Methods: A total of 1272 patients who applied to Selçuk University Faculty of Medicine, Family Medicine Smoking Cessation Polyclinic for bioresonance treatment between October 2010 and September 2019 were included in this study. These patients were treated with bioresonance therapy for a total of 3 sessions per month to quit smoking.

Results: MORA bioresonance therapy (MORA BT) was the most preferred method of quitting smoking in the group that succeeded on the 3rd day, 7th day, 15th day, 1st month and 2nd months. However, there were no statistically significant differences between the successful and unsuccessful groups. No significant difference was found when MORA BT was compared with all other treatment methods (p=0.132).

Conclusion: This study presents the first protocol to compare bioresonance therapy with other smoking cessation treatments in a large sample group, based on fagerstrom nicotine addiction test scores in Turkey. Bioresonance therapy was found to be effective in smoking cessation, which increases the importance of the study and shows that bioresonance therapy is very effective in smoking cessation.

Keywords: Bioresonance therapy, smoking, smoking cessation

Introduction

Tobacco use, particularly smoking addiction, adversely affects public health and is the leading cause of preventable morbidity, mortality, and poor quality of life worldwide. The World Health Organization (WHO) reports that cigarette smoking is responsible for over 8 million deaths yearly (1). More than 7 millions of these deaths are directly related to the use of tobacco. Smoking continues to be a serious problem worldwide. smoking causes lung cancer, stroke, and heart disease (2). According to the WHO data, smoking restriction policies give good results in many countries. Also, most smokers who are aware of the dangers of tobacco want to quit. The demand for medical treatment methods used in smoking cessation has increased in recent years. Those who find these methods expensive, find the treatment process long, or fail to obtain results from medical treatment have turned to alternative treatments.

Quitting smoking at any time is primarily a beneficial step for a person's health and for public health. Recently, recommended intervention methods for quitting smoking include medication, nicotine replacement therapy (NRT), hypnosis, education, behavioral intervention, etc. (3). NRT was found to be superior to a placebo, increasing abstinence rate up to twofold, and the efficacy of bupropion and varenicline have also been proven through randomized trials (4,5). Although some side effects occur, such as nausea, insomnia, and headache, the consensus among experts is that NRT, bupropion, and varenicline are currently the first-line pharmacological therapies for smoking cessation today (6,7). According to the literature in recent years, complementary and alternative therapies in addition to medical treatments have become highly preferred for treating smoking cessation. The most popular methods are as follows; ear, transdermal and laser acupuncture, hypnosis, bioresonance therapy, electrostimulation, phytotherapy, and homeopathic therapies (3,8,9,10).

It has been proven that our cells emit electromagnetic signals and receive signals from the environment. When the normal electromagnetic balance of our cells is disturbed, diseases occur in the body due to pathogenic microorganisms (11). Bioresonance (MORA therapy) is a holistic, non-invasive therapy used for treating many diseases. The main principle of treatment is to improve overall health by detecting the electromagnetic frequency emitted by the affected organism and applying the frequency at the opposite frequency. This biophysical therapy was developed by German doctor Franz Morell and electrical technician Erich Rasche in the 1970s. Having long-term experience in electroacupuncture, the doctor developed bioresonance therapy because of long tests (12). Nowadays,

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modern non-medical searches have increased for treating diseases. It is also believed that interest in complementary and alternative medicine therapies will increase even more over time (13).

There is increasing evidence in the literature that alternative therapies such as bioresonance, acupuncture, and hypnosis are effective in smoking cessation. The aim of this study was to investigate the success rates of patients receiving MORA therapy as a smoking cessation treatment, to examine the effectiveness of bioresonance therapy combined with NRT therapy in quitting smoking, to determine the effectiveness of bioresonance therapy in quitting smoking, and to evaluate the results.

Methods

Study Population and Design

A total of 1272 patients who applied to Selçuk University Faculty of Medicine, Family Medicine Smoking Cessation Polyclinic for bioresonance treatment between October 2010 and September 2019 were included in this study. These patients underwent a total of three sessions of bioresonance treatment at 15-day intervals to quit smoking. The success rates of the patients at the first and third months were recorded by questioning by face-to-face interviews and telephone checks. Smoking cessation patients were followed up on cessation day, after 7 days, 15 days, 1 month, 2 month and 3 months at the outpatient clinics, and then followed up with phone calls by researchers (it was free outdoor phone line) in the sixth month, first year, and during the second year following bioresonance therapy and recommended medication treatment. Patients who could not be reached during follow-up visits were not included in the study.

Ethical Approval and Informed Consent

The protocol of this study was reviewed and approved by the Ethics Committee of Selçuk University (approval number: 2019/264, date: 16.10.2019). An informed consent form was obtained from all patients or their legal representatives.

Overall Function and Clinical Evaluation

The sociodemographic characteristics of the individuals who applied to quit smoking, such as gender, age, height, weight, occupation, current complaints, and diagnosed medical diseases, were questioned. During the initial visit, any risk, presence of major depressive disorder, and presence of chronic medical illness were reviewed. Physical examination of all patients was performed, and the amount of carbon monoxide (CO) in the breath was measured. The Fagerstrom Test for Nicotine Dependence (FTND) was used to assess each patient's smoking addiction. According to FTND; 0-2 means very little nicotine dependence; 3-4 means low nicotine addiction; 5 indicates moderate nicotine dependence; 6-7 means high nicotine addiction; 8-10 means very high nicotine dependence. The study was analyzed using the chi-square test. Therefore, according to FTND, two groups were created: moderate and lower levels of nicotine dependence (0-5) and higher levels of nicotine dependence (6-10). Patients diagnosed with major depressive disorder and other psychiatric disorders at the first application were referred to the psychiatry clinic. These patients did not receive smoking cessation therapy.

Statistical Analysis

All data were recorded using the IBM Statistical Package for the Social Sciences (SPSS) 22.0 computer program (Armonk, NY). Frequency (n), percentage (%), mean ± standard deviation, minimum-maximum values were used as descriptive statistics to evaluate the data obtained from the study. The normality of the data was checked by the Kolmogorov-Smirnov normality test. The Kruskal-Wallis H test was used to compare more than two groups. All analyses were conducted within a 95% confidence interval. A $p<0.05$ level was considered significant for statistical significance.

Results

A total of 1272 patients were interviewed, 991 of whom were male. The mean age of participants was 40.69±1.32 years. Table 1 summarizes the sociodemographic characteristics of the study population. When the patients were evaluated according to body mass index; 18.6% (n=236) were obese. The mean CO of patients was 12.64±7.96. Only 37.7% (n=480) of patients reported that they were very high nicotine dependence. 94.3% (n=1200) of patients preferred MORA bioresonance therapy as a treatment method for smoking cessation (Table 1).

Table 2 summarizes the classification of the treatment methods used by patients for smoking cessation according to the smoking cessation time. MORA bioresonance therapy was the most preferred method to quit smoking in the successful group on the 3rd day and 1st month (Table 2).

Table 3 represents the comparison of Fagerstrom Test Scoring with treatment methods. Compared to all other treatment methods, MORA bioresonance treatment; it was not found to be statistically effective in all nicotine addiction groups (p=0.132) (Table 3).

Discussion

Studies with large sample sizes and low risk of bias regarding MORA bioresonance therapy and smoking cessation interventions are very few in the literature. Concerning the results of this study, the effectiveness of bioresonance therapy was found to be more significant than that of all other treatment methods used in smoking cessation. Smoking is a complex and difficult phenomenon that includes psychological, physical, environmental, and familial factors. Nicotine is unfortunately just as addictive as other drugs like cocaine and heroin. Despite many effective and different smoking cessation treatments, there is still a large gap in this area. Studies show that a current smoker tries quitting smoking an average of 30 times or more before successfully quitting for 1 year or more (14).

There are many treatment methods that affect the smoking cessation effect. A review reported that acupuncture was less effective than nicotine gum. Additionally, there is no evidence that acupuncture is any less (or more) effective than behavioral interventions used to quit smoking (15). Vincent and Richardson showed that acupuncture is as effective as other treatment modalities in the early stages of nicotine withdrawal (16). For electrostimulation, six studies provide confidence that electrostimulation has no greater effect than placebo on smoking cessation (15). A review reported that bead and ear acupuncture were more economical than nicotine patches. In addition, they described

that acupuncture had a similar effect to NRT on smoking cessation and defined that acupuncture with an educational smoking program, counseling, or moxibustion was more effective as monotherapy in terms of prolonged smoking cessation (3).

In another study, Pihtili et al. (17) documented the efficacy of bioresonance therapy. According to the results of this study; bioresonance therapy is clinically effective in smoking cessation and does not have any side effects. Eisenberg et al. (18) according to their meta-analysis, the most successful results at the pharmacological level were obtained using varenicline. Oncken et al. (19) defined that 0.5 mg and 1.0 mg of varenicline tartrate twice daily were effective in smoking cessation. Marakoğlu et al. (20) in a study in which the patients showed the rate of smoking cessation in the 2nd year; the success rate (19.9%) of those using bioresonance therapy + varenicline was significantly higher than those using bioresonance therapy + bupropion (16%). These results are consistent with the findings of a randomized controlled trial conducted by Jorenby et al. (21). Barnes et al. (22) because of their meta-analysis study; they concluded that there is little evidence to determine whether hypnotherapy is more effective at smoking cessation than other forms of behavioral support or quitting unaided. Jang et al. (23) showed that

Table 1. Sociodemographic characteristics of patients (n=1272)

Characteristics	**n**	**%**
Gender		
Male	991	77.9
Female	281	22.1
Age (years) mean ± SD (min.-max.)	40.69±1.32 (17-76)	
Age (years) categorical		
17-34	416	32.7
35-44	394	31.0
45 and ↑	462	36.3
Height (cm) mean ± SD (min.-max.)	172.41±8.52 (145.0-199.0)	
Weight (kg) mean ± SD (min.-max.)	78.21±14.86 (43.0-156.0)	
BMI (kg/m^2) mean ± SD (min.-max.)	26.25±4.29 (14.74-46.46)	
BMI categorical		
Underweight (<18.50)	20	1.6
Normal weight (18.5-24.99)	508	39.9
Overweight (25-29.99)	508	39.9
Obesity (>30.00)	236	18.6
Occupation		
Student and housewife	175	13,8
Retired	149	11.7
Officer	302	23.7
Self-employment	646	50.8
CO mean ± SD	12.64±7.96	
FTND		
Very little ND	47	3.7
Little ND	141	11.1
Moderately ND	151	11.9
High ND	453	35.6
Very high ND	480	37.7
Packet/years smoking mean ± SD (min.-max.)	29.62±22.22 (1-256)	
Treatment methods		
MORA BT	1200	94.3
MORA BT + varenicline	24	1.9
MORA BT + bupropion	13	1.0
MORA BT + NRT	35	2.8
Total	**1272**	**100**

Values are presented as number (%) or mean ± standard deviation (range). BMI: Body mass index, min.: Minimum, max.: Maximum, CO: Carbon monoxide, FTND: Fagerstrom Test for Nicotine Dependence, ND: Nicotine dependence, MORA BT: MORA bioresonance therapy, NRT: Nicotine replacement therapy, SD: Standard deviation

Table 2. Classification of the treatment methods used by patients for smoking cessation according to smoking cessation time

Methods	Succesful group		Unsuccessful group			
	n	%	n	%	x^2	p
3rd day						
MORA BT	1080	91.0	107	9.0	4.340	0.227
MORA BT + V	24	100.0	0	0.0		
MORA BT + B	11	84.6	2	15.4		
MORA BT + NRT	29	85.3	5	14.7		
Total	**1114**	**90.0**	**114**	**9.1**		
1st month						
MORA BT	823	69.6	360	30.4	3.560	0.313
MORA BT + V	16	72.7	6	27.3		
MORA BT + B	8	61.5	5	38.5		
MORA BT + NRT	17	54.8	14	45.2		
Total	**864**	**69.2**	**385**	**30.8**		
3rd month						
MORA BT	583	50.0	584	50.0	4.540	0.209
MORA BT + V	14	60.9	9	39.1		
MORA BT + B	4	30.8	9	69.2		
MORA BT + NRT	12	38.7	19	61.3		
Total	**613**	**49.7**	**621**	**50.3**		
6th month						
MORA BT	448	39.6	683	60.4	0.662	0.882
MORA BT + V	9	37.5	15	62.5		
MORA BT + B	4	30.8	9	69.2		
MORA BT + NRT	11	35.5	20	64.5		
Total	**472**	**39.4**	**727**	**60.6**		
1st year						
MORA BT	386	35.3	707	64.7	5.771	0.123
MORA BT + V	6	26.1	17	73.9		
MORA BT + B	1	7.7	12	92.3		
MORA BT + NRT	8	27.6	21	72.4		
Total	**401**	**34.6**	**757**	**65.4**		
2nd year						
MORA BT	312	30.9	699	69.1	1.679	0.642
MORA BT + V	5	25.0	15	75.0		
MORA BT + B	2	18.2	9	81.8		
MORA BT + NRT	3	21.4	11	78.6		
Total	**322**	**30.5**	**734**	**69.5**		

MORA BT: MORA bioresonance therapy, V: Varenicline, B: Bupropion, NRT: Nicotine replacement therapy

Table 3. Comparison of FTND according to the treatment method

	MORA BT		MORA BT + V		MORA BT + B		MORA + NRT		Total		x^2	p
FTND	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**		
0-5	320	94.4	10	2.9	4	1.2	5	1.5	339	100.0	5.619	0.132
6-10	880	94.3	14	1.5	9	1.0	30	3.2	933	100.0		
Total	**1200**	**94.3**	**24**	**1.9**	**13**	**1.0**	**35**	**2.8**	**1272**	100.0		

MORA BT: MORA bioresonance therapy, V: Varenicline, B: Bupropion, NRT: Nicotine replacement therapy, FTND: Fagerstrom Test for Nicotine Dependence

traditional and complementary medicine interventions did not have a statistically significant effect on increasing the success rate of smoking cessation. However, promising new results in auricular acupressure and hypnosis are also available in the literature (24,25).

Smoking is a difficult behavior to quit and quitting smoking requires a strong will. There are many factors affecting the quitting effect of smoking cessation, and we agree that it is important to compare different smoking cessation treatments. This study presents the first protocol to compare bioresonance therapy with other smoking cessation treatments in a large sample group, based on FTND scores in Turkey. In addition, there is a rapid increase in smoking cessation rates after the age of 45, and the smoking cessation rate for young people is less than 10% (26). In our study, 63.7% of our patients were younger than 45 years of age. Despite this, the fact that bioresonance therapy was found to be effective in smoking cessation increases the importance of the study and shows that bioresonance therapy is very effective in smoking cessation.

Study Limitations

One of the strengths of the study is that it includes all those who are the least likely to quit smoking and those who have the most difficulty in sustaining abstinence. Another strength of the study is that it evaluates the effect of bioresonance therapy on smoking cessation with 2-year data. In Turkey, the government pays for other pharmacological treatments used in smoking cessation from time to time. The patient's payment of money out of her own pocket for bioresonance treatment may have also affected the smoking cessation effect. Another study strength is that it was conducted in a large sample group by experienced physicians in an experienced smoking cessation clinic. There is no study in the literature similar to our study.

Conclusion

When MORA bioresonance treatment was compared with all other treatment methods, no statistically significant difference was found between the groups. Bioresonance treatments; Although it seems to be effective in many studies, there is a need for more scientific studies and more data to be presented. When the studies in the literature are examined, it can be said that bioresonance therapy can be used for supportive purposes in chronic diseases, combating addiction, and especially in cases where conventional medical practices are inadequate. Bioresonance treatments are becoming more widespread day by day both in the world and in our country and are in demand from patients; it can already be predicted that they will become much more widespread soon. We believe that this study will provide beneficial evidence for further studies on bioresonance therapy. It would also be beneficial to examine this study with larger randomized placebo-controlled double-blind studies comparing bioresonance with other pharmacological methods.

Ethics Committee Approval: The protocol of this study was reviewed and approved by the Ethics Committee of Selçuk University (approval number: 2019/264, date: 16.10.2019).

Informed Consent: An informed consent form was obtained from all patients or their legal representatives.

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Relationship between Sarcopenia and Respiratory Functions in Geriatric Male COPD Patients

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ABSTRACT

Introduction: Sarcopenia can be defined as the loss of skeletal muscle mass and strength, especially with aging. In total, 21.6% of patients with chronic obstructive pulmonary disease (COPD) have sarcopenia. In our study, we investigated whether the evaluation of respiratory muscles can be correlated with peripheral muscle measurement and what kind of relationship is between sarcopenia and pulmonary function tests.

Methods: A retrospective observational study conducted in a single center included 75 male COPD patients admitted to the pulmonary rehabilitation unit. The data were obtained from the hospital information management system and patient files.

Results: The mean age of 75 male patients included in the study was 65±9 years, 76% had a history of smoking, and 46% had comorbidities. Sarcopenia was detected in 20 patients, 16 of whom were over 65 years of age. While the mean Handgrip was 50, Quadriceps 36, and Pinchmeter 17 in all age groups, it was 58, 38, and 17 in the over 65 age group, and 21, 21, and 12 in the 65 age group with cachexia, respectively. There was no statistical relationship between sarcopenia and forced expiratory volume 1 (FEV1), forced vital capacity, FEV1/FEV, Global Initiative for Chronic Obstructive Lung Disease stages, modified Medical Research Council, and COPD assessment test scores in patients over 65 years of age ($p>0.05$).

Conclusion: Although it was observed that the frequency of malnutrition and sarcopenia was higher than normal in the COPD patient group over 65 years of age, a decrease in pulmonary function tests and a decrease in effort capacity due to sarcopenia were observed, a statistically significant result was reached due to the insufficient number of cases.

Keywords: COPD, sarcopenia, pulmonary function tests, geriatrics male

Introduction

With the gradual increase in the elderly population worldwide, geriatric syndromes and chronic diseases due to aging are increasing. Geriatric syndromes are defined as clinical conditions that are seen in elderly patients, impair quality of life, progress with atypical symptoms that cannot be revealed by disease definitions, and increase morbidity and mortality rates. In addition to sarcopenia, conditions such as delirium, syncope, falling, fragility, incontinence, polypharmacy, dementia, dehydration, and pressure sores are also called geriatric syndromes (1,2).

Sarcopenia can be defined as the loss of skeletal muscle (SM) mass and strength, especially with aging. It was first defined by Rosenberg (3) as a decrease of muscle mass associated with aging, and most recently with European Working Group on Sarcopenia in Older People 2 (EWGSOP2) in 2019. It is a syndrome characterized by progressive and widespread decrease of SM strength and mass, which increases the risk of negative consequences such as limitation in physical movement, low quality of life, and death. It has been redefined as muscle disease that is common in older individuals but can also occur early in life (3,4). Its prevalence varies widely, from 6.8% to 19.1% by country, according to the EWGSOP (5,6).

Previous investigations have shown that diaphragm muscle strength (MS) and mass decrease with age. Transdiaphragmatic pressure measurement was used to measure the diaphragmatic strength. In some studies, it was determined that there was a slight correlation between the strength of the RM and that of the other muscles, and that RM strength was slightly correlated with extremity MS or hand grip strength in the elderly (7,8). In a study examining young people, a slight correlation was found between the diagnosis of sarcopenia and the SM mass index, knee extensor strength, and hand grip test (9).

In our study, we investigated whether the evaluation of RM, which is an indirect way of evaluating sarcopenia in COPD, which is common in the geriatric population, can be correlated with peripheral muscle measurement and what kind of relationship is between sarcopenia and pulmonary function tests.

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Methods

A retrospective observational study conducted in a single center included 75 male COPD patients admitted to the pulmonary rehabilitation unit of a training and research hospital between January 2021 and June 2022. Patients with demographic data, comorbidities, modified Medical Research Council (mMRC), and COPD assessment test (CAT) scores, respiratory function values, Handgrip, Quadriceps and Pinchmeter values from the hospital information management system and patient files were included in the study.

The study was approved by the University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023 - 451, date: 28.12.2023). Verbal and written consent was obtained from the patients in accordance with the Declaration of Helsinki and our hospital practice.

Height measurement: Height was measured with a stadiometer with the weight of the participants distributed on both feet, heels together, and head in a Frankfort plane, arms hanging freely from the shoulders to the sides. A single measurement was taken from the participants.

Body weight and body fat percentage measurement: A bioelectric impedance measurement device (Tanita Body Composition Analyzer) was used to determine the body fat and body weight percentage of the patients. Measurements were performed while the patients were upright and motionless, ensuring that both feet stood equally on the scales. Patients were informed about the measurement procedures before the test and were instructed to avoid heavy exercise and alcohol consumption for the last 24 h, caffeine for the last 4 h, and food for the last 2 h (10).

Body mass index (BMI) = weight (kg)/height (m^2) was calculated using the formula.

Evaluation of Malnutrition and Evaluation of Muscle Mass

The diagnosis of malnutrition was made according to GLIM criteria (11). We used the Mini Nutrition Assessment-Short Form questionnaire (MNA-SF) as a malnutrition screening tool, and a score below 12 indicates risk of malnutrition (12). The diagnosis of malnutrition was confirmed when at least one phenotypic and at least one etiological criterion was detected in accordance with GLIM recommendations.

Phenotypic criteria:

1. Unintentional weight loss: decrease of more than 5% of body mass in less than 6 months or decrease of more than 10% in more than 6 months,

2. Low BMI (kg/m^2): BMI <20 under 70 years of age, BMI <22 over 70 years of age,

3. Low muscle mass (LMM): It was evaluated based on appendicular lean mass measurement, Supplementary Lean Mass (ALM) calculation, and an ALM index representing ALM (kg) and height squared (m^2). Appendicular fat-free mass measurement was performed using the electrical bioimpedance method.

Etiological Criteria

Reduction or assimilation of food intake was noticed in subjects who reported any decrease in food intake in the past 3 months on the MNA-SF questionnaire.

Sarcopenia Evaluation

The Find-Assess-Confirm-Significance of Cases (FACS) algorithm was followed, sarcopenia screening was performed with the SARC-F questionnaire (≥4 points indicate the risk of sarcopenia), and all patients were diagnosed with sarcopenia, regardless of the SARC-F results. This protocol complies with EWGSOP2 recommendations for all patients with clinically suspected sarcopenia and is associated with the possibility of the COPD patient group being sarcopenic (13,14).

Evaluation of Muscle Strength

A hand grip test and hand dynamometer were used to measure upper extremity MS. The hand grip test was performed with the patient in a sitting position, with the arms bent 90° at the elbow and arm joints, with an accuracy of 0.1 kg. After both upper extremities were tested twice, all results were averaged. In accordance with the EWGSOP2 recommendations, values of 16 kg for women and 27 kg for men were used as low MS cutoff points (15). The chair standing test was used to evaluate lower extremity MS (16). Patients who repeatedly rose from the chair five times by crossing their arms over their chests. Results shorter than 15 s were considered as low lower extremity MS. According to the FACS algorithm, patients with decreased MS are diagnosed with decreased MS (13).

Hand Grip Force Measurement

A digital hand dynamometer with an adjustable grip handle measuring in the range of 5.0-100.0 kg and an accuracy of 0.1 kg was used to measure the participants' hand grip force (HGF). During the measurements, the participants were asked to look across with their feet shoulder-width apart, in a standing position, with the elbow in full extension. Before the measurement, the dynamometer was adjusted according to the hand sizes of the participants. The user is instructed to hold the dynamometer in a comfortable grip position (not in flexion and extension), with the index finger flexed 90°. Participants were instructed to squeeze the handle with all their strength for 3 s. During the test, they were instructed not to hold their breath and not to shake the dynamometer. The participants' grip strength measurements from both hands were taken three times, and the highest value was taken in "kg" for statistical evaluation. There was a break of at least 60 s between each trial.

Pulmonary Function Tests

Spirometry results were obtained from the hospital's electronic patient data system. The post-bronchodilator forced expiratory volume 1 (FEV 1)/forced vital capacity (FVC) ratio of all patients participating in the study was found to be lower than 70%, in accordance with the diagnostic criteria of COPD specified in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guide (1). The severity of the obstruction was classified according to the FEV1 value in accordance with the GOLD guideline: In the classification consisting of four categories, FEV1

≥80% was determined in mild obstruction, FEV1 ≥50% in moderate obstruction, FEV1 ≥30% in severe obstruction, and FEV1 <30% in very severe obstruction.

Statistical Analysis

All statistical analyses were performed using SPSS 21.0 (IBM Statistical Product and Service Solutions version 21 Inc., Chicago, USA) program. In the study, descriptive statistics were reported, including the mean (standard deviation), median (interquartile range), and percentage. The Kolmogorov-Smirnov test was used to determine whether the continuous variables showed normal distribution or not. Pearson's chi-square and Fisher's exact tests were used to determine the difference between categorical variables. Values with a p-value of 0.05 were considered statistically significant.

Results

Our study included 75 male patients who visited our chest diseases outpatient clinic, and their mean age was 65±9 (45-86). There was a smoking history in 76% of the patients, and their average cigarette consumption was 22 pk/year. The mean duration of COPD diagnosis was 8 years, and 46% had a comorbid condition. The most common comorbidity is cardiovascular disease (19%). The mean FEV1 was 1.3 lt (44%), FVC 2.2 lt (59%), and FEV1/FVC 59. The groups of patients according to GOLD staging, CAT, and mMRC scores are given in Table 1.

HGF measurement was below 33 in 16 (37%) of 43 patients over 65 years of age. There was no statistically significant decrease in HGF in patients aged 65 years with a diagnosis of COPD for 5 years or more. When the reference value for sarcopenia was taken as 33, a statistically significant decrease was found ($p<0.05$). When patients over 65 years of age with and without sarcopenia were compared, FEV1, FVC, FEV1/FEV, GOLD stages, mMRC and CAT score, hospitalization in the last 1 year, number of attacks in the last 1 year, admission to the emergency department in the last 1 year, and emphysema and emphysema on thorax computed tomography. There was no statistical difference between bronchiectasis and peripheral blood eosinophilia ($p>0.05$). When patients over 65 years of age with sarcopenia were compared with those under 65 years of age without sarcopenia, no statistical difference was found between FEV1, FVC, FEV1/FEV, GOLD staging, mMRC, and CAT ($p>0.05$).

While the number of patients under 65 years of age with sarcopenia was found to be 4, and the number of patients who needed nutritional support was 2 (6.5%), 16 patients over 65 years of age with sarcopenia and who needed nutritional support were found to be 6 (13.6%). No statistically significant relationship was found between sarcopenia and nutritional support ($p>0.05$). While the mean FEV1 of the group receiving nutritional support was 1.05 lt, the mean FEV1 of the patients with sarcopenia was 1.26 lt. Respiratory function tests of patients who were malnourished and started on nutritional support were lower than those in the sarcopenia group, but no statistically significant difference was detected ($p>0.05$). While 72% of patients over 65 years of age with sarcopenia had GOLD stages 3 and 4, this rate was 54% in the group without sarcopenia.

Groups according to the GOLD staging of COPD patients aged 65 years and over, mMRC and CAT scores, PFT parameters, Handgrip, Quadriceps and Pinchmeter measurement results are given in Table 2.

Discussion

With the gradual increase in the elderly population worldwide, geriatric syndromes and chronic diseases due to aging are increasing. Geriatric syndromes are defined as clinical conditions that are seen in advanced age, impair quality of life, progress with atypical symptoms that cannot be revealed by disease definitions, and increase morbidity and mortality rates. In addition to sarcopenia, conditions such as delirium, syncope, falling, fragility, incontinence, polypharmacy, dementia, dehydration, and pressure sores are also called geriatric syndromes (1,2). The inflammatory nature of COPD brings with it increased sarcopenia and fragility in the advancing age group.

While sarcopenia can be defined as a loss in SM mass and strength that occurs especially with aging, according to EWGSOP2, it is a syndrome characterized by progressive and widespread loss of SM mass and strength, which increases the risk of adverse outcomes such as limitation in physical movement, low quality of life and death, and in the elderly. It has been redefined as muscle disease, which is common in individuals but can also occur in the early stages of life (3,4).

Studies have shown that diaphragm MS and mass decrease with age. In the literature, it was determined that there was a slight correlation between the strength of the RM and the strength of the other muscles, and that RM strength was slightly correlated with extremity MS or

Table 1. mMRC and CAT scores of groups according to GOLD staging

	n	% (valid)
GOLD stage	(16 missing)	
1	1	2
2	22	37
3	22	37
4	14	24
CAT scores	16.1±8.3 (2-24)	
Symptom score according to the CAT		
≥10	23	77
<10	7	23
mMRC scores	2.5±1.2	
mMRC scores	(7 missing)	
0	1	2
1	19	28
2	11	16
3	22	32
4	15	22
Handgrip average	50.7±20.8 (9-92.5)	
Quadriceps average	36.4±14.1 (15.5-105.5)	
Pinchmetre average	17.5±4 (9.7-26.2)	

GOLD: Global Initiative for Chronic Obstructive Lung Disease, mMRC: modified Medical Research Council, CAT: COPD assessment test

Table 2. Patient characteristics according to age groups

	<65 ages (n=31)	≥65 age (n=44)	p
BMI	26.6±5.6	25.1±4.4	0.246
BMI			
Normal	21 (67)	30 (81)	0.431
Cachectic	5 (16)	4 (11)	
Obese	5 (16)	3 (8)	
COPD diagnosis duration	7.5±4.9	8.7±5.1	0.326
FEV1	1.4±0.6	1.3±0.5	0.3944
FEV1 (%)	42±16	45±17.9	0.489
FVC	2.4±0.9	2.1±0.7	0.160
FVC (%)	41±12	35±7.2	0.817
FEV1/FVC	57±12	56±12	0.826
GOLD stage	(26)	(35)	
1	0	1	0.765
2	9	13	
3	9	13	
4	8	8	
CAT score	14.6±6.4	17.2±9.6	0.405
Symptom score according to the CAT	(13)	(17)	
≥10	11	12	0.427
<10	2	5	
mMRC score	2.4±1.2	2.6±1.2	0.563
Handgrip average	58.3±21	45.8±19.5	0.013
Quadriceps average	38.5±17	34.3±10.2	0.333
Pinchmetre average	17.6±4.4	17.4±3.7	0.915

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, FEV1: Forced expiratory volume 1, FVC: Forced vital capacity, GOLD: Chronic Obstructive Lung Disease, CAT: COPD assessment test, mMRC: modified Medical Research Council

hand grip strength in the elderly (5,7,8). In a study conducted with young people, a slight correlation was found between the diagnosis of sarcopenia and the SM mass index, knee extensor strength, and hand grip test (9).

Changes in body structure and malnutrition are the most common comorbid conditions in patients with COPD and negatively affect the prognosis (3,4,7,8). Studies show that 30%–60% of COPD patients do not receive adequate nutrition (9,17,18), 20 to 40% have LMM (3,4), and 15 to 21.6% patients have sarcopenia (19,20). Normally, an adult consumes 36 to 72 calories a day to breathe. COPD patients with severe obstruction can consume 10 times more energy. It is not always possible to meet the increased calorie need with a diet (21). Sarcopenia and malnutrition negatively affect the prognosis of COPD, causing a decrease in exercise tolerance, an increase in the risk of hospitalization, and a decrease in the quality of life (4,19,20). Malnutrition and sarcopenia negatively affect the prognosis of COPD, causing a decrease in exercise tolerance, an increase in the risk of hospitalization, and a decrease in the quality of life (4,19,20).

In our study, sarcopenia was found in 37% of male patients with COPD over the age of 65 years, and the mean duration of COPD disease was 7 years. The prevalence of sarcopenia increased by 14.5% with age and GOLD stage, but no differences were shown with gender and quadriceps muscle weakness (14.9% vs. 13.8%, p=0.40) (22). While the rate of sarcopenia was found to be 21% in men over 65 years of age in a general population assessment from Japan, 11% in a systematic review, and 6% in another study conducted in our country, it was found to be high in our study because it was found in the group of patients with COPD in our country, which is a country with a low socio-economic status (8,17). It has been shown in previous studies that BMI and sarcopenia cannot be evaluated in patients with COPD (23).

Deniz et al. (20) showed that there is a significant relationship between diaphragm thickness and peak (Peak Expiratory Flow) and sarcopenia. Kaluźniak-Szymanowska et al. (21), similar to the study he conducted, found that pulmonary function tests were lower in the malnourished and sarcopenic group over 65 years of age, they were in the GOLD stage 3-4 group, and their mMRC scores were higher. However, we think that the lack of a statistically significant result is due to the insufficient number of our cases.

Study Limitations

Because the study consisted of patients participating in pulmonary rehabilitation, it was not representative of the entire COPD population and was designed retrospectively. We also evaluated the GLIM etiological

criterion of reduced food intake using subjective responses to the MNA-SF questionnaire. The lack of multivariate analysis is another limitation of our study. We can emphasize that women were not included in the study because we could not provide a statistically homogeneous distribution in our limited sample size, but no gender difference was observed in sarcopenia in copd patients in the literature. We can also discuss the fact that COPD causes sarcopenia on its own and is not compared with <65 years of age.

Conclusion

Although it was observed that the frequency of malnutrition and sarcopenia was higher than normal in the COPD patient group over 65 years of age, a decrease in pulmonary function tests and a decrease in effort capacity due to sarcopenia, a statistically significant result was reached due to the insufficient number of cases. We think that large series with control group and prospective studies are needed.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023 - 451, date: 28.12.2023).

Informed Consent: Verbal and written consent was obtained from the patients in accordance with the Declaration of Helsinki and our hospital practice.

Authorship Contributions: Surgical and Medical Practices - K.K., S.T.O., H.A., S.S.; Concept - K.K., S.T.O., F.T.A.; Design - K.K., S.T.O., S.S.; Data Collection or Processing - K.K., S.T.O., F.T.A., H.A.; Analysis or Interpretation - K.K., S.T.O., H.A.; Literature Search - K.K., S.T.O., F.T.A., S.S.; Writing - K.K., S.T.O.

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

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Comparison of COVID-19 RT-PCR-Positive Patients in Oro-Nasopharynx Samples with RT-PCR Results in Simultaneous Stool Samples, Prospective Study

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ABSTRACT

Introduction: The definitive diagnosis of coronavirus disease-2019 (COVID-19) infection is made by polymerase chain reaction (PCR) tests on nasopharyngeal and oropharyngeal swab samples. However, the presence of viral RNA has also been identified in stool samples. In this study, we aimed to investigate the relationship between severe acute respiratory syndrome-coronavirus-2 positivity in stool and the outcomes of COVID-19 disease.

Methods: Fifty-four patients who were hospitalized between April-June 2020 and had positive COVID-19 PCR tests in nasopharyngeal and oropharyngeal swab samples were included in the study. PCR was performed on the stool samples of all patients. In addition, laboratory findings, clinical data, and computed tomography (CT) results of these patients were recorded and analyzed.

Results: Among the patients, 13 out of 28 (46.4%) with positive fecal PCR test results were female, whereas 11 out of 26 (46.4%) with negative fecal PCR test results were female. Furthermore, 19 out of 28 patients (67.9%) with positive fecal PCR test results recovered, whereas 23 out of 26 patients (88.5%) with negative fecal PCR test results recovered. Notably, patients with fecal PCR-positive results exhibited more severe dyspnea, higher blood pressure, abnormal CT findings, and elevated D-dimer levels. Moreover, compared with patients with negative PCR results, those with positive fecal PCR results had lower levels of procalcitonin, hemoglobin, hematocrit, and lymphocytes.

Conclusion: Considering the relationship between stool PCR positivity and the prognosis of the disease and laboratory test results, routine stool PCR tests may be useful, especially in COVID-19 patients presenting with gastrointestinal symptoms.

Keywords: COVID-19, fecal PCR, enteric pathogen, SARS-CoV-2

Introduction

The new coronavirus infection, which began in Wuhan in 2019, was officially named coronavirus disease-2019 (COVID-19) by the World Health Organization. On February 20th, 2020, due to the escalating numbers of cases with over 75,000 patients and 2,130 deaths in five continents, COVID-19 was declared a pandemic. It is generally regarded as a respiratory disease, with its main clinical manifestations being fever, cough, shortness of breath, weakness, and joint pain. To diagnose the infection, nasopharyngeal swab samples are taken from patients exhibiting these symptoms, and polymerase chain reaction (PCR) tests are employed to detect viral RNA. PCR tests are also used during the treatment and follow-up processes.

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Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) causes this emerging pandemic (1). Outbreaks of emerging infectious diseases pose a significant challenge and threat to healthcare providers because of the limited information available about these diseases.

COVID-19 primarily spreads through contact with respiratory droplets or contaminated surfaces and primarily affects the respiratory system (2). Previous studies have detected coronaviruses in various bodily samples, such as nasal or nasopharyngeal swabs, sputum, conjunctival scraps, urine, feces, tears, endotracheal aspirate, bronchoalveolar lavage, blood, and lung tissues (3,4). Although the infection is commonly detected in nasopharyngeal swab samples, it has been observed that the RNA of the virus can also be found in stool samples. Furthermore, this positivity in stool samples may persist even after nasopharyngeal swab samples show negative results.

The aim of our study was to evaluate and interpret the relationship between clinical findings, laboratory test results used in the follow-up and treatment of COVID-19 patients, and stool PCR test results.

Methods

Study Population

The study was approved by the University of Health Sciences Turkey, Hamidiye Faculty of Medicine Clinical Research Ethics Committee (approval number: 2021.02.11-84, date: 11.02.2021).

Our study was conducted on 54 patients clinically diagnosed with COVID-19 hospitalized in the intensive care unit and COVID-19 clinics between April and June 2020 at University of Health Sciences Turkey, Sultan 2. Abdulhamid Khan Training and Research Hospital in İstanbul, Turkey. Patients were included in this study according to the inclusion and exclusion criteria stated below: (a) clinically confirmed COVID-19 patients (b) serum C-reactive protein, D-dimer, ferritin, complete blood count, and the patients whose nasopharynx samples were PCR positive at diagnosis (c) patients who have been appropriately clinically monitored and can be reached; (d) without other inflammatory diseases and (e) non-malignant.

Swab Samples of Patients

In the University of Health Sciences Turkey, Sultan 2. Abdulhamid Khan Training and Research Hospital's accredited laboratory, patient naso-oropharyngeal swab samples were examined. Using a Rotor-Gene® Q MDx device (Self-screen B.V., Biothof 15-1, 1098 RX Amsterdam, The Netherlands), viral RNA was extracted using Bio-speedy® viral nucleic acid buffer (Bioexen LTD, Turkey), and real-time polymerase chain reaction (RT-PCR) was performed using the Bio-speedy® COVID-19 RT-qPCR kit with primers and probes targeting the SARS-CoV-2 nucleocapsid (N) gene fragment. A positive outcome was defined as a computed tomography (CT) value of ≤38. The kit's specificity was 100% and its analytical sensitivity was 98.7%. Patients who tested positive for PCR had their nasopharynx and stool samples taken every week.

Using the spin clone method and Anatolia's Bosphore viral DNA-RNA extraction kit, stool viral RNA was extracted. The Bosphore Novel Coronavirus (2019-nCov) Detection Kit from Anatolia (Anatolia Geneworks, Anatolia Diagnostics and Biotechnology Products Inc., İstanbul, Turkey) was used for RT-PCR. In accordance with the manufacturer's instructions, automated RT-PCR amplification and detection of PCR products were performed using an Abbot m2000 RT-PCR device (Abbott Molecular 33 Inc., Des Plaines, IL). A CT value below 32 was considered a positive result.

Outcomes

The demographics, baseline characteristics, and laboratory and radiological findings of patients with COVID-19 were recorded from the hospital database. The symptoms of the patients on admission, comorbidities, physical and laboratory findings, chest CT imaging findings, intubation/intensive care requirement, and survival outcomes were recorded and analyzed.

Statistical Analysis

The analyses in the study were performed using SPSS 15.0 software. In the statistical analysis, numerical data for continuous variables were presented as medians and quartile ranges (P 25-75). Categorical variables are expressed as numerical percentages. Student's t-test was applied for normally distributed variables, and Mann-Whitney U test was applied for non-normally distributed variables. The chi-square (χ^2) test or Fisher's exact test was used to examine classified variables, with statistical significance set at p-values <0.05.

Results

A total of 54 patients, 24 (44.4%) women and 30 (55.6%) men, were included in the study. Thirteen of 28 patients (46.4%) with positive fecal PCR test results were female, whereas 11 of 26 patients (46.4%) with negative fecal PCR test results were female (p=0.76). The age of patients ranged between 20 and 90 years. The median age of patients with a fecal PCR test positive was 63.68±17.67 while 54.65±21.8 in fecal PCR test-negative patients (p=0.119). Nineteen of 28 patients (67.9%) with positive fecal PCR test results recovered, whereas 23 of 26 patients (88.5%) with negative fecal PCR test results recovered (p=0.069).

Dyspnea (p=0.014), hypertension (p=0.045), and CT grade (p=0.02) were statistically significantly higher in patients with fecal PCR-positive compared with PCR-negative patients. Clinical signs and symptoms, comorbidities, mechanical ventilation needs, and CT findings are summarized in Table 1.

Procalcitonin (p=0.027), hemoglobin (p<0.001), hematocrit (p<0.001), and lymphocyte (p=0.04) values were statistically significantly lower in patients with fecal PCR-positive compared with those with fecal PCR-negatives. Only the D-dimer levels (p=0.025) among the laboratory findings were statistically significantly higher in patients with fecal PCR positivity. Laboratory and physical findings of patients with COVID-19 at admission are shown in Table 2.

Discussion

Fecal PCR test results were positive in 28 of 54 patients. According to the study data, dyspnea and concomitant hypertension were significantly more common in fecal PCR-positive patients, and it was shown that CT

Table 1. Clinical characteristics of patients with COVID-19

		SARS-CoV-2 RNA in feces						p
		Positive (n=28)		Negative (n=26)		Total		
		n	%	n	%	n	%	
Clinical signs and symptoms								
Dry cough	a	15	53.6%	15	57.7%	30	55.6%	0.761
	p	13	46.4%	11	42.3%	24	44.4%	
Dyspnea	a	10	35.7%	18	69.2%	28	51.9%	**0.014***
	p	18	64.3%	8	30.8%	26	48.1%	
Nausea/vomiting	a	23	82.1%	24	92.3%	47	87.0%	0.267
	p	5	17.9%	2	7.7%	7	13.0%	
Diarrhea	a	23	82.1%	24	92.3%	47	87.0%	0.267
	p	5	17.9%	2	7.7%	7	13.0%	
Fatigue	a	8	28.6%	12	46.2%	20	37.0%	0.181
	p	20	71.4%	14	53.8%	34	63.0%	
Comorbidities								
Diabetes mellitus	p	3	10.7%	4	15.4%	7	13.0%	0.61
	a	25	89.3%	22	84.6%	47	87.0%	
Hypertension	a	11	39.3%	4	15.4%	15	27.8%	**0.045***
	p	17	60.7%	22	84.6%	39	72.2%	
COPD	p	5	17.9%	4	15.4%	9	16.7%	0.81
	a	23	82.1%	22	84.6%	45	83.3%	
Chronic kidney disease	p	3	10.7%	2	7.7%	5	9.3%	0.7
	a	25	89.3%	24	92.3%	49	90.7%	
Cardiovascular disease	n	10	35.7%	7	26.9%	17	31.5%	0.48
	p	18	64.3%	19	73.1%	37	68.5%	
	a	26	96.3%	26	100.0%	52	98.1%	
Mechanical ventilation need and CT scan findings								
Mechanical ventilation (None: 0 NIMV: 1 IMV: 2)	0	12	42.9%	18	69.2%	30	55.6%	0.13
	1	8	28.6%	3	11.5%	11	20.4%	
	2	8	28.6%	5	19.2%	13	24.1%	
CT findings (grade) Grade 0: None Grade 1: Partially Grade 2: Moderate Grade 3: Advance	0	4	14.3%	13	50.0%	17	31.5%	**0.02***
	1	11	39.3%	9	34.6%	20	37.0%	
	2	8	28.6%	2	7.7%	10	18.5%	
	3	5	17.9%	2	7.7%	7	13.0%	

COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COPD: Chronic obstructive pulmonary disease, CT: Computed tomography, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, a: Absent, p: Present, n: Not known

grade and D-dimer levels were significantly higher in patients with a positive test. However, the procalcitonin, hemoglobin, hematocrit, and lymphocyte values were found to be significantly lower.

Bioinformatic studies have revealed the presence of cells in the human lung and gastrointestinal system that contain angiotensin-converting enzyme 2 (ACE2) receptors. These ACE2 receptors are involved in epithelial cells in the esophagus and nutrient-absorbing enterocyte in the small and large intestines. When the virus infects these cells in the gastrointestinal system, it results in increased permeability in the gastrointestinal mucosal wall, manifesting as diarrhea or watery stool in the patient. Previous studies have reported that viral RNA was detected in stool samples of patients diagnosed with COVID-19, even if their nasal/pharyngeal swabs were negative (5). Our study, which included 54 patients diagnosed with COVID-19 through nasopharyngeal and oropharyngeal sampling, revealed fecal PCR positivity in 28 (58.4%) of these patients, indicating fecal sampling as a potentially valuable alternative or additional method.

Continuous PCR-RNA test positivity in feces suggests that viruses are released from infected gastrointestinal cells. Wong et al. (6), in a meta-analysis examining 17 studies, reported that the pooled detection rate of SARS-CoV-2 PCR positivity in stool was 43.7% based on the number of patients and 33.7% based on the number of samples. Stool PCR positivity was observed to be higher in patients with more severe disease, gastrointestinal symptoms, and female gender. Parasa et al. (7) also

Table 2. Laboratory and physical findings of patients with COVID-19 at admission

	SARS-CoV-2 RNA in feces			p
	Positive (n=28)	Negative (n=26)	Total	
Temperature, °C	37.68±0.84	37.79±1.06	37.73±0.94	0.788
Heart rate, bpm	87.11±22.35	81.54±9.83	84.43±17.55	0.931
O_2 saturation	92.75±2.79	93.58±2.8	93.17±2.79	0.375
Respiratory rate (rpm)	17±2.8	16.08±3.89	16.54±3.38	0.169
Urea (mg/dL)	133.67±80.94	141.5±102.7	137.09±89.62	0.970
Creatinine (mg/dL)	2.18±1.9	17.23±79.54	9.28±54.58	0.544
AST (U/L)	131.46±212.27	56.76±44.28	96.23±160.37	0.412
ALT (U/L)	123.46±191.91	64.12±64.22	95.47±148.06	0.123
D. bil. (mg/dL)	1.4±2.09	0.35±0.32	0.92±1.63	0.164
LDH (U/L)	896.71±529.07	723.17±464.01	818.45±503.48	0.237
CRP (mg/L)	126.32±83.82	86.17±78.58	108.21±83.17	0.078
Sedimentation	96.2±29.47	69±49.65	83.47±42.03	0.082
Ferritin (ng/mL)	1457.63±3431.44	633.6±940.6	1097.12±2657.22	0.339
Procalcitonin	3.31±3.22	4.68±13.19	3.95±9.18	**0.027***
CK (U/L)	103.62±101.34	174.1±386.61	138±278.22	0.958
CKMB (ng/mL)	4.38±6.49	5.48±9.5	4.99±7.68	0.623
D-dimer (ng/mL)	6033.54±7044.56	2056.83±2434.93	4166.92±5708.33	**0.025***
Fibrinogen (mg/dL)	618.13±208.74	529.75±192.01	577.02±203.7	0.113
WBC (10^3x mm^3)	8.65±4.68	7.6±3.76	8.17±4.27	0.321
HGB (g/dL)	10.1±2.1	13.45±5.37	11.68±4.3	**0.001***
HTC (%)	31.28±5.91	39.14±12.31	34.98±10.18	**0.001***
MCV (fL)	88.42±7.56	87.42±10.28	87.95±8.87	0.086
PLT (10^3x mm^3)	173.79±97.45	207.35±71.58	189.62±87.07	0.051
MPV (fL)	10.65±1.21	10.19±1.06	10.44±1.16	0.134
NEUT (10^3x mm^3)	7.38±4.88	5.28±3.48	6.39±4.36	0.121
LYM (10^3x mm^3)	0.82±0.6	1.25±0.79	1.02±0.72	**0.040***
EOS (10^3x mm^3)	0.06±0.12	0.05±0.08	0.05±0.1	0.455
pH	7.39±0.12	7.38±0.12	7.39±0.12	0.943
PCO_2 (mmHg)	41.78±15.75	43.27±10.24	42.35±13.75	0.385
PO_2 (mmHg)	53.8±17.54	55±20.16	54.26±18.29	0.790
SaO_2 (%)	78.93±15.13	77.62±21.91	78.43±17.71	0.804
HCO_3 (mmol/L)	24.34±5.23	24.35±4.63	24.34±4.94	0.901
Lactate (mmol/L)	2.51±1.23	2.02±1.02	2.32±1.16	0.202

COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, D. bil.: Direct bilirubin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CK: Creatine kinase, CKMB: Creatine kinase MB isoenzyme, WBC: White blood cells, HGB: Hemoglobin, HTC: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet, MPV: Mean platelet volume, NEUT: Neutrophil, LYM: Lymphocyte, EOS: Eosinophil, PCO_2: Partial pressure of carbon dioxide, PO_2: Partial pressure of oxygen, SaO_2: Oxygen saturation, HCO_3: Bicarbonate

reported viral RNA shedding in feces in 40.5% of COVID-19 patients, with 12% manifesting gastrointestinal symptoms. In our study, only seven patients (12.9%; 7/54) had gastrointestinal symptoms (nausea/vomiting and diarrhea). However, the fecal PCR test was positive in five of these seven patients. Considering the detection of viruses in feces and positive rectal swabs in a substantial number of patients and the correlation between diarrhea and stool positivity, we recommend routine PCR testing of feces in COVID-19 patients, particularly those presenting with gastrointestinal symptoms. We also suggest that transmission-based precautions for hospitalized patients should be continued if a fecal PCR test for COVID-19 is positive (8-10).

Our study also revealed that patients with SARS-CoV-2 RNA-positive fecal results had different laboratory findings than those with negative results. These findings generally correlated with the recent meta-analysis of Ghahramani et al. (11), which compared patients with severe and mild disease. Interestingly, in our study, procalcitonin levels were lower in patients with positive fecal PCR tests. In contrast, Xu et al. (12) indicated

that higher procalcitonin levels were more prevalent in patients with severe disease.

In addition, our study emphasizes the importance of evaluating patients who describe gastrointestinal complaints in the patient group diagnosed with COVID-19. Liu et al. (13) reported that there were not enough data to show an association between gastrointestinal symptoms and severe COVID-19 disease, but we observed that those with gastrointestinal symptoms had symptoms for a longer duration. Tariq et al. (14) reported that gastrointestinal symptoms were observed in 20% of COVID-19 patients and that more high-quality evidence is needed to explore factors causing mortality in these patients. Therefore, testing for COVID-19 should be performed using both respiratory and stool samples, if available (15).

In our study, diarrhea, nausea, and/or vomiting (13%) were the most common gastrointestinal symptoms. In a recent meta-analysis by Suresh Kumar et al. (16), it was emphasized that nausea and/or vomiting are very common gastrointestinal symptoms in patients diagnosed with COVID-19. Interestingly, we found that hypertension was more common in patients with PCR-positive stool. Zhang et al. (17) reported that hypertension significantly increased the risk of severe COVID-19. One can speculate that there may be a relationship between hypertension and SARS-CoV-2 PCR positivity in feces in terms of disease severity, but larger, prospective, and randomized studies are needed to confirm this.

Patients with fecal PCR-positive and -negative results exhibited differences in clinical and laboratory findings. PCR results in stool sampling may be crucial for the detection and follow-up of this disease, especially considering the low rate of PCR positivity and high rate of false-negative results in nasopharyngeal and oropharyngeal swab samples.

Study Limitations

Our study has some limitations. If we count the reasons for our small number of cases; 1. The limited number of PCR test kits that are examined by fecal method and the necessity to be performed very carefully. 2. Fecal PCR test kits are difficult to access and finance because of their high cost. For these reasons, we could not include more cases in our study.

Conclusion

Fecal PCR testing presents a promising alternative or supplementary diagnostic method for COVID-19, particularly in cases where respiratory swabs may yield false-negative results. It could aid in more accurate and timely diagnosis, contributing to better disease management and control. Our findings shed light on the potential benefits of incorporating fecal sampling in COVID-19 testing protocols, and we recommend further research to better understand its implications on disease severity and transmission.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Hamidiye Faculty of Medicine Clinical Research Ethics Committee (approval number: 2021.02.11-84, date: 11.02.2021).

Informed Consent: It was obtained.

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Diurnal Variation of Fetomaternal Doppler and Fetal Cardiac Function Parameters in the Hospitalized Pregnancies: A Cross-Sectional Study

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ABSTRACT

Introduction: To assess changes in blood flow in the uterine, fetal cerebral, and umbilical arteries (UA) by Doppler ultrasound and alterations in the variability of fetal heart rate (FHR) as well as fetal cardiac performance by fetal echocardiography between the 7.00 a.m. and 7.00 p.m. periods in pregnancies ranging from 24 to 39 weeks.

Methods: Fifty pregnant participants underwent a customized fetal examination on the same day during both study periods, including Doppler measurements of the umbilical artery pulsatility index (UA-PI), fetal middle cerebral artery-pulsatility index (MCA-PI), middle cerebral artery-peak systolic velocity (MCA-PSV), cerebroplacental ratio, uterine artery-pulsatility index (UtA-PI), FHR, and fetal movements as well as various Doppler parameters of the fetal heart such as left isovolumetric contraction and relaxation times, mitral E- and A-wave velocities, the E/A ratio, K-index, filling time, and the myocardial performance index.

Results: During the PM period, there was a meaningful increase in the MCA-PSV compared with the AM period. Conversely, the resistance in the MCA, particularly the PI, was found to be lower than that in the AM period. In addition, the FHR measured in the PM period increased compared with that in the AM period. The maternal UtA-PI and fetal UA-PI examined in the AM and PM periods were comparable. In addition, when all cardiac parameters examined in the study periods were compared, no significant difference was observed.

Conclusion: The findings reveal that Doppler parameters observed during the study periods may change during the day and that the fetal cardiac function parameters, previously not assessed together, may not change during the day. Subsequent investigations can validate these observations using serial measurements of Doppler parameters in healthy and complicated gravidas.

Keywords: Circadian rhythm, Fetomaternal Doppler ultrasound, myocardial performance index

Introduction

Fetal Doppler ultrasound is crucial in prenatal medicine and obstetrics (1). It is used for screening, evaluating the health of the fetus, and monitoring pregnancies that are problematic. It has been demonstrated to have notable advantages in enhancing perinatal results and functioning as a tool to inform obstetrical decisions and decrease the requirement for neonatal intensive care (2).

Umbilical artery (UA) Doppler provides important information about fetal circulation. During healthy pregnancies, the fetoplacental unit expands as the pregnancy advances, ensuring sufficient oxygen and nutrition transport to support fetal growth (3,4). The umbilical artery pulsatility index (UA-PI) serves as a critical tool for evaluating placental function, where increased resistance within the UA indicates placental impairment and associated with intrauterine growth restriction (5,6).

The middle cerebral artery (MCA) Doppler flow velocity measurement is useful in several clinical scenarios, including the assessment of fetal anemia, fetal hypoxia, and other conditions that might affect the fetal circulatory system. It offers data on how the fetus adapts to decreased oxygen levels. A lower level of middle cerebral artery pulsatility index (MCA-PI) indicates an adaptive decrease in vascular resistance to the fetal brain, which is usually referred to as the "brain-sparing effect" (7,8). The cerebroplacental ratio (CPR) was obtained by dividing the MCA-PI by the UA-PI. This ratio provides valuable information on both the condition of the placenta and the fetal response. It has been found to be a more accurate indicator of perinatal outcome than analyzing the MCA-PI and UA-PI separately (9-11). Peak systolic velocity (PSV) is a significant Doppler blood flow measurement in MCA that holds clinical importance. Fetal anemia increases MCA-PSV when the viscosity of blood decreases because of a decrease in the concentration of red blood cells (12).

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The myocardial performance index (MPI), also commonly referred to as the Tei index, is an echocardiographic parameter used to assess fetal cardiac function. It was first described by Tei et al. (13) and is calculated as the total of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) divided by ejection time (ET). If there is an abnormality in the cardiac function of the fetus, it will result in a prolonged isovolumetric time and a shortened ET, leading to an increase in the MPI (14-16).

Circadian rhythms are physiological processes that adhere to an approximately 24 h pattern, regulate various physiological functions in our bodies, and are predetermined according to cyclic changes in the environment. The circadian rhythm of pregnancy is intricate; the mother, placenta, and fetus are separate circadian units that communicate with one another (17,18).

The suprachiasmatic nucleus (SNS) is a biological clock that receives information from the environment and imposes a circadian pattern. The SNS develops very early in pregnancy. Therefore, the fetus has a circadian rhythm and receives circadian input from the mother (19). The fetus is invariably subjected to the maternal internal environment's inherent rhythms, such as cortisol, heart rate, body temperature as well as the mother's resting activity; rhythms generated by maternal melatonin crossing placenta unchanged and food intake (20).

The fetal examination needs to be performed at different times of the day according to patient and physician schedules. The various times of the day (morning, afternoon, evening) are not expected to have a major effect on the parameters evaluated, and fetal monitoring is independent of circadian rhythms (21). However, the authors described diurnal variations in several fetal physiological parameters, including heart rate, movements, and breathing (22,23).

There is little information on whether there is a diurnal variation in the parameters of fetal, placental, and maternal uterine blood flow. The objective of this investigation was to ascertain whether day-to-day variations in fetal, placental, and maternal Doppler parameters exist. We also saw if there was any change in intraday fetal cardiac performance, which has not been researched in any previous study.

Methods

This hospital-based prospective cross-sectional study was conducted at the Perinatology Center of University of Health Sciences Turkey, Haseki Training and Research Hospital, which is associated with the University of Health Sciences, in the Sultangazi community of İstanbul. The study was carried out after receiving consent from the University of Health Sciences Turkey, Haseki Training and Research Hospital Local Ethics Committee (approval number: 240-2023, date: 20.12.2023) in accordance with the relevant clinical ethics guidelines and the current Declaration of Helsinki. Before performing any procedures, each pregnant woman was given detailed explanations regarding the aim and nature of the procedures, and their informed written consent was obtained.

The study included women with 24-39 weeks of singleton pregnancies hospitalized for diagnostic purposes within the indication in our perinatology clinic and were not expected to give birth. The gestational age was ascertained with the use of first trimester ultrasonography. In addition, age, gravidity, parity, fasting glucose, and body mass index were recorded for all gravidas enrolled in the study.

The study conducted in 2023 had 78 gravidas, each holding a single fetus. Multiple pregnancies, employment of pharmaceutical drugs that potentially impact the fetoplacental and fetal circulatory systems, and fetuses exhibiting malformations and chromosomal anomalies were excluded. The gravidas that participated in the study were first examined by ultrasound at 7 a.m. while fasting, and the following parameters were collected: head circumference (HC), biparietal diameter (BPD), femur length (FL), abdominal circumference (AC), estimated fetal weight (EFW), uterine artery-pulsatility index (UtA-PI), UA-PI, middle cerebral artery peak systolic velocity (MCA-PSV), MCA-PI, CPR, fetal heart rate (FHR), and fetal movements (FM). She was then called back at 7 p.m. when she was full of rested, and the same parameters were checked by ultrasonography. They all ate the same type of food, adjusted to their diet, and served in the hospital at the same time.

All ultrasonography was performed by a single clinician (S.T.). The individual, unaware of subject allocation until the complete collection and analysis of data, conducted each session with a duration of 15 ($\pm$5) minutes. All sonographic studies were conducted, including color Doppler and pulsed Doppler ultrasound. Doppler assessments were performed without FM or respiration. In addition, the beam angle was maintained at 20°. UA Doppler tracings were taken on the free surface of the umbilical cord. MCA was sampled from the proximal section, close to its origin from the internal carotid artery (24).

To obtain the left MPI and other fetal cardiac parameters; initially, a 4-chamber perspective of the fetal heart was acquired, followed by a slight angled probe toward the apex to capture the aorta's origin. The Doppler sample volume was opened to 3 mm and positioned on the ascending aorta's lateral wall, situated beneath the aortic valve (AV) and just above the mitral valve (MV). The insonation angle was kept as close to 0° as possible and was always less than 30° (Figure 1). In addition, the E/A waveform consistently exhibited positive flow. However, the aortic blood flow waveforms were negative. The subsequent time intervals were estimated as follows: IVCT was estimated from the moment MV closed to AV opening, ET from AV opening to closure, and IVRT from AV closure to MV opening. MPI was determined by dividing the sum of IVCT and IVRT by ET.

Statistical Analysis

Analyses were performed using IBM SPSS v22.0 (USA). For descriptive statistics, the values of mean with standard deviation and median with range were used to present the numeric data. After Kolmogorov-Smirnov test to examine the normality of clinical and Doppler ultrasound parameters, the comparisons of study parameters were performed using the paired t-test or Wilcoxon signed-rank test. For categorical variables, the McNemar's test was used. To determine significances, p-value of less than 0.05 was chosen.

Results

In 2023, a cohort of 78 gravidas with singleton gestations was enrolled in this study. However, only 50 gravidas could be included in the study.

Of the remaining 28 subjects, they were excluded because of unsuitable fetal heart position or difficult assessment of the fetal heart.

The findings of 50 gravidas whose data could be fully collected during the study period were analyzed. In this study of 50 cases, 8 (16%) were normal healthy gravidas, 13 (26%) were gravidas with threatened preterm labor, 11 (22%) were gravidas with gestational diabetes (GDM), 8 (16%) were gravidas with fetal growth restriction, 5 (10%) were gravidas with anemia, and 5 (10%) were gravidas with type 2 diabetes.

Maternal and fetal characteristics are listed in Table 1. The mean values for the maternal age were 30.0±5.9 years. The median values for gravidity were 2 (1-11), parity was 1 (0-3), gestational age was 33 (24-39) weeks, BPD was 34 (25-38) weeks, HC was 33 (24-38) weeks, AC was 33 (23-41) weeks, FL was 33 (24-38) weeks, and EFW was 1950 (649-3210) g. The median values for body mass index were 27.4 (20.1-45.8) and fasting glucose was 76 (62-135) mg/dL. There were no abnormal findings related to amniotic fluid and placenta and except for 3 fetuses, all others were head presentation.

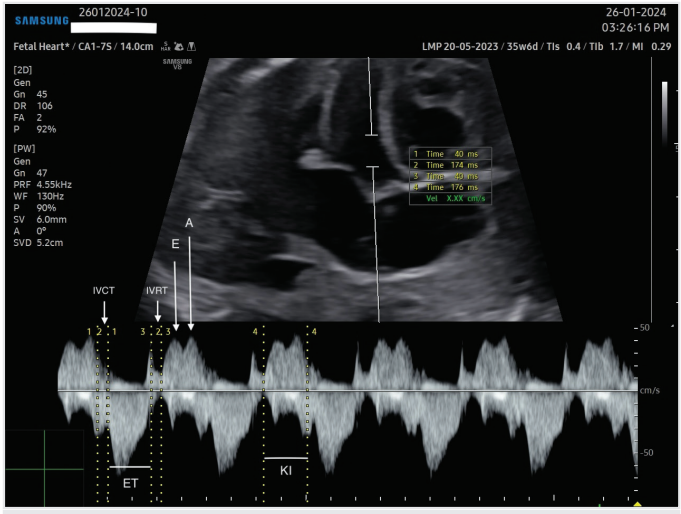

Figure 1. Measuring and calculating the myocardial performance index. A representative image indicating measurements of myocardial performance index
IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, KI: Filling time, E: Mitral E wave velocity, A: Mitral A wave velocity, ET: Ejection time

Table 1. Baseline clinical maternal and fetal characteristics (n=50)

Characteristics	Value
Maternal age, y	30.0±5.9
Gravidity	2 (1-11)
Parity	1 (0-3)
Gestational age at study, week	33 (24-39)
BMI, kg/m^2	27.4 (20.1-45.8)
Fasting glucose, mg/dL	76 (62-135)
BPD, mm	34 (25-38)
HC, mm	33 (24-38)
AC, mm	33 (23-41)
FL, mm	33 (24-38)
EFW, g	1950 (649-3210)

BMI: Body mass index, BPD: Biparietal diameter, HC: Head circumference, AC: Abdominal circumference, FL: Femur length, EFW: Estimated fetal weight

Table 2 shows that the mean values for FHR was 135±7 beats/min in the AM period and 141±5.6 beats/min in the PM period. The mean FHR difference between the AM and PM periods was statistically significant (p=0.001). There was also a significant difference in the number of FM observed on ultrasound at 15 min between the AM and PM periods. The median MCA-PSV values were 41 (24-57) cm/s in the AM period and 51 (31-61) cm/s in the PM period. The mean difference in MCA-PSV between AM and PM was statistically significant (p=0.001) and the MCA-PI values measured in the PM period were significantly lower than the MCA-PI values measured at the AM period (1.4±0.19 vs. 1.6±0.2; p=0.001). The median values of CPR measured during the PM period. were significantly lower than those during the AM period [1.4 (0.4-3.6) vs. 1.5 (0.4-4.2); p=0.001]. Maternal UtA-PI and UA-PI were not statistically different between the AM and PM periods. The fetal cardiac parameters measured at the AM and PM periods are depicted in the Table 3. There were no significant differences in the Doppler parameters E, A, IVCT, IVRT, MPI, and filling time measured at the AM and PM periods (p>0.05).

Discussion

In our study, the MCA-PSV measured at 7 p.m. was significantly higher than that measured at 7 a.m., whereas the MCA-PI was significantly lower. As a result, CPR at 7 p.m. was significantly lower than that at 7 a.m. In addition, the FHR and movement in the afternoon were significantly

Table 2. B-mode and Doppler ultrasonographic findings of the study population (n=50)

	AM	PM	p
Mean UtA-PI	1.1 (0.4-2.1)	1.1 (0.5-1.9)	0.848
UA-PI	1 (0.4-4.2)	1.1 (0.6-2)	0.651
MCA-PI	1.6±0.2	1.4±0.19	0.001
MCA-PSV, cm/s	41 (24-57)	51 (31-61)	0.001
CPR	1.5 (0.4-4.2)	1.4 (0.4-3.6)	0.001
FHR, bpm	135±7	141±5.6	0.001
FM			
No	20 (40%)	5 (10%)	0.001
Yes	30 (60%)	45 (90%)	

UtA: Uterin artery, PI: Pulsatility index, UA-PI: Umbilical artery-pulsatility index, MCA-PI: Middle cerebral artery-pulsatility index, MCA-PSV: Middle cerebral artery-peak systolic velocity, CPR: Cerebroplacental ratio, FHR: Fetal heart rate, FM: Fetal movements

Table 3. Fetal cardiac parameters of the study population (n=50)

	AM	PM	p
E, cm/s	33±7	33±5	0.759
A, cm/s	45±9	44±8	0.863
E/A	0.7±0.1	0.7±0.1	0.246
IVCT, ms	31 (24-38)	33 (24-40)	0.021
IVRT, ms	36±4.3	36±4.3	0.824
MPI, ms	0.4 (0.35-0.43)	0.4 (0.35-0.44)	0.126
KI	0.3±0.04	0.3±0.04	0.175

E: Mitral E wave velocity, A: Mitral A wave velocity, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, MPI: Myocardial performance index, KI: Filling time

higher than those in the morning. In our study, the UA-PI and mean UtA-PI in the morning and afternoon were not significantly different.

We found two studies that noted the effect of circadian rhythm on fetal and maternal Doppler. The first study, having a considerably similar design, had a wide range of gestational weeks and included both healthy and complicated gravidas like our participants. In this study, no significant change in the circadian rhythm was found in any of the Doppler parameters (25). In the other study involving healty pregnant women in their third trimester, the increase in MCA-PSV and decrease MCA-PI in the afternoon are smilar to our study (21). MPI and other cardiac parameters were not evaluated in either study.

In the current study, Doppler parameters at 7 a.m. were evaluated when the patient was fasting. The values at 7 p.m. were evaluated when the patient was full. Because the gravidas in the study were hospitalized, they all ate the same meals at the same time according to their diet. Opheim et al. (26) evaluated Doppler parameters before and after a meal. In this study, MCA-PSV evaluated when the pregnant woman was full was found to be high and MCA-PI was found to be low. In our study, the increase in PSV and decrease in PI of the MCA evaluated in the afternoon, when the pregnant woman was satiated, were similar to those found in this study (26).

The fetal Doppler waveform can be influenced by many factors (27). The factors involved are the angle of insonation and the region of measurement (28), technical factors like ultrasound settings, gestational age, FHR (29,30), fetal breathing (31,32) or hiccups, FM, and circadian rhythm (25). In our study, it is likely that technical factors did not significantly influence our study. Measurements were conducted using an identical instrument and by the same clinician. Measurements were obtained when fetal breathing and movement were not present.

In our study, FHR increased significantly in the afternoon, which may affect Doppler parameters. A limitation of our study is that we did not adjust the MCA Doppler parameters according to FHR. With the exception of a few studies (33), previous studies have ignored this. Another limitation of this study is the lack of neonatal outcomes and the relatively small number of cases. However, the number of cases was kept small because each patient was examined twice and the appropriate position for cardiac evaluation was waited. If the position was not favorable for fetal heart evaluation, the patient was given two more chances for a favorable position. If the fetal heart was not in the appropriate position, the patient was excluded.

When fetal cardiac parameters measured at 7 a.m. and 7 p.m. were compared, there were no significant differences. Studies on MPI, previously used to assess fetal cardiac function, have been shown that Oral Glucose Tolerance testing does not affect MPI (34), but some conditions such as fetal growth restriction (35), oligohydramnios (36) and maternal diabetes (tip 1, tip 2 and unregulated GDM) (37) increase MPI. In this study, we observed that circadian rhythm did not significantly affect fetal cardiac function. However, as this is the first study on this subject, further studies with a larger number of cases are needed.

This study demonstrated that circadian rhythms influence some Doppler parameters but not those related to cardiac function. Therefore, time of day should be taken into account when evaluating Doppler parameters. However, larger studies are necessary to develop a definitive nomogram for this purpose.

Conclusion

In conclusion, among the Doppler parameters examined in AM and PM in gravidas at 24 to 39 weeks of gestation, MCA-PSV was found to be significantly increased in PM, whereas MCA-PI was found to be significantly decreased. FHR was found to be increased in PM, contrary to other studies. As shown in previous studies, circadian rhythm affects Doppler parameters. However, more work is needed on this. However, fetal cardiac parameters did not change significantly in the AM and PM periods, and circadian rhythm did not affect fetal performance. As this is the first study on this topic, further studies are required.

Ethics Committee Approval: The study was carried out after receiving consent from the University of Health Sciences Turkey, Haseki Training and Research Hospital Local Ethics Committee (approval number: 240-2023, date: 20.12.2023) in accordance with the relevant clinical ethics guidelines and the current Declaration of Helsinki.

Informed Consent: Informed written consent was obtained.

Authorship Contributions: Concept - A.Ö.; Design - A.Ö.; Data Collection or Processing - S.T.; Analysis or Interpretation - S.T., A.Ö.; Literature Search - S.T., A.Ö.; Writing - S.T., A.Ö.

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

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Quantitative Analysis of the Weakening Effect of Cortical Windows in Non-Osteoporotic and Osteoporotic Proximal Femurs

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ABSTRACT

Introduction: Cortical windows in the proximal femur are used in musculoskeletal tumor surgery for both biopsy and curettage purposes. This study aimed to evaluate the effect of cortical windows on the weakening of the proximal femur under axial and rotational loading using finite element analysis and determine the safe widths, levels, and axial positions.

Methods: The proximal femurs of a healthy 37-year-old male and an osteoporotic 76-year-old female were 3D modeled using computed tomography scans. A total of 192 different models were created with 225 mm-long oblong windows with widths of 10, 12.5, 15, and 17.5 mm at 8 different levels and 3 different axial locations. Each model was tested for axial and rotational loading up to failure point.

Results: The safe maximum width for all levels and both bones was found to be 10 mm ($p<0.001$). Anterolateral and posterolateral placement of cortical windows did not offer biomechanical advantages under axial loading ($p>0.05$).

Conclusion: The study quantitatively shows that keeping the width of the cortical window below 15 mm and proximal to the lesser trochanter is an important factor in keeping the fracture risk low during biopsy procedures. Additionally, anterolateral or posterolateral placement of cortical windows does not offer any biomechanical advantages. The findings of this study can help clinicians to avoid iatrogenic fractures during biopsy and curettage procedures.

Keywords: Femur, finite element analysis, biomechanics, bone biopsy

Introduction

The proximal femur is a common location for bone lesions. In younger patients, most lesions are due to primary bone tumors such as unicameral bone cysts or aneurysmal bone cysts (1); whereas in older patients, most lesions in the proximal femur are metastatic lesions (2). Curettage is used in primary lesions such as unicameral bone cysts (3). In elderly patients, open bone biopsy may be employed in cases of unknown primary origin or for local augmentation purposes (2).

Curettage and open bone biopsies are performed through windows in the cortical bone. In the proximal femur lateral (4) or posterolateral approaches (5) are recommended as the optimal biopsy route. This leaves a defect in the cortex, which may create an area of difference in the elastic modulus and as such a stress-riser effect (6). Consequently, a complication of this procedure is fracture at the biopsy site (5). Clark et al. (7) established in cadaver femora that oblong holes with rounded ends afford the greatest residual strength, and increasing the width causes a significant reduction in strength. There have also been reports of subtrochanteric fractures after femoral neck fracture fixation with screws if the screws cluster around the lesser trochanter (8). There is no widely accepted cut-off value in the literature for the safe maximum width of the window, whether it makes any difference to do it postero- or anterolaterally, as well as the relative weakening effect of the level of window in the failure load.

This study systematically analyzes the effect of different widths, levels and axial locations for the cortical windows effect on non-osteoporotic (NOP) and osteoporotic (OP) proximal femur using quantitative computed tomography (CT) based FE modeling.

Methods

The İstanbul Physical Therapy and Rehabilitation Training and Research Hospital Ethics Committee approvals were obtained for the study (IRB: 2024-04). Informed consent was obtained from the patients for anonymous use their imaging and demographic data.

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CT Data and FE Modeling

Proximal femur CT scans of a healthy 37-year-old male (Slice thickness: 1.0 mm) and an OP 76-year-old female (Slice thickness: 1.0 mm) who presented with a pelvic fragility fracture on the ipsilateral side were used for this study. The bone was modeled using triangular shell elements with a thickness of 0.4 mm and a size of 3 mm for the outer surface of the cortical bone, and tetrahedral solid elements with a size of 3 mm were used for the rest of the bone. There were approximately 27,000 triangular plates and 180,000 tetrahedral elements in both models. The elastic modulus and strength of each element were calculated by converting Hounsfield units into Young's modulus and yield strength according to Keyak et al. (9). Figure 1 shows the difference in bone quality between the two femurs.

Loading and Constraint Conditions

For both models, the femoral shaft was cut perpendicular to the mechanical axis about 12 cm from the lesser trochanter for the biomechanical setup. The distal one third was restrained (Figure 2a). Axial loading was simulated with a force vector applied to the joint surface along the mechanical axis of the femur, which was set to be 6° from the anatomic axis (Figure 2b). Rotational loading was simulated with a force vector directed posterior to anterior acting on the femoral head (Figure 2c). The loading area and direction of the force on the femoral head were consistent between all cases.

Generation of the Bone Window Model

Eight window levels were defined for both models. The uppermost window had its proximal border approximately 10 mm from the tip of the greater trochanter. The window moved exactly 10 mm distally in each level. A description of the levels in terms of their proximal and distal ends is summarized in Table 1. All windows had a uniform height of 225 mm. Four different widths of 10, 12.5, 15, and 17.5 mm were used. Axially, the windows were cut either anterolaterally, posterolaterally, or at the midline (Figure 3). Figure 4 shows a midline cortical window of 12.5 mm width at level 4. For the two models, a total of 192 cortical windows were created.

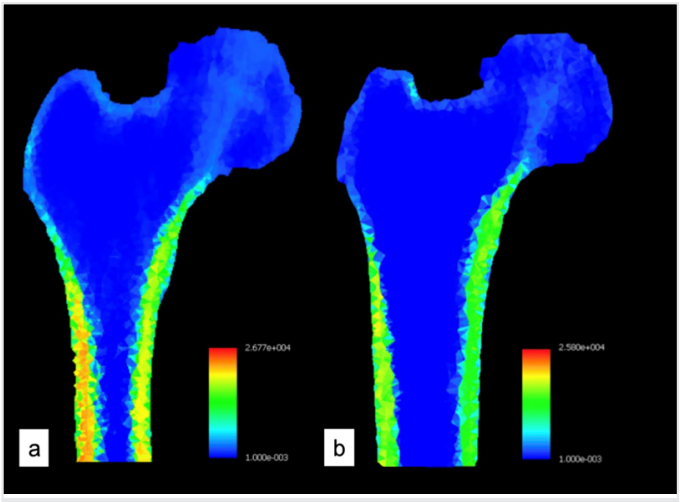

Figure 1. Coronal sections of (a) non-osteoporotic (NOP) and (b) osteoporotic (OP) femurs. Note the high Young's modulus at the lateral cortex of NOP as well as the prominent primary compressive trabeculae compared to OP femur

Simulation

Each of the 192 models with cortical windows was tested for axial and rotational loading, resulting in a total of 384 analyses. In each case, the applied load started at 25 N and then increased to 25 N at each step until there was a failure of more than five surface elements. The load to failure in the NOP femur without a cortical window was 4525 N for axial loading and 950 N for rotational loading. The load to failure in the OP femur without a cortical window was 2350 N for axial loading and 925 N for rotational loading. Failure under axial load occurred in the neck in both cases, whereas failure under rotational load occurred just above the lower constraint in the shaft.

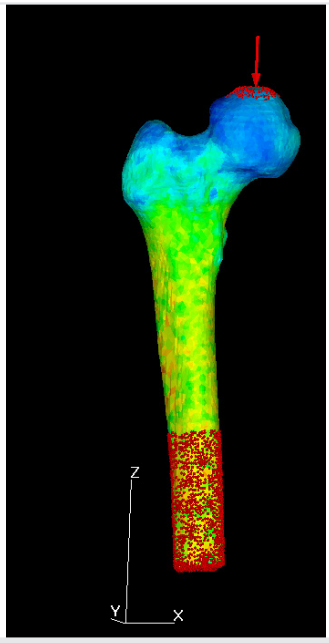

Figure 2. The load direction, area and the distal constraint are shown

Table 1. Description of the proximal and distal ends of the cortical windows

Level	Description
1	Starts approximately 1 cm below the tip of GT at the level of the superior femoral neck, ends above LT
2	Starts approximately at the level of mid-femoral neck, ends above LT
3	Starts approximately at the level of the inferior femoral neck, ends above LT
4	Starts below the GT, ends at the upper half of LT
5	Starts at the proximal end of the LT, ends at the lower end of the LT
6	Starts at the midpoint of LT and ends below LT
7	Starts at the inferior half of the LT, ends below the LT
8	Starts below LT and ends below LT

GT: Greater trochanter, LT: Lesser trochanter

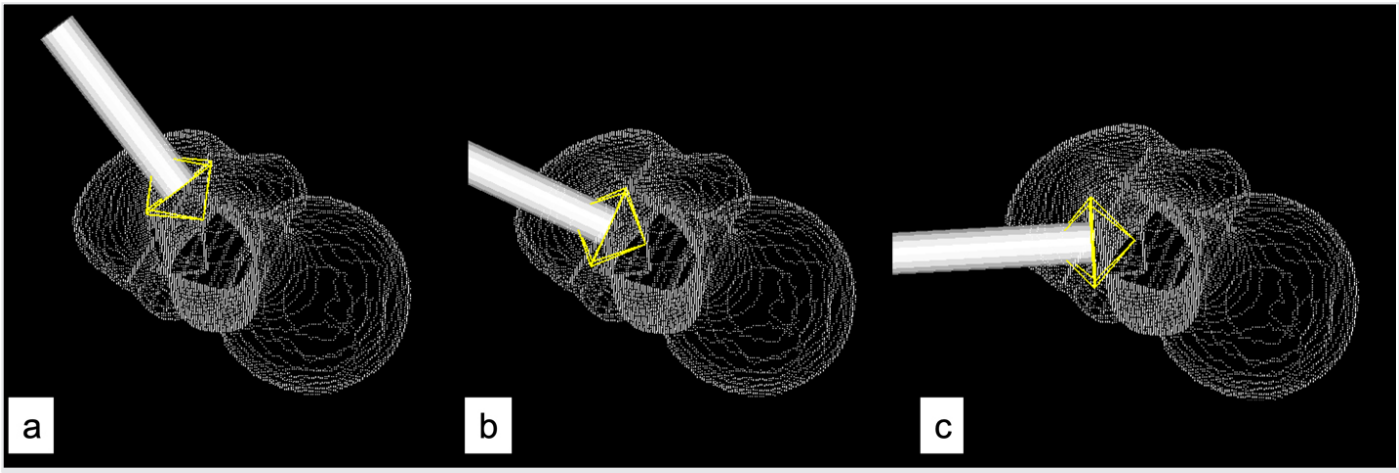

Figure 3. Axial position of the posterolateral (a), midline (b), and anterolateral (c) windows

Statistical Analysis

The load to fracture in both models was reported using descriptive statistics. Python and SPSS (Chicago, IL) were used for statistical analysis and graphical representation. A $p<0.05$ was accepted as significant. One-Way ANOVA test was used to compare the failure loads between anterolateral, midline and posterolateral windows for each width for both axial and rotational loading. Linear regression was used to study the correlation between the level of the window and the fracture load. The chi-square test was used to establish the significance of increased risk of fracture through the cortical window.

Results

Non-Osteoporotic Bone Model

The One-Way ANOVA test used to compare the fracture loads for anterolateral, midline and posterolateral windows showed that for all cases in the NOP model, there was no difference in making the window posterolateral, at the midline or anterolaterally in terms of average load to failure in both axial ($p>0.05$) and rotational loading ($p>0.05$).

For axial loading, no reduction in fracture load or fracture through the cortical window was observed with a 10 mm wide cortical window. Five cases of iatrogenic fractures were observed with a 12.5 mm window, seven cases with a 15 mm window and eight cases with a 17 mm window. No iatrogenic fracture or decrease in fracture load occurred at or above level 4. Figure 5 shows the scatter plots of the fracture loads for each window width except for 10 mm with regression lines. For windows below level 4, linear regression suggests that on average, an additional decrease of 6.5% in the fracture load is expected for each level below the 12.5 mm window ($r^2=0.48$, $\beta=-292.5$, $p=0.004$), an additional decrease of 7.5% is expected for the 15 mm window ($r^2=0.40$, $\beta=-340.0$, $p=0.01$), and an additional decrease of 11% is expected for the 17.5 mm window ($r^2=0.80$, $\beta=-497.5$, $p<0.0001$).

19/20 iatrogenic fractures (95%) occurred in windows at level six or lower and at and above 12.5 mm width. There was a significant association between fracture status and location [$\chi^2=13.39$, $p<0.05$, odds ratio (OR): 330]. Fractures were more likely to occur inside these parameters (63%) than outside (4%), when compared to the expected values.

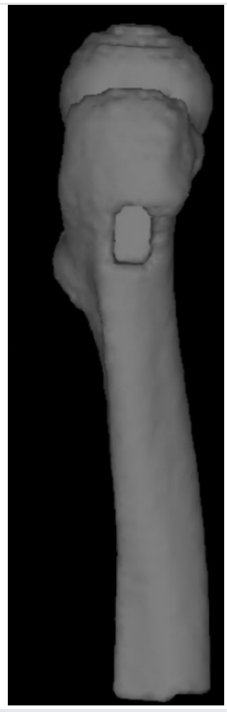

Figure 4. Example of a midline 12.5 mm-wide cortical window

For rotational loading, no reduction in fracture load or iatrogenic fracture was observed with a 10 mm wide cortical window. Two cases of iatrogenic fractures occurred with a 12.5 mm window, one with a 15 mm window and three with a 17.5 mm window. All iatrogenic fractures, except the 17.5 mm window at level 8, failed under a similar load as the native bone.

Osteoporotic bone model

The One-Way ANOVA test used to compare the fracture loads for anterolateral, midline, and posterolateral windows showed that for most cases in the OP model, there were no differences observed except for the posterolateral window in the 12.5 mm ($p=0.02$) and 15 mm ($p=0.004$) widths and for anterolateral, midline, and posterolateral windows for the 17.5 mm width ($p<0.001$) where a significant decrease in rotational failure load was observed.

For axial loading, no reduction in fracture load or iatrogenic fracture was observed with a 10 mm wide cortical window. One case of iatrogenic fractures were observed with 12.5 mm window, 8 cases with 15 mm window and 9 cases with 17 mm window. No iatrogenic fracture or decrease in fracture load occurred at or above level 3. Figure 6 shows the scatter plots of the fracture loads for each window width of 15 and 17.5 mm with regression lines. For windows below level 3, linear regression suggests that on average an additional decrease of 2.9% in the fracture load is expected for each level below with 15 mm window (r^2=0.23, β=-66.5, p<0.05) and an additional decrease of 7.7% is expected for 17.5 mm window (r^2=0.39, β=-177.1, p<0.01).

For rotational loading, no reduction in fracture load or iatrogenic fracture was observed with a 10 mm wide cortical window. Four cases of iatrogenic fractures occurred with a 12.5 mm window, 10 with a 15 mm window, and 11 with a 17.5 mm window. There was a significant reduction in fracture loads when the window was made posterolateral (Figure 6). The posterolateral cortical window resulted in an additional 8.8% decrease in rotational fracture load with each level (r^2=0.74, β=-79.5, p<0.0001).

17 of 18 fractures (94%) occurred at level four or lower and at or above 15 mm width. There was a significant association between fracture status and location (χ^2= 5.68, p<0.05, OR: 1235). Fractures were more likely to occur inside these parameters (63%) than outside (2%) compared to the expected values.

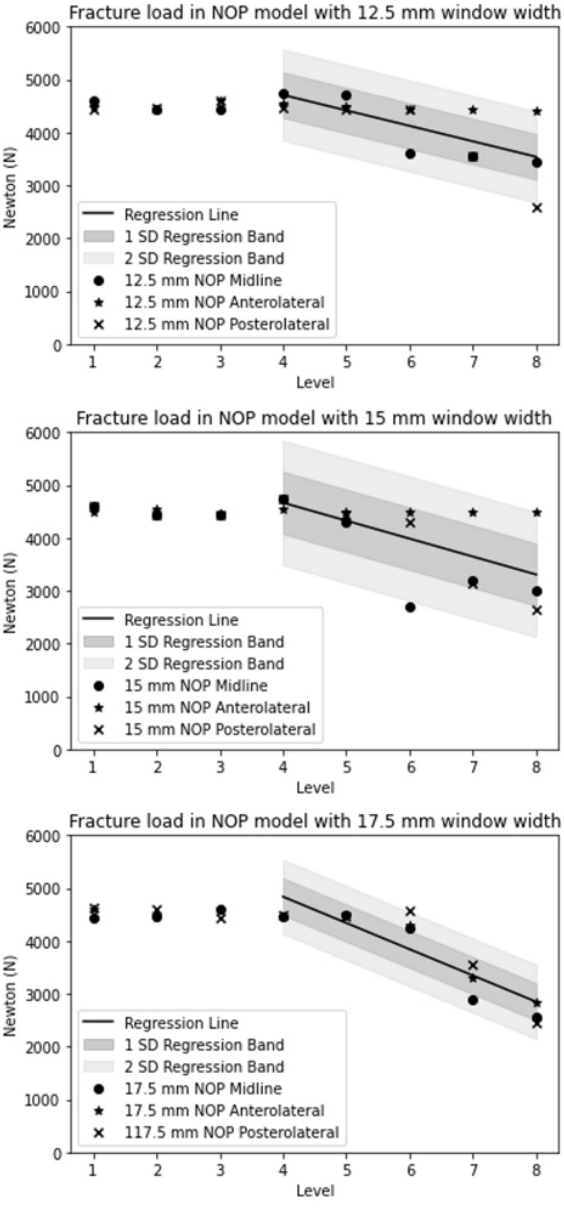

Figure 5. Fracture loads in the non-osteoporotic bone model under axial loading for 12.5, 15, and 17.5 mm wide windows

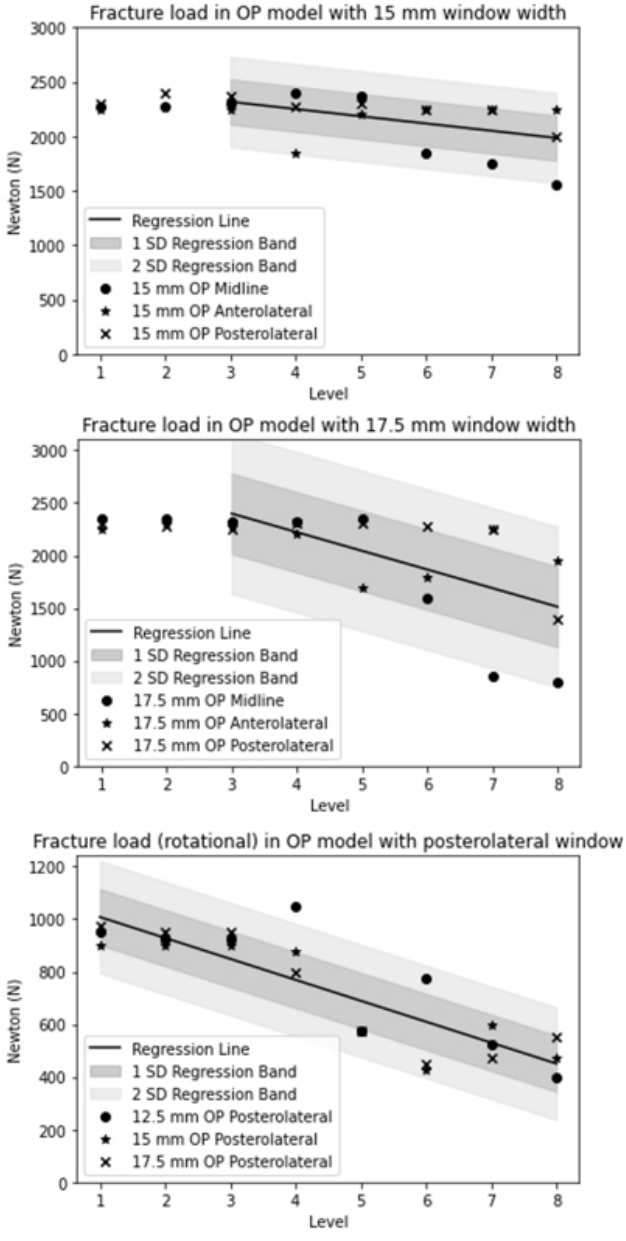

Figure 6. Fracture loads in the osteoporotic bone model under axial loading for 15 and 17.5 mm Windows and fracture load under rotational loading for 12.5, 15, and 17.5 mm posterolateral windows

All cases of fractures under axial loading in the NOP femur occurred at higher loads than in the native OP bone.

Discussion

There are three main options for studying the effects of these factors on iatrogenic fracture risk after bone biopsy. Observation studies, while frequently performed, do not allow for the control of every variable. Another option would be cadaver studies, which are expensive and hard to obtain in many institutions. In contrast to these options, one of the main advantages of FEA is the ability to change variables in a controlled simulation to perform numerous analyses and detailed investigations.

In a similar study, Hayashi et al. (10) found 15 mm to be the critical width for bone biopsy. In contrast to their study that used younger patients, we compared the OP and NOP femurs and still concluded that 15 mm is a critical value for fracture risk. In addition, our results indicate that 12.5 mm cortical windows are almost as safe as 10 mm windows. Although there were fractures in Levels 7 and 8 in the NOP group but not in the OP group, this was because the NOP patient had a much higher failure load than the OP patient and the older femur failed through the neck before it was put under sufficient stress for the 12.5 mm window to be a problem.

A novel part of this study is looking at the effects of anterolateral, midline, and posterolateral windows, which might also have value beyond tumor and trauma surgery. Anterolateral cortical windows, for example, are used for component removal in revision arthroplasty, and the effects of cortical windows at different axial positions and levels can provide insight in such situations (11-13). The hypothesis behind the anterolateral and posterolateral windows was the possibility of safely enlarging the windows as the window is moved away from the lateral cortex, which has the largest tension forces. This was not the case. The posterior to anterior force at the femoral head with a fixed shaft was tested to simulate the rotational moment at the proximal femur. Failure under rotational loading was not as sensitive to the size and level of the cortical windows as failure under axial loading, except for the posterolaterally placed windows. Under axial loading, 10 mm and 12.5 mm windows did not decrease load to failure, and failure still occurred through the neck in the OP bone. There is a moderate to high correlation of the window level with a decrease in fracture loads in larger window widths. It does not provide meaningful protection for the axial loading in both models, and in the OP bone, it significantly decreases the rotational strength of the femur.

The results also indicate a moderate to high correlation of the window level with the decrease in fracture loads in larger window widths. These are significant because of the large forces acting on the hip joint. Bergmann et al. (14) reported that average load at hip joint is 238% of body weight when walking at 4 km/h, and 260% of body weight when going downstairs. More significantly, in another study from the same lead author, the peak forces at the hip during stumbling were reported to be twice those during other activities, which in some cases corresponded to more than eight times the body weight (15). Thus, small decreases in fracture loads might correspond to fractures with low-energy trauma.

The decrease in failure load for axial loading in our study was similar to the results reported by Hayashi et al. (10). They have reported up to a 32% percent decrease in fracture load between biopsy levels 2 and 3 for 15 mm wide windows, and up to a 51% percent decrease between biopsy levels 2 and 3 for 20 mm wide windows, within one standard deviation. Note that although iatrogenic fractures in the NOP bone occurred in 12.5 wide windows, these were still under higher loads than those applied to the OP bone.

An improvement over this model would be to include the tension effect of the hip abductors. Tsai et al. (16) reported that the abductor force at the greater trochanter can be as high as 71.4% of the joint contact force. The abductors contribute to the tension forces at the lateral cortex and possibly increase the occurrence of fractures and decrease the strength with windows below their attachment site. Another improvement would be to study the effect of cyclical loading. This would ideally require the use of cadaver femora. Hsu et al. (17), in their study investigating subtrochanteric fractures after multiple screw fixation of femoral head, demonstrated that it might take up to 120,000 cycles for failure.

Study Limitations

There are a few limitations to this study. We included only one sample for OP and NOP femurs. One of the main advantages of FEA is the ability to draw meaningful conclusions with small sample sizes because of the ability to test the same model under different conditions. Salášek et al. (18), for instance, used a single pelvis CT model to study fixation biomechanics in sacral fractures. However, a larger sample size as well as more patients from both sexes would allow us to detect smaller differences as well as draw conclusions for each gender.

Conclusion

Cortical windows for biopsy or curettage may significantly weaken the bone. There seems to be no biomechanical advantage in making the window anterolateral or posterolateral instead of midline. Our results show that if large windows need to be made, keeping the width of the cortical window below 15 mm and the lower end higher than the midpoint of the LT is an important factor in keeping the fracture risk low in both OP and NOP bone.

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Informed Consent: Informed consent was obtained from the patients for anonymous use their imaging and demographic data.

Authorship Contributions: Surgical and Medical Practices - E.Ö.; Concept - E.Ö., E.Ç., A.B.; Design - E.Ö., A.B.; Data Collection or Processing - E.Ö., A.B.; Analysis or Interpretation - E.Ö., S.Y., E.Ç.; Literature Search - E.Ö., S.Y., E.Ç., O.B.; Writing - E.Ö., O.B.

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Determination of Depression Levels and Affecting Factors of the Residents in a Training Hospital

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ABSTRACT

Introduction: Residency training may lead to the development of depressive conditions with possible academic and professional consequences. We determined the levels of depression in resident medical doctors (RMDs) and assess the factors influencing depression.

Methods: This prospective cross-sectional questionnaire study was conducted on RMDs working in tertiary research hospital in İstanbul. Participation in the study was voluntary. A questionnaire was distributed to the RMDs participating in the study, and the Beck Depression Inventory-II (BDI-II) was used to measure depression levels. This study was presented as a paper at the 5th Eurasian Congress on Emergency Medicine and 12th Turkish Emergency Medicine Congress, November 10-13, 2016 (Antalya, Turkey).

Results: A total of 161 RMDs were included in the study (participation rate: 68.8%). Of the RMDs, 65 (40.4%) had depressive symptoms (BDI-II >13). An exploratory analysis of possible risk factors showed that working night shifts, length of residency, and department in which the resident worked were factors for the development of depressive symptoms. There was no association between BDI-II scores and age, gender, marital status, number of children, living alone, recent loss of a loved one, presence of chronic illness, diagnosis of depression, or use of antidepressant medication.

Conclusion: There is a high prevalence of depressive symptoms among RMDs, especially night workers, who have less experience in their residency. Active assessment of these RMDs to evaluate their depressive symptoms is important. Preventive measures and educational programmes to improve working conditions need to be reviewed.

Keywords: Resident doctors, depression, Beck Depression Inventory

Introduction

Depression is the most commonly observed psychiatric disorder worldwide, and there is a high level of consensus on its pathophysiology. It has become a global health issue, contributing to an 8-15% loss of functionality in developed countries (1,2). The current understanding of depression is that it is a psychiatric disorder characterized by emotional, cognitive, behavioral, and physical symptoms. Standards for diagnosing depression have been established to address the challenges in making an accurate diagnosis. These include the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases, which aim for universality (3). Depression evaluation scales can be categorized as self-assessment or clinician evaluation. Examples of depression scales include the Beck and Zung scales, which involve self-evaluation, and the Hamilton, Calgary, and Montgomery-Asberg Scales, which involve clinician evaluation (4-8). The Beck Depression Inventory (BDI) was developed by Beck et al. (4) to measure behavioral symptoms of depression in adults. The BDI was later revised in 1978 as the BDI-IA and in 1996 as the BDI-II. The BDI-II was developed in response to changes in diagnostic criteria for Major Depressive Disorder outlined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. It is widely used by healthcare professionals and researchers in various settings as an assessment tool (9,10). Hisli (11) translated the BDI into Turkish and conducted a validity and reliability study.

Resident medical doctors (RMDs) receive diverse education across different specialties, with some residency training programs lasting four years and others lasting five years in Turkey. Factors such as marriage or delivery may extend the residency period, particularly for female RMDs. While prolonged residency time can increase experience, it can also lead to weariness. The literature contains numerous studies on depression severity in relation to RMDs in Turkey and other countries (12-20). These studies are divided into two types: department-based and institute-based,

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similar to our own study. In addition, the department-based depression studies were separated according to the specialty of residency as family physicians, anesthesiology, surgery, etc. Depression can affect a person's quality of life. It is known that as the level of depression increases, so does emotional burnout, which leads to a decrease in individual performance (21). Depression can lead to mistakes by physicians and can also contribute to the development of burnout. This condition can have negative consequences for both physicians and patients. To reduce depression, it may be beneficial to take precautions to improve working conditions and increase job satisfaction. One approach could be to follow the example of working hours in other countries, as suggested by previous studies (21-23). Moreover, it is essential to conduct nationwide studies to determine the levels of depression among healthcare professionals using a representative sampling strategy. The findings of these studies can then be used to update the conditions and factors that affect depression levels among healthcare workers.

The current study determined the prevalence of depression among RMD patients in one of İstanbul's largest research hospitals and to investigate its relationship with related risk factors.

Methods

Study Design

This was a prospective, observational, descriptive study conducted in 2012 at a training and research hospital in İstanbul with 234 RMDs. The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 333, date: 27.10.2022). The questionnaires were anonymous and distributed to all RMDs present at the hospital during the study period. Seventy-three (31.2%) of the RMDs did not complete or return the questionnaire and were considered as "loss data." The study assessed the remaining 161 (68.8%) RMDs (28.2±2.7 years) from surgical departments (n=56, 34.8%) and internal departments (n=105, 65.2%) using the BDI-II and a questionnaire to evaluate personal data.

Data Collection

Informed consent was obtained from the participants through face-to-face interviews. The study included a descriptive questionnaire and the BDI scale. The research data were collected using self-reported questionnaires, which consisted of two parts: a descriptive questionnaire and the BDI-II. The BDI-II was completed by the participants themselves and consisted of 14 titles with questions specific to their personal and professional lives. During the creation of the questions, we examined similar studies (21) to evaluate whether participants had environmental factors related to depression. These factors included age, gender, marital status, having children, living alone, recent loss of a loved one, presence of chronic disease, previous diagnosis of depression, use of antidepressant medication, residency department at work, current duration of residency, working status (night shift or daylight), and number of night shifts worked. The doctors working between 17.00 and 08.00 are on the night shift, whereas those working between 08.00 and 17.00 are on the day shift.

Depression Scale

The BDI-II depression scale is a self-evaluation tool that assesses depression risk and measure depression severity. The scale comprises 21 self-assessment statements and uses a quadruple Likert-type measurement. Participants were asked to rate how they felt over the past two weeks, with each question offering at least four possible answer choices of varying intensity. The scale's maximum score is 63 points, and the minimum is 0 points. The BDI-II's most recent cut-off points for depression severity were minimal depression (0-13 points), mild depression (14-19 points), moderate depression (20-28 points), and severe depression (30-63 points) (9,10).

Statistical Analysis

The study results were analyzed using the "SPSS Statistics 20.0" program. Descriptive statistics are presented as mean ± standard deviation. For comparison of more than two groups, variance analysis (ANOVA) was used with post-hoc Tukey's correction for multiple comparisons after conducting the Kolmogorov-Smirnov test. Numerical data were analyzed using Pearson's correlation, and the correlation coefficient was calculated. The statistical analysis of the numerical data employed the independent t-test, whereas the sequencing and comparison of the obtained results used the chi-square test. The Kruskal-Wallis test was applied to quantitative variables with more than two independent groups when normal distribution was not present. All analyses were performed using a two-sided significance level of 0.05 to determine the statistical significance of observed differences within the 95% confidence interval. This study was presented as a paper at the 5th Eurasian Congress on Emergency Medicine and 12th Turkish Emergency Medicine Congress, November 10-13, 2016 (Antalya, Turkey).

Results

Out of the 161 RMDs that participated in the study, the mean age was 28.2±2.7 years (range; 24-45 years), with 35.4% being female and 42.9% being married (Table 1). The mean duration of residency was 29.6±16.6 months (range; 3-66 months). Only statistically significant data were found in the subgroup analysis of the current duration of the residency, specifically in the night shift group. The other variables did not yield statistically significant results. The duration of residency in the night shift group was significantly shorter than that in the daylight group, at 28.4±16.3 months and 36.8±17.0 months, respectively (independent t-test, p=0.23). This suggests that the night shift group may be less experienced than the daylight group. Only 24 (14.9%) RMDs were included in the daylight group. According to this study, most participants were from the night shift and inexperienced groups, as determined by their shorter duration of residency. The night shift group had an average of 6.7±2.4 night shifts per month (within a range of 2-12 night shifts per month).

The mean score on the BDI-II was 12.4±9.0 (range; 0-57), indicating minimal depression, the lowest category on the BDI-II. Of the participants, 28 (17.4%) were classified as moderately or severely depressed (BDI-II ≥20). There was no statistically significant correlation between age and

Table 1. Description of the sample

Variables		Total	
		n	%
Gender	Male	104	64.6
	Female	57	35.4
Marital status	Married	69	42.9
	Single	92	57.1
Had at least one child	Yes	12	7.5
	No	149	92.5
Lived alone	Yes	46	28.6
	No	115	71.4
Lost a loved one recently	Yes	31	19.3
	No	130	80.7
Presence of a chronic disease	Yes	11	6.8
	No	150	93.2
Had reported depression	Yes	22	13.7
	No	139	86.3
Used antidepressant	Yes	8	5
	No	153	95
Department	Surgical	87	54
	Non-surgical	74	46
Residency specialty	Internal medicine	27	16.8
	Emergency medicine	21	13
	General surgery	14	8.7
	Otolaryngology	13	8.1
	Anesthesiology	10	6.2
	Orthopedics	10	6.2
	Family medicine	9	5.6
	Physical therapy	8	5
	Infection disease	7	4.3
	Neurology	6	3.7
	Ophthalmology	6	3.7
	Gynecology/ obstetrics	6	3.7
	Neurosurgery	5	3.1
	Biochemistry	5	3.1
	Radiology	5	3.1
	Pathology	4	2.5
	Dermatology	3	1.9
	Urology	2	1.2
Work type	Night shifts	137	85.1
	Daylight	24	14.9
BDI-II	Minimal	96	59.6
	Mild	37	23
	Moderate	22	13.7
	Severe	6	3.7

BDI-II scores (Pearson correlation, $p>0.05$). The correlation coefficient between the duration of residency and BDI-II was 0.160, indicating a statistically significant negative correlation (Pearson correlation, $p=0.043$). This suggests that as the duration of residency decreased in the RMDs, the BDI-II score increased. There was a statistically significant decrease in the average BDI-II score between the night shift and daylight groups, with scores of 13.1±9.2 points and 8.8±7.1 points, respectively (independent t-test, $p=0.03$). In addition, there was a statistically significant positive correlation between the number of night shifts and the BDI-II score, although the correlation was weak (Pearson correlation, 0.203, $p=0.01$). No statistically significant differences were found among the RMDs in terms of gender, marital status, having children, living alone, recent loss of a loved one, presence of chronic disease, previous diagnosis of depression, and use of antidepressant medication during the study period with the BDI-II (Independent t-test, $p>0.05$).

Examining the distribution of departments, it was found that 87 (54%) of the RMDs were residents in surgical departments. RMDs in anesthesiology, emergency medicine, general surgery, neurosurgery, obstetrics and gynecology, otorhinolaryngology, ophthalmology, orthopedics, and urology were assigned to the surgical departments. RMDs specializing in biochemistry, dermatology, family medicine, infectious disease, internal medicine, neurology, pathology, physical medicine and rehabilitation, and radiology were assigned to non-surgical departments. The group sizes of the departments were unequal, and the internal medicine department had the highest number of RMDs (n=27, 16.8%). When the RMDs were evaluated with their respective departments, statistically significant differences were found in the BDI-II scores (ANOVA, $p=0.03$). The gynecology and obstetrics department had the highest average BDI-II score (23.3±13.4) and was classified as a moderate depression group. When compared with other departments, the BDI-II average was found to be statistically significantly high for physical medicine and rehabilitation (5.6±2.4, $p=0.16$), orthopedics (4.2±3.5, $p=0.03$), and pathology departments (4.0±1.4, $p=0.48$). The second-highest BDI-II mean was found to be statistically significantly higher in the Otorhinolaryngology department (17.7±9.3) and in the orthopedics department (4.2±3.5, $p=0.22$) in the mild depression group. There were no statistical differences found when comparing the other departments. Similarly, no statistical differences were found when comparing the surgical and non-surgical departments.

Discussion

Depressive symptoms are common among patients with RMDs. A study found that healthcare workers experience depression more frequently than the public (20). Depression has been classified into burnout-related and non-burnout-related categories, with burnout-related depression having a more difficult course. A review identified 15 heterogeneous articles on resident burnout. Research suggests that burnout levels are high among residents and may be associated with depression and problematic patient care (24). Studies have shown that residents experience depression at a higher rate than their peers who are not pursuing careers in medicine. Therefore, RMDs are at a higher risk of morbidity during their undergraduate years. Prevalence rates of depression among medical students and residents vary widely from 2%

to 35%. The highest rates have been reported among residents, ranging between 27% and 35% (17). When examining comparable studies in the literature, it is challenging to compare the distribution of depression levels because of the use of different depression screening methods and ratings based on various criteria, such as high-risk groups per medical specialization, years of experience and gender. In a study conducted by Demir et al. (12), on 156 individuals with RMDs in Turkey, the probable distribution of depression was found to be 16%. Similarly, our study found that the moderate/severe depression group was 17.4%. Identifying the causes of high levels of depression in healthcare workers may aid in the development of protective and preventive measures.

Reported risk factors for developing depression include gender (12,17), duration of residency (19), marital status, and living alone (13,25,26). In the general population, women have a higher lifetime risk of depression than men. Similarly, studies on RMDs have consistently shown higher rates in women (12,17,18,27). However, a review of studies comparing depressive symptoms by gender in medical students found no difference by gender (28). In our study, we did not find a link between gender and depression levels because the average number of RMDs in men and women was similar. This may explain why the number of male RMDs in our study was higher than that of female RMDs.

According to the study by Demir et al. (12), they said that age, marital status, hospital department, duration of residency, number of night shifts, and duration of exposure to daylight in the work environment were not associated with depression, but some studies suggest a relationship between night work and depression. For example, in a study of anesthetic RMDs in Turkey by Saricaoğlu et al. (29), it was reported that there was a direct relationship between insomnia, decreased attention, low performance, and night shifts. The intensive work schedule of healthcare workers, especially those working night shifts, leads to insomnia and fatigue. In our study, the mean BDI-II of RMD working night shifts was found to be significantly higher. There was also a statistically significant positive correlation between the number of night shifts and BDI-II. According to our study, this means that as the number of night shifts increased, so did the BDI-II.

Goebert et al. (17) reported significant differences in reporting depression among medical students by years of training, but not among RMDs. Similar to our study, Ozyurt et al. (26) reported that burnout and depression decreased with increasing years of practice. Conflicting results have been reported in studies comparing marital status with depression. However, various studies conducted in Turkey, such as our study, reported that marital status had no relationship with job satisfaction, burnout, and depression levels (13,14,30).

Study Limitations

A limitation of this study is that most of this study was formed from the night shift group and inexperienced group of residents. As two influential factors on depression were found high percentage, there was generally a high determined percentage in depression levels. Other limitations include the small number of participants and the fact that the scale was presented for statistical analysis based on scores and no categorization was used.

Although the junior doctors working in the emergency department work 24 hours a day, some of the junior doctors working in other clinics work the day shift, while others continue to work the night shift. The junior doctors who participated in the study were not grouped according to the departments in which they worked, and analysing the total number of junior doctors was one of the limitations of our study. In addition, in this study, we did not find any difference between the depression levels of RMDs in the surgical and medical departments. According to our study, the length of residency is a factor that influences depression. However, we need to study this again with groups that have the same length of residency in each department, as this may lead to different results. Also, a participation rate of 68.8% may indicate a response bias, e.g. non-participants in the survey may be more depressed than participants.

Conclusion

This study highlights the importance of an ongoing assessment of the mental health of residents. In conclusion, the BDI-II was used to assess the depression levels of RMDs, and it was found that night shift work, length of stay, and the department in which they worked were factors in the development of depressive symptoms. In addition to a better knowledge of the characteristics of depressive symptoms, our findings could help us to develop programmes specifically designed for RMDs to prevent the development of depression.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 333, date: 27.10.2022).

Informed Consent: Informed consent was obtained from the participants through face-to-face interviews.

Authorship Contributions: Concept - M.B.G., Ö.D.; Design - M.B.G., H.T., Ö.D.; Data Collection or Processing - M.B.G., B.G.G.; Analysis or Interpretation - H.T., Ö.D.; Literature Search - M.B.G., B.G.G.; Writing - M.B.G., Ö.D.

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Comparison of Coronary Artery Calcium Score and Serum Calcium, Phosphorus, and Gamma-Glutamyl Transferase Levels in Patients with Coronary Artery Imaging by Multi-Sectional Computed Tomography with Chronic Ischemic Heart Disease Prediagnosis

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ABSTRACT

Introduction: Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Calcification of the coronary artery wall is a definite indicator of coronary atherosclerosis. Calcium scores in coronary arteries (CAC) can be detected by multidetector computed tomography (MDCT) before any cardiac event occurs. Gamma-glutamyl transferase (GGT) is a biomarker for oxidative stress and a proatherogenic marker for its indirect contribution to the biochemical process resulting in low-density lipoprotein cholesterol oxidation. Studies have shown that serum inorganic phosphorus levels are an independent risk factor for cardiovascular mortality. In our study, we evaluated the correlation between MDCT, CAC score, and the risk of coronary events predicted by evaluating this score according to age, gender, and serum GGT, calcium, and phosphorus levels.

Methods: In this retrospective study, 190 patients with a prediagnosis of CAD, laboratory investigations and MDCT were included. Patients were divided into three groups as low, intermediate, and high based on the risk of coronary events determined by the evaluation of CAC scores according to age and gender.

Results: In our study, a statistically significant result was found between high serum phosphorus and GGT levels and CAC and coronary event high risk groups classified according to this score ($p<0.05$). No significant result was found with high calcium level ($p>0.05$).

Conclusion: The correlation of phosphorus and GGT levels, which are considered independent risk factors for CAD, with CAC, which is an indicator of atherosclerosis in coronary arteries, was significant.

Keywords: Coronary artery calcium score, calcium, phosphor, gamma-glutamyl transferase

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. CAD risk factors were first identified in the Framingham Heart Study in 1948 and later were confirmed by numerous studies. Non-modifiable risk factors are; gender, family history of premature CAD (CAD in a primary male relative before the age of 55 years and CAD in a primary female relative before the age of 65 years), age, racial background, and history of vascular disease. Modifiable risk factors are; diabetes mellitus, hypertension, hypercholesterolemia, smoking, central obesity, sedentary lifestyle, and hyperhomocysteinemia (1). Calcification of the coronary artery is a definite indicator of coronary atherosclerosis (2). Calcium scores in coronary arteries (CAC) can detect ischemic heart disease before the development of any cardiac event. CAC shows the current cardiac status of the patient and possible future pathologies (valvular heart disease, CAD) and provides the physician with the necessary information in this respect. In many studies, the coronary calcium score has been found to be a prognostic parameter with a high predictive value for severe cardiac events within 3-5 years in asymptomatic patients (3). Using multidetector computed tomography (MDCT), we can visualize coronary artery calcification non-invasively, sensitively, and safely (4-6).

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Serum gamma-glutamyl transferase (GGT) levels provide information about hepatobiliary diseases and alcohol consumption (7,8). Studies in the literature have demonstrated the pathway of GGT activity in the pathogenesis of atherosclerosis and its involvement in oxidative events related to atheroma plaque formation (9). GGT activity has been detected in pathological studies performed in coronary artery plaques (10,11). Studies have supported the idea that serum GGT levels have prognostic and predictive value for CAD formation.

Phosphorus is a mineral with many functions in our body. Regulation of body phosphorus content is an important homeostatic requirement due to its important functions such as cellular signal transduction, energy production and transfer, membrane transport, participation in the catalytic activity of many enzymes, and bone mineral formation (12). Experimental and clinical data from recent studies have identified a role for elevated serum phosphorus levels in the pathogenesis of vascular damage. Recent studies have shown that higher blood phosphorus and phosphorus-calcium combination levels in patients with a history of chronic kidney disease (CKD) are related to increased cardiovascular disease mortality by causing coronary atherosclerosis and coronary calcification (13-15).

Many studies in the medical literature are attempting to produce diagnostic or prognostic tools that provide the highest benefit and lowest cost. In our study, we assessed the correlation between MDCT, which is an excellent non-invasive radiological examination method to detect CAD, the CAC calculated by this imaging method, and the risk of coronary events predicted by evaluating this score according to age and gender, and serum GGT, calcium, and phosphorus levels, which have been accepted as independent risk factors for ischemic heart disease in recent studies.

Methods

Patients admitted to University of Health Sciences Turkey, İstanbul Training and Research Hospital with a prediagnosis of CAD and who underwent coronary artery imaging with MDCT were retrospectively analyzed. Age, gender, hemogram, and biochemistry parameters were obtained from the file information (Table 1). CAC score, plaque volume, and parameters related to the risk of coronary events obtained from radiological reports based on the table formed by the assessment of this information according to sex and age were obtained. CAC score below 100 was considered low risk, and above 400 was considered high risk. CAC score between 100 and 400 was considered moderate risk. Patients aged between 3570 years with renal failure and known CAD were excluded from the study.

Technique

Sixteen-detector MDCT was used to obtain non-contrast volumetric axial slices with 0.1 cm slice diameter, 0.5 mm reconstruction, 0.75 mm collimation, and interval synchronized with ECG. Calcium scoring was evaluated in the left anterior descending artery, left main coronary artery, right main coronary artery, and circumflex artery according to the Agatston score using the "Siemens Calcium Scoring Software" (Figure 1).

Statistical Analysis

The correlation between the CAC score and the risk of coronary events and GGT, calcium, and phosphorus values was evaluated. SPSS 15.0 for Windows software was used for statistical analysis. Descriptive statistics are given as numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. The correlations between the numerical variables were analyzed by Spearman's correlation analysis because parametric test conditions could not be met. Because the numerical variables compared in the two independent groups did not fulfill the normal distribution condition, they were compared using the Mann-Whitney U test. Numerical variables in more than two independent groups were analyzed by ANOVA when a normal distribution condition was provided and by the Kruskal-Wallis test when a normal distribution condition was not provided. Subgroup analyses were performed with

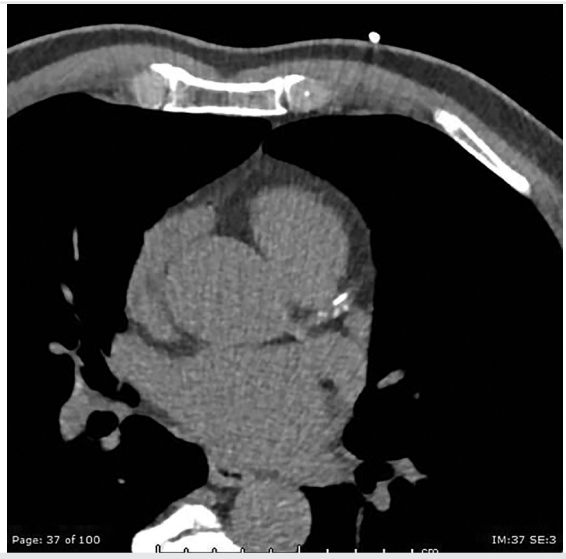

Figure 1. Calcified plaques in the left main coronary artery were detected in a 61-year-old male patient. The calculated Agatston score was 201, and the patient was considered to be at moderate risk for ischemic heart disease

Table 1. Patient characteristics

Number of patients (n)		190
Age mean ± SD (min.-max.)		53.6±9.0 (35-70)
Gender n (%)	Male	104 (54.7)
	Female	86 (45.3)
Plaque volume mean ± SD (min.-max.)		126.1±296.2 (0-2780)
CAC score mean ± SD (min.-max.)		139.5±358.2 (0-3569)
Coronary event risk n (%)	Low	105 (55.3)
	Intermediate	44 (23.2)
	High	41 (21.6)
GGT mean ± SD (min.-max.)		42.8±53.6 (6-559)
Calcium mean ± SD (min.-max.)		9.4±0.7 (4.6-10.7)
Phosphorus mean ± SD (min.-max.)		3.6±0.7 (2.1-5.2)
Calcium X phosphorus mean ± SD (min.-max.)		34.8±6.5 (20-50.5)

SD: Standard deviation, min.: Minimum, max.: Maximum, CAC: Calcium scores in coronary arteries, GGT: Gamma-glutamyl transferase

Tukey's test in the parametric test and the Mann-Whitney U test in the non-parametric test and were interpreted with Bonferroni correction. The ratios of categorical variables in the independent groups were tested by chi-square analysis. The factors determining the numerical variables were analyzed using linear regression analysis with the backward elimination method. P<0.05 was accepted as the statistically significant level.

Results

A total of 190 patients (104 males and 86 females) who underwent coronary artery imaging with MDCT and with a prediagnosis of CAD were included in the study. Demographic data of the patients are presented in Table 1. The mean age of the patients included in the study was 53.6±9.0 years. The mean plaque volume and CAC score were 126.1±296.2 and 139.5±358.2, respectively. According to the evaluation results, 55.3% of the patients had low coronary risk, 23.2% had intermediate risk, and 21.6% had high coronary risk. The mean GGT, calcium, phosphorus and CaxP values were 42.8±53.6, 9.5±0.6, 3.7±0.6 and 34.8±6.5, respectively.

A significant difference was found in the mean age, GGT, P, and CaxP in the coronary event risk groups (p<0.001, p=0.008, p<0.001, p<0.001, p<0.001) (Table 2). In the group with a high-risk of coronary events, mean age, P, and CaxP were significantly higher than in the low and intermediate groups (Table 3). The differences between the groups with low and intermediate risk of coronary events were not significant (Figure 1-4, Table 3). Mean GGT was significantly higher only in the high group compared to the low group. No significant difference was found in the gender ratios and Ca averages of the groups (Table 2).

In the model created to analyze the determinants of coronary artery calcium score, CaxP, age, and gender were found to be the most significant factors by multivariate linear regression analysis with the backward elimination method (p<0.001 p=0.002 p=0.024) (Table 4).

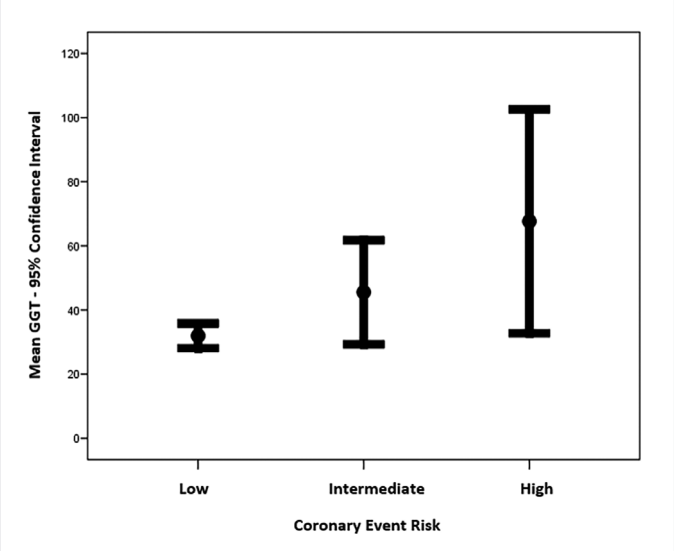

Figure 2. Risk of coronary events according to GGT levels
GGT: Gamma-glutamyl transferase

Discussion

We found that; the correlation of phosphorus and GGT levels, which are considered independent risk factors in predicting ischemic heart disease, with CAC, which is an indicator of atherosclerosis, was significant. This result will be helpful in our clinical practice in the early diagnosis and treatment of ischemic heart disease.

To date, many studies, including long-term follow-up investigations of the correlation of serum GGT activity with long-term metabolic syndrome development, cardiovascular disease development, and mortality, have been conducted (16). Studies have shown that GGT is an important marker of the probability of coronary heart disease independent of cardiovascular disease risk factors in the long term, and moderate increases in the reference range reflect a significant increase in the probability.

In 1993, Block et al. (17) unexpectedly described the correlation of increased serum GGT levels with cardiac mortality while conducting

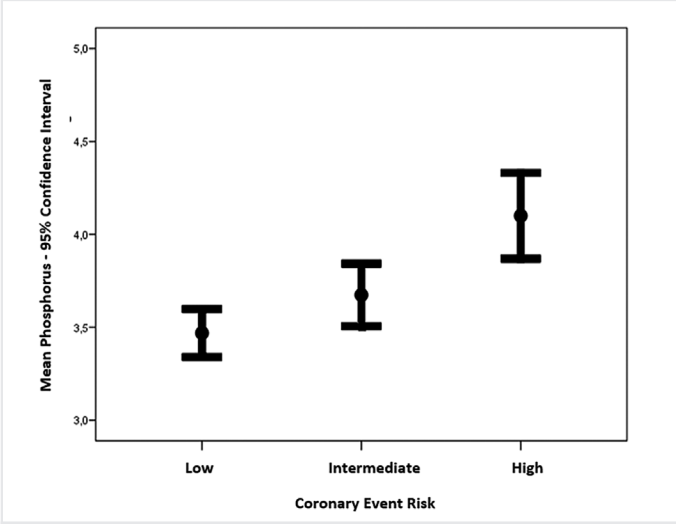

Figure 3. Risk of coronary events according to phosphorus levels

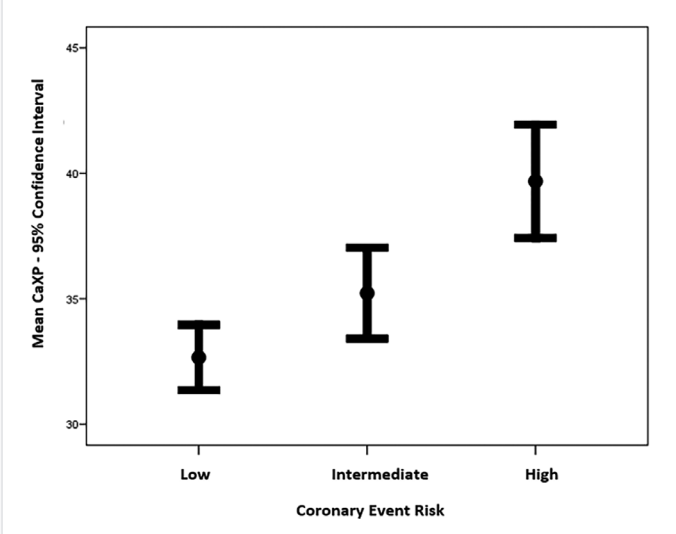

Figure 4. Risk of coronary events according to CaxP levels
CaxP: Calcium X phosphorus

Table 2. Coronary artery disease risk 1

Low		Coronary artery disease risk			
		Intermediate	High	p-value	
Age mean ± SD (min.-max.)		51.2±9.0 (35-68)	54.7±7.8 (36-69)	58.8±8.1 (41-70)	<0.001
Gender n (%)	Male	53 (50.5)	27 (61.4)	24 (58.5)	0.409
	Female	52 (49.5)	17 (38.6)	17 (41.5)	
GGT mean ± SD (min.-max.)		32.0±17.7 (6-124)	45.6±49.4 (9-279)	67.7±96.8 (13-559)	0.008
CA mean ± SD (min.-max.)		9.4±0.7 (4.7-10.6)	9.6±0.3 (9-10.4)	9.7±0.4 (9.1-10.6)	0.069
P mean ± SD (min.-max.)		3.5±0.6 (2-5.3)	3.7±0.5 (2.8-4.9)	4.1±0.6 (2.8-5.2)	<0.001
CaxP mean ± SD (min.-max.)		32.7±6.0 (20-48.8)	35.2±5.5 (26.9-47.0)	39.7±6.3 (28.5-50.5)	<0.001

SD: Standard deviation, min.: Minimum, max.: Maximum, CA: Calcium, CaxP: Calcium X phosphorus, GGT: Gamma-glutamyl transferase, P: Phosphoru

Table 3. Coronary artery disease risk -2

	Coronary artery disease risk		
	Low vs. intermediate	Low vs. high	Intermediate vs. high
Age	0.020	<0.001	0.011
GGT	0.166	0.002	0.114
P	0.045	<0.001	0.004
CaxP	0.073	<0.001	0.006

CA: Calcium, CaxP: Calcium X phosphorus, GGT: Gamma-glutamyl transferase, P: Phosphorus

Table 4. Predictors of the coronary artery calcium score

	B	Beta	p-value
Constant	-695,031		
CaxP	17,479	0.316	<0.001
Age	10,164	0.253	0.002
Gender	-129,200	-0.180	0.024

CaxP: Calcium X phosphorus

studies on the damage caused by alcohol use in the organism using laboratory test results.

Reynolds et al. (18) investigated the correlation between serum GGT levels and new cardiovascular events and mortality, new metabolic syndrome, and cardiovascular risk factors in a prospective study of 3451 Framingham Offspring Study participants with an average follow-up time of 19 years. A correlation was found between high GGT activity and the risk of cardiovascular events and cardiovascular mortality. The results of this study support the notion that GGT activity is an important marker in predicting cardiovascular risk (18).

GGT has emerged as a new risk factor in addition to traditional cardiovascular risk factors. It has been observed in epidemiological studies that high values of GGT activity in the normal reference range are a strong independent marker for metabolic syndrome and cardiovascular events in the long term, a prognostic value in coronary heart disease, and an independent correlation with all causes of mortality. Further studies are needed to determine whether drugs used for treating atherosclerosis affect serum GGT activity, which contributes to the formation of atherosclerosis. Further research should be conducted to determine the most risky combination by examining the correlation of biochemical activation of GGT in atheroma plaque with global serum activity, inflammation markers, and plasma lipoproteins, develop aggressive treatment approaches, help prognostically classify patients, and prevent future adverse cardiac events and mortality.

In our study, blood GGT levels were significantly higher in patients with a high-risk of ischemic heart disease detected by coronary CT angiography. This finding will be beneficial in the early diagnosis and treatment of ischemic heart disease, but it should be supported by controlled studies involving more patients.

The dose-dependent correlation between cardiovascular disease and phosphorus levels in the abnormal range that can be seen in late renal disease is known. In this process, which ends with widespread vascular calcification, observational studies in dialyzed patient populations have shown that high serum phosphorus levels are correlated with cardiovascular events and mortality (19,20). This correlation has led investigators to associate elevated serum phosphorus levels in the reference range with ischemic heart disease in patients with normal renal function. Studies in the literature have shown that serum phosphorus levels are an independent risk factor for the development of cardiovascular events and cardiovascular mortality in patients with or without CAD with normal renal function.

In a study conducted by Dhingra et al. (21) with a mean follow-up of 16.1 years in 3,368 adult Framingham study participants without a history of cardiovascular disease and with normal kidney function, high serum phosphorus values and calcium-phosphorus composite values at the reference range were correlated with an increased risk of cardiovascular disease. It has been mainly reported that subjects with serum phosphorus values higher than 3.5 mg/dL within the reference range have a 1.55-fold higher risk of cardiovascular events than subjects with ≤2.8 mg/dL. In addition, in this study, it was shown that serum phosphorus levels were directly proportional to total/high-density lipoprotein cholesterol ratio and age and proportional to body mass index and systolic blood pressure, which are risk factors for cardiovascular disease. Blood calcium levels were not correlated with the risk of cardiovascular disease. This study is important in terms of being the first study to explain the independent correlation of high serum phosphorus levels with cardiovascular disease risk in a population-based sample of males and females without cardiovascular disease or CKD (21).

According to studies in the literature, the association between high P and cardiovascular events was independent of other traditional risks and the amount of P in the diet. We did not investigate dietary calcium

and phosphorus intake in our patient population. Additionally, since vitamin D was not measured in every patient, we could not examine its relationship with CAD. Park et al. (22) showed that lower serum P concentrations within the previously claimed normal range were associated with lower Agatston score; this suggests that people with normal kidney function have less coronary artery calcification.

In the prospective study by Foley et al. in 3015 healthy young adults as part of the Risk of CAD development in young adults study, the relationship between serum phosphorus levels and the degree of coronary artery calcification determined by CT imaging at 15 years was investigated. A significant correlation was found between high serum phosphorus levels and coronary artery calcification. In this study, high serum phosphorus levels were shown to be a risk factor for the development of coronary atherosclerosis in healthy young adults (23).

Treatment methods continue to support the hypothesis that correcting the calcium-phosphorus balance in end-stage CKD improves cardiovascular outcomes. Further studies involving more patients are needed to evaluate whether high serum phosphorus levels lead to the risk of cardiovascular events and mortality in patients with normal kidney function, and to elucidate the underlying mechanism and provide preventive or therapeutic interventions in the future.

Study Limitations

Our study has certain limitations, such as being a retrospective design, being a single-center study, and having a limited number of patients. Therefore, prospective studies with a larger number of patients are required. However, it should be considered an effective study in terms of demonstrating the effectiveness of non-invasive and low-cost screening in the early detection of CAD, which is the most common cause of death worldwide.

Conclusion

The results showed a significant correlation between the coronary artery calcium score and serum GGT and phosphorus levels. In our clinical practice, we can use these two laboratory data as useful predictive markers in patients with suspected ICH. Further studies on this subject are needed.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee (approval number: 594, date: 23.01.2015).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices - İ.G.; Concept - İ.G., H.P.; Design - İ.G., H.P.; Data Collection or Processing - İ.G., G.B.S., S.A.; Analysis or Interpretation - İ.G.; Literature Search - İ.G.; Writing - İ.G.

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Features of the Liver Sonoelastography Findings in Patients with Type 1 Diabetes Mellitus in Childhood

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ABSTRACT

Introduction: The prevalence and association of type 1 diabetes mellitus (T1D) and non-alcoholic fatty liver disease (NAFLD) have been explored; however, no study has examined liver parenchyma elasticity in pediatric T1D patients without NAFLD. Two-dimensional shear wave sonoelastography (2D-SWE) can effectively detect and grade fibrosis in liver diseases that can be seen in T1D patients. The aim of this study was to analyze the 2D-SWE results of the liver in T1D children without NAFLD to identify any potential effects early.

Methods: This prospective case-control study included 53 T1D patients (11.4±3.2 years) and 50 healthy children [12.5 (6) years]. None of the individuals were obese. Both groups had normal grayscale echogenicity, lipid profiles, and liver enzyme levels, ruling out NAFLD. The mean elasticity value was calculated as kiloPascal (kPa) by measuring in the right lobe of the liver. Correlations between elasticity and aspartate aminotransferase (AST), alanine aminotransferase, fasting blood glucose (FBG), duration of diabetes mellitus, and hemoglobin A1c (HbA1c) were evaluated and compared. $P<0.05$ indicates statistical significance.

Results: T1D had a higher liver 2D-SWE [5.4 (2.5) kPa] than controls (4.5±0.8 kPa) ($p<0.05$). T1D had a lower AST and a higher FBG than controls ($p<0.05$). The mean HbA1c of T1D was 8.3(2.4) mmol/mol and correlated with the duration of diabetes. FBG values and kPa values were correlated ($p<0.001$). There was no correlation between other variables and liver kPa (all; $p>0.05$).

Conclusion: Although liver function tests, lipid profiles, and grayscale ultrasonography showed no abnormalities in our pediatric T1D patients, increased liver parenchymal stiffness detected by 2D-SWE compared with the healthy group indicated hepatic involvement. Therefore, 2D-SWE follow-up may help detect liver involvement and NAFLD before grayscale and laboratory findings arise. Long-term follow-up studies involving a larger population of T1D patients would be beneficial in establishing quantitative reference values for 2D-SWE and will enhance the literature on this topic.

Keywords: Shear wave elastography, type 1 diabetes mellitus, liver, NAFLD, pediatric

Introduction

Type 1 diabetes mellitus (T1D) is frequent among wealthy children and is associated with metabolic dysregulation and liver abnormalities. The primary cause is autoimmune damage to pancreatic insulin-secreting beta cells (1). Organ-specific autoantibodies in patients with T1D indicate several immunological disorders (2). The autoimmune mechanism that leads to this disease may potentially produce autoimmune hepatitis (AIH), according to the literature (1). AIH type 2 liver/kidney microsomal autoantibodies target cytochrome *P4502D6*, whereas T1D carboxypeptidase *H3351* shares an amino acid motif. Other organs with comparable protein sequences can be affected by tissue-specific autoantibodies. This cross-reactive immunological mechanism can induce autoimmune illness in susceptible individuals (2). Non-alcoholic fatty liver disease (NAFLD) (3), the most common pediatric liver disease, is expected to become a clinical problem as T1D patients become more obese. In patients with T1D, blood sugar and insulin fluctuations inhibit glycogenesis and glycogenolysis and cause glycogenic hepatopathy, whereas insulin treatments promote glycogenic accumulation. Tight glycemic control can suddenly improve or regress GH. On ultrasound (US), hyperechogenic liver and/or hepatomegaly may be seen in children with T1D due to excess glycogen or fat. In T1D, they can mimic each other and confuse the diagnosis (1,4). Steatosis, a precursor to fibrosis, may have different Two-dimensional shear wave sonoelastography (2D-SWE) elasticity than reversible GH. Non-invasive quantitative data can distinguish these two illnesses and be used alongside clinical data to diagnose and treat them. NAFLD-type liver disease has been identified as an early indicator of metabolic disorders. Chronic hyperglycemia, poor glycemic management, high-fat, low-carbohydrate diets, and hypoglycemia phobia in patients with T1D may contribute. Normal-weight T1D patients should be tested for NAFLD to reduce cardiometabolic risk (5). Liver biopsy,

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the gold standard for identifying fibrosis, is invasive, expensive, and less common in children because it may cause pain or bleeding. Practical, non-invasive methods are essential in daily practice (6). Standard US is the first imaging modality used to diagnose fatty liver, but it is insensitive in identifying mild steatosis, differentiating it from steatohepatitis, or staging fibrosis (7). 2D-SWE, transient elastography (TE), and point shear wave sonoelastography (pSWE), as well as MR elastography, have been used to non-invasively measure liver stiffness (8-10). TE, commonly known as FibroScan, is a promising radiographic approach for staging hepatic fibrosis that resembles liver biopsy in predicting liver-related outcomes across chronic liver disorders. These include chronic viral hepatitis, NAFLD, non-alcoholic steatohepatitis, AIH, and primary biliary cirrhosis (1). Diagnostic distinguishing of T1D liver illnesses such as AIH and glycogenic hepatopathy can be helped by 2D-SWE (11). SWE can effectively evaluate liver fibrosis in juvenile patients with NAFLD. Guidelines support this reliable, non-invasive method for the detection of steatohepatitis and hepatic fibrosis (9,12).

Unlike TE, 2D-SWE analyzes tissue elasticity simultaneously with B-mode assessment and based on anatomy. 2D-SWE uses targeted US scanning to collect strain images of tissue responses generated by local mechanical compression (13). SWE predicts hepatic fibrosis (14). Quantitative maps and hardness-based elastography colors can quantify 2D-SWE homogeneity (13). SWE includes vibration-controlled transient elastography, pSWE, and 2D-SWE. 2D-SWE generates liver tissue elasticity maps in real time using a large tissue area. 2D-SWE region of interest (ROI) gives a broad field of view, rapidity, high patient compliance, and good observer [intraclass correlation coefficient (ICC): 0.93-0.95] and interobserver (ICC: 0.88) coefficients (15).

Current guidelines indicate elastography for NAFLD suspicion, although there is inadequate data for children (15). pSWE and 2D-SWE were not mentioned in practice guidelines due to inadequate data (12). Further 2D-SWE research in pediatric patients is required.

There are no studies evaluating the normal elasticity of the liver parenchyma in pediatric T1D patients. In addition, parenchymal elasticity may have begun to be affected during the subclinical period when NAFLD gray scale US and laboratory findings are not established. Considering these factors, we aimed to evaluate liver findings and clinical data with 2D-SWE in children with T1D without NAFLD and to obtain data for early detection of possible changes in liver elasticity.

Methods

This study was conducted in accordance with the Helsinki Declaration's standards. University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee approved the study (approval number: 2022/514/225/5, date: 11.05.2022). Written informed consent was obtained from the patients' parents.

Study Design and Population

This study was conducted as a prospective case-control study in a single centre.

The study involved 65 pediatric patients aged 4 to 17 diagnosed with T1D under the care of a pediatric endocrinologist. Key parameters assessed included age, gender, fasting blood glucose (FBG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin A1c (HbA1c), duration of diabetes mellitus, gray-scale US, and sonoelastography findings (kPa values). The inclusion criteria comprised individuals diagnosed with T1D by a pediatric endocrinologist for at least 6 months, with a C-peptide level <1 mmol/L at diagnosis, and at least one positive diabetes antibody (anti-insulin, anti-islet, or anti-glutamic acid decarboxylase). In the case group, 3 patients were excluded because of elevated body mass index (BMI) standard deviation score (SD score) (>1) during elastography measurement; 4 patients were excluded because current blood tests could not be obtained; 2 patients were excluded because of concomitant hypothyroidism and celiac disease; and 3 patients were excluded because of suspicious hyperechogenicity in grayscale US evaluation. Consequently, the study included a total of 53 patients. Lipid panels were available for all patients with T1D in the study, and none exhibited hyperlipidemia.

The control group comprised children aged 4 to 17, matched for age and gender with the case group. These healthy individuals were admitted to our clinic for various reasons, had no diagnosed diseases, showed no abnormalities in laboratory tests, and were not on any medication. Written informed consent was obtained from the subjects' parents before inclusion in the study. The exclusion criteria encompassed any history of diseases or medication use affecting liver parenchyma and the presence of hepatomegaly or hepatosteatosis on grayscale evaluation. Neither the T1D patients nor the control group were obese.

Grayscale and Shear Wave Elastography Techniques

A Samsung RS85 F4N/WR device with a convex probe (CA1-7A/FR43Hz/16 cm) was used for grayscale and elastography measurements. We evaluated liver size and the presence of steatosis using gray-scale ultrasonography. We measured the liver size at the midclavicular line and assessed hepatomegaly using reference values (16). We assessed steatosis using visual analysis with optimal gain adjustment (17). Measurements were performed blindly by a single radiologist with at least 5 years of expertise in sonoelastography. All measurements were performed under optimal fasting conditions. All measurements were performed with the patient in the supine position, with the right arm in maximal abduction and in the mid-respiratory phase. No pressure was applied to the probe, and the operator's hand was kept steady during the SWE measurements. An adequate US gel was used for elasticity measurements. The 2D-SWE technique employed in our study generates real-time tissue elasticity maps, with harder tissues depicted in red and softer tissues in blue (15). Shear wave speed measurements were algebraically converted to Young's modulus (kPa) to evaluate tissue stiffness. Measurements were taken using a 10 mm ROI, positioned 2 cm away from vascular structures and the subcapsular region in the right lobe of the liver, which is less susceptible to respiratory artifacts and offers better imaging (Figure 1). Each patient underwent 10 acceptable measurements, with an interquartile range (IQR)/median of 30%. The mean was recorded as the modulus of elasticity (kPa).

Analysis Technique

From the files of T1D patients, HbA1c, diabetes age, and laboratory data were noted. In both groups, NAFLD was excluded because of the

presence of normal echogenicity, normal lipid profile, and normal liver enzyme values on gray scale ultrasonography. The correlation between SWE kPa values and diabetes age, ALT, AST, and FBG in the last 6 months before the study and mean HbA1c% in the last year was studied. AST and ALT levels lower than 35 U/L were deemed normal. The SWE kPa values of the liver were compared between the T1D and healthy groups.

Statistical Analysis

The SPSS version 25 statistical package program was used for statistical analyses. Descriptive statistical methods (mean, SD, number of units, minimum-maximum, percentage) were used to summarize the data. The Shapiro-Wilk test was used for normality tests of continuous variables. In the case group, age, AST, and FBG variables showed a normal distribution ($p>0.05$), whereas in the control group, liver size, liver kPa, AST, and FBG variables showed a normal distribution. Statistical tests were performed according to normality. In cases of normality, two-group variables were analyzed by an Independent samples t-test, and in cases of non-normality, Mann-Whitney U tests were used to investigate the significance of differences between means. To find the relationships between two continuous variables, Pearson correlation coefficients were obtained in cases of normality, and Spearman-Rho correlation coefficients were obtained in cases of non-normality. The Fisher's exact test was used for the independence test between two categorical variables with two groups. The significance level was set at 0.05 for all tests.

Results

Considering the exclusion criteria, we included 103 children: 53 with T1D and 50 healthy controls aged 4-17 years. In the case group, age, AST, and FBG variables were normally distributed, whereas in the control group, liver size, liver kPa, AST, and FBG variables were normally distributed (all; $p>0.05$).

Table 1 shows the AST, ALT, FBG, gender, age, liver size, liver SWE, HbA1c, diabetes duration, and BMI values for the subjects. Significant differences were observed in AST, FBG, and liver kPa values between the case and control groups (all; $p<0.05$), with the case group showing higher FBG and liver kPa values. Gender distribution was similar between the study and control groups ($p=0.207$), and mean age did not significantly differ between groups ($p=0.247$). The mean HbA1c (mmol/mol) in T1D cases was 8.3 (2.4) mmol/mol. The distribution of HbA1c levels in T1D patients (n=53) was as follows: HbA1c <7 (n=10), 7≤ HbA1c <9 (n=26), 9≤ HbA1c <11 (n=9), and HbA1c ≥11 (n=8). None of the T1D patients or the control group were obese, with no statistically significant difference in BMI values between the groups ($p=0.60$).

When we evaluated the correlations between age, duration of diabetes, and HbA1c and FBG values in the T1D group, 38% correlation between duration of diabetes and HbA1c values was significant ($p<0.05$), whereas the correlations between age and FBG and HbA1c and between duration of diabetes and FBG, which were negatively correlated, were not significant ($p=0.4$, $p=0.06$, $p=0.9$, respectively).

There was no statistically significant difference in the mean values of FBG, HbA1c, and liver kPa based on gender ($p=0.274$, $p=0.169$, and $p=0.884$, respectively).

When we evaluated the correlation between liver kPa values and AST, ALT, FBG, HbA1c, diabetes duration, and liver size; we found a significant correlation between liver kPa and FBG (CC=0.311; $p=0.001$). We did not find a significant correlation between other variables and liver kPa value (all; $p>0.05$).

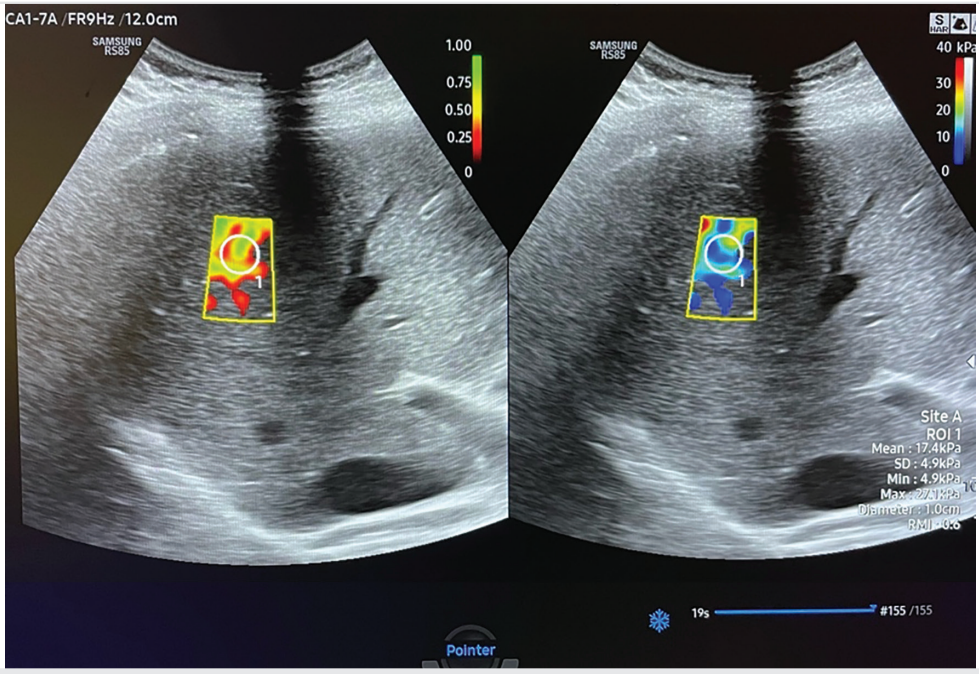

Figure 1: ROI selection and 2D-SWE map of SWE measurements of the liver
ROI: Region of interest, 2D-SWE: Two-dimensional shear wave sonoelastography

Table 1. Distribution of AST, ALT, FBG, gender, age, liver size, liver SWE, HbA1c, and duration of diabetes in the groups

	Case (T1D)	Control	p-value
AST (U/L)	18.5±5.4	21.4±6	0.011[1]
ALT (U/L)	12 (5.5)	11.5 (6)	0.307[2]
FBG (mg/dL)	247.8±69.4	88.6±6.12	0.000[2]
Gender, n (%)			
Female	32 (60.4)	35 (70)	0.207[3]
Male	21 (39.6)	15 (30)	
Age (year)	11.4±3.2	12.5 (6)	0.247[2]
Liver size (cm)	120.7 (18.3)	118.1±11.2	0.228[2]
Liver SWE (kPA)	5.4 (2.5)	4.5±0.8	0.000[2]
HbA1c (mmol/mol)	8.3 (2.4)		
Duration of diabetes (years)	2 (2)	-	-
Body mass index (kg/m^2)	17.7±3.09	17.98±2.37	0.60

Numeric data are presented as median (interquartile range), mean ± standard deviation, [1]: T-test, [2]: Mann-Whitney U test, [3]Fisher's exact test, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FBG: Fasting blood glucose, SWE: Shear wave sonoelastography, HbA1c: Hemoglobin A1c, T1D: Type 1 diabetes mellitus

Discussion

In this study, we evaluated the clinical findings and 2D-SWE liver stiffness changes in pediatric T1D patients with normal BMI and no abnormalities in gray scale US, liver function tests, and lipid profile. We found that liver tissue stiffness was increased in our patients compared to the healthy controls. In this respect, we believe that our study contributes to the literature as a first.

In the literature, liver disease incidence in patients with T1D ranges from 20% to 31%, whereas NAFLD incidence in the pediatric population varies from 0% to 27% (18,19). Patients with T1D are at risk of developing long-term liver damage, necessitating costly and invasive investigations and treatments. Thus, the use of imaging for the early diagnosis and monitoring of hepatopathy, along with its incorporation into guidelines, is crucial. SWE has been reported as an effective quantitative imaging biomarker for assessing liver parenchymal stiffness and detecting NAFLD and is included in adult screening guidelines because of its high sensitivity and specificity (7,9,12,20-22). Elastography is recommended for suspected NAFLD, but 2D-SWE data in the pediatric population are limited (23). Our findings suggest that 2D-SWE can detect liver involvement early and accurately in pediatric T1D patients. In our study, our 2D-SWE findings were not correlated with biopsy, but there is a biopsy-referenced study in the literature stating that 2D-SWE is an alternative reference standard to TE, and there is also a study reporting that it is more effective than TE (15,24). In healthy children, TE (FibroScan) studies reported mean liver elasticity values of 4.4-5.6 (mean 4.7) kPa (25). In the literature, reference 2D-SWE liver stiffness values for healthy children were found to be 4.29±0.59 kPa by Galina et al. (26) and 6.58±1.46 by Franchi-Abella et al. (27). We found a 2D-SWE liver stiffness value of 4.5±0.8 kPa in healthy children. Our findings will contribute to the literature because of the novelty of 2D-SWE and limited pediatric data.

Harman et al. (28) reported that T1D is associated with an unrecognized burden of chronic liver disease, which may be caused by oxidative damage, lipid accumulation, glycogenosis, autophagy, and apoptotic factors, and that age and gender may affect the severe inflammatory response in patients (18). However, we found no effect of gender on the mean values of FBG, HbA1c and hepatic kPa ($p>0.005$). This may be due to differences in the chronic burden of the disease or the severity of the inflammatory response in our patients.

In the literature, there are studies that detected fatty liver in patients with T1D (1). Chronic hyperglycemia, poor glucose control, oxidative stress, and exogenous insulin administration are effective in intrahepatic fat homeostasis (29). In fact, it was reported by Al-Hussaini et al. (30) that 60% of patients with abnormal sonographic findings improved in 6 months with successful glucose management. In our study, no fatty liver was detected sonographically in any of our T1D patients; however, liver stiffness was increased on 2D-SWE compared with that in healthy subjects. This may be an early imaging finding of impaired intrahepatic fat homestasis; therefore, long-term follow-up data may be useful.

Exogenous insulin use and obesity double the risk of NAFLD in T1D patients with poor glycemic control (HbA1c >7%) (31). Subcutaneous insulin injections do not reach the liver via the portal vein, similar to endogenous insulin production, suggesting insulin resistance and increased insulin demand (29). Recent studies have also shown that patients with T1D have higher insulin sensitivity than non-diabetics (5). Hyperglycemia and impaired insulin clearance saturate glycogen synthesis pathways and redirect them to lipogenic pathways, leading to NAFLD. In our patients, high HbA1c values (median/IQR: 8.3/2.4), a significant correlation between diabetes duration and HbA1c, and a significant correlation between liver kPa and FBG may support early hepatic involvement. However, while a strong correlation between liver stiffness and HbA1c has been reported in the literature (31); we could not detect a significant correlation with kPa despite our high HbA1c values. However, the strong correlation between diabetes duration and HbA1c in our patients ($p<0.05$) supports long-term poor glycemic control.

In the literature, it has been reported that NAFLD can be seen in normal weight subjects, and this may be an early warning sign of metabolic disorder (18,19). This may be due to chronic hyperglycemia, high-fat

low-carbohydrate diet and sedentary life with concern of hypoglycemia in T1D patients. It has also been reported in animal studies that the fatty acid translocase CD 36, which is tightly linked to the development of fatty liver, is significantly increased in T1D livers (18). Early diagnosis is also important for the prevention of metabolic diseases. Therefore, 2D-SWE can be used as a quantitative imaging biomarker in the liver follow-up of T1D patients, especially those with poor glycemic control, even if they have normal BMI values, as in our study population, for early diagnosis due to the risk of NAFLD development.

GH, which is a sonographic mimicking condition, may be a factor in the variability in the incidence of NAFLD reported in the literature in pediatric-juvenile T1D cases. Although biopsy is the gold standard for the detection of fat content and fibrosis in the liver, its invasiveness is a major problem in diagnosis and especially in follow-up in the pediatric population. Steatosis, a precursor to fibrosis, may result in higher 2D-SWE liver stiffness values than GH, a reversible condition. The quantitative data provided by 2D-SWE in diagnosis and response to treatment can be easily used in the pediatric population to differentiate between reversible GH.

The increased degree of liver parenchymal stiffness on 2D-SWE in our pediatric T1D patients compared with the healthy group may be due to one or more of the processes mentioned above. What is important here is to determine non-invasive methods that can be used in harmony with the clinic in the follow-up of the cases and can also be standardized by providing quantitative data. In the literature, it has been reported that differences in diagnostic and identification methods play a role in the heterogeneity in the incidence of NAFLD and that AST and ALT values are unreliable in the detection of NAFLD (31). In this context, 2D-SWE can be used in pediatric patients as an easily accessible imaging method with high reproducibility and patient compliance.

Study Limitations

Our study had several limitations. First, its cross-sectional design prevented us from establishing causal relationships because of the lack of long-term follow-up. Additionally, the absence of histological confirmation via liver biopsy, considered the gold standard diagnostic method for excluding NAFLD, posed a limitation. Furthermore, the small sample size, absence of comparative evaluation with T1D patients with NAFLD, limited existing literature on this group, and the inability to draw conclusions about long-term liver involvement and NAFLD development among our patients further restricted our study's scope.

Conclusion

Although liver function tests, lipid profiles, and grayscale ultrasonography showed no abnormalities in our pediatric T1D patients, increased liver parenchymal stiffness detected by 2D-SWE compared with the healthy group indicated hepatic involvement. Therefore, we believe that 2D-SWE could serve as a valuable imaging method for the early detection and monitoring of potential hepatopathy in pediatric T1D patients. Long-term follow-up studies involving a larger population of T1D patients would be beneficial in establishing quantitative reference values for 2D-SWE.

Ethics Committee Approval: University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee approved the study (approval number: 2022/514/225/5, date: 11.05.2022).

Informed Consent: Written informed consent was obtained from the patients' parents.

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Correlation Between Albuminuria and Thyroid Function in Patients with Chronic Kidney Disease

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ABSTRACT

Introduction: Decreased renal function is a significant public health issue, increasing the risk of various adverse outcomes. Thus, identifying potentially modifiable factors associated with the onset of chronic kidney disease (CKD) is imperative. Although CKD has been demonstrated to impact thyroid function through various mechanisms; there remains insufficient and contentious data regarding the association between albuminuria and thyroid function in patients diagnosed with CKD. This study aimed to elucidate the association between albuminuria and thyroid function tests in patients with CKD.

Methods: We conducted a cross-sectional analysis involving 232 patients with CKD. Patients were categorized on the basis of albuminuria levels, measured by the urinary albumin/creatinine ratio (ACR), following the KDIGO 2012 criteria: ACR1 <30 mg/gr, ACR2 30-300 mg/gr, and ACR3 >300 mg/gr. Thyroid stimulating hormone (TSH), free thyroxine (free T4), and free triiodothyronine (free T3) levels were measured to assess thyroid function.

Results: The ACR among subjects ranged from 1.0 mg/g to 10260.0 mg/g, with a mean urinary ACR of 485.7±1250.9 mg/g. Among the patients, 47.4% (n=110) had an ACR <30 mg/g, 25.4% (n=59) had an ACR 30-300 mg/g was, and 27.1% (n=63) had an ACR >300 mg/g. TSH levels ranged from 0.3 to 14 mU/L, free T3 ranged between 0.6 and 4.8 ng/L, and free T4 ranged from 5.5 to 17.8 ng/L. No significant differences were observed in TSH, free T4, and free T3 values among the ACR1, ACR2, and ACR3 groups ($p>0.05$). A significant positive correlation was found between glomerular filtration rate and free T3 ($r=0.395$, $p<0.05$), whereas a significant negative correlation was noted between ACR and free T3 ($r=-0.264$, $p<0.05$).

Conclusion: Our findings suggest that albuminuria may contribute to a reduction in free T3 levels in patients with CKD. However, it is crucial for physicians to recognize that CKD patients with elevated albuminuria levels may exhibit abnormal thyroid function.

Keywords: Chronic kidney disease, albuminuria, thyroid function, free T3

Introduction

Decreased renal function is a prevalent public health challenge, leading to various adverse consequences. Hence, identifying modifiable factors associated with the onset of chronic kidney disease (CKD) is paramount (1,2). CKD manifests as a persistent loss of renal function or damage, often stemming from conditions such as diabetes mellitus (DM) and hypertension. Despite efforts to manage CKD risk factors, renal function decline persists, suggesting the existence of additional, undiscovered risk factors (3). Proteinuria has emerged as a predictive indicator for cardiovascular events, progression to end-stage kidney disease, and mortality in CKD patients, including DM and glomerulonephritis (4-6). Nevertheless, it is still unknown how thyroid function and proteinuria in CKD are related.

Thyroid hormone exerts numerous effects on almost all tissues, highlighting its pivotal role in physiological functions. Therefore, thyroid dysfunction can precipitate various complications in several terminal organs, including the kidney. CKD manifests diverse effects on thyroid function, with alterations in thyroid function levels often correlating with glomerular filtration rate (GFR) levels (7,8). Although the precise interplay between the thyroid and kidney diseases remains incompletely elucidated, accumulating research and the evidence suggest a bidirectional relationship between these conditions (9,10).

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It is widely recognized that albumin, transthyretin, and thyroxine-binding globulin (TBG) are the key serum proteins that bind to thyroid hormones. Consequently, depletion of levothyroxine, TBG, or both can result in (subclinical) hypothyroidism, particularly in young individuals, especially when proteinuria is in the nephrotic range (11). Furthermore, patients presenting with concurrent nephrotic syndrome and hypothyroidism may require higher doses of thyroid replacement therapy (12).

The relationship between baseline kidney function or the onset of CKD and a comprehensive panel of thyroid indicators, including thyroid-stimulating hormone (TSH), free triiodothyronine (free T3), and free thyroxine (free T4), remains poorly understood (13). These indicators have yet to be fully characterized for their association with clinical categories of albuminuria severity in patients with CKD. Thus, the purpose of this study was to elucidate the association between thyroid function tests and albuminuria in patients with CKD.

Methods

Study Design

This cross-sectional prospective study explored the correlation between albuminuria and thyroid function tests among patients with CKD admitted to the Nephrology and Family Medicine outpatient clinic of a Tertiary Referral Hospital from December 1, 2022, to March 1, 2023. The sample size was determined using the G*Power program based on the effect size derived from the relevant literature. Upon reviewing a reference study (11), the effect size reflecting the correlation between the two variables was calculated as 0.183. Consequently, it was determined that 229 individuals should be enrolled in the study, as per power analysis, ensuring 80% power and a significance level of 0.05, based on a two-way hypothesis for CKD individuals. This study protocol received approval from the Local Ethical Committee of Non-invasive Clinical Research at University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 392, date: 23.12.2022), in accordance with the ethical principles outlined in the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013 (www.wma.net).

Patients aged between 18 and 65 years who attended our outpatient clinics from December 1, 2022, to March 1, 2023; and met at least one of the CKD criteria persisting for more than 3 months were recruited for the study. CKD criteria included a decreased GFR (<60 mL/min) and/or markers of kidney damage such as albuminuria [albumin excretion rate ≥30 mg/24 hours; albumin-to-creatinine ratio (ACR) ≥30 mg/gr], abnormalities in urine sediment, structural irregularities identified via imaging, abnormalities detected through histological examination, anomalies related to tubular disorders, and a medical history including kidney transplantation.

Patients were categorized according to the severity of albuminuria, as per the KDIGO 2012 criteria: ACR1 (<30 mg/gr), ACR2 (30-300 mg/gr), and ACR3 (>300 mg/gr). Exclusion criteria comprised individuals below 18 or above 65 years of age, known thyroid disorder necessitating treatment with levothyroxine or thionamide and/or the existence of antibodies targeting thyroid peroxidase, and use of medications known or potential effects thyroid hormone function [such as current or previous use of steroids or furosemide, anticonvulsants (carbamazepine or phenytoin), high-dose amiodarone, heparin or estrogen replacement therapy or anticancer drugs]. According to the inclusion/exclusion criteria, patients were initially informed about the study, and 232 subjects who agreed to participate in the study were enrolled. The height and weight of the patients were measured during outpatient clinic visits, and routine blood tests were conducted.

Laboratory Diagnostics

The following information was recorded: Height, weight, age, gender, body mass index (BMI), and concomitant conditions (dyslipidemia, ischemic heart disease, hypertension, DM, and so forth). Weight (kg)/height (m^2) was the formula used to compute BMI. Routine blood tests, including hemoglobin, hematocrit (HCT), fasting blood glucose, urea, creatinine, GFR, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), TSH, free T4, free T3, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein, serum albumin, urinary ACR, parathyroid hormone (PTH), (calcium, phosphorus, ferritin, vitamin-D) were collected.

Statistical Analysis

Descriptive statistical techniques were used to summarize the data, which included the mean, standard deviation, median, minimum, maximum, frequency, and percentages. The variable distribution was assessed using the Kolmogorov-Smirnov test. The chi-square test was used to examine qualitative independent data, whereas analysis of variance (ANOVA) and Kruskal-Wallis (Mann-Whitney U test) were used to investigate quantitative independent data. Correlations were investigated using Spearman correlation analysis. SPSS version 28.0 was used for statistical analyses.

Results

Demographic characteristics and laboratory findings of patients with CKD are presented in Table 1. Among the 232 patients included in the study, 129 (55.6%) were female and 103 (44.4%) were male, with a mean age of 51.6±10.3 years. Urinary ACR measurements ranged from 1.0 mg/g to 10260.0 mg/g, with a mean of 485.7±1250.9 mg/g. TSH measurements ranged from 0.3 to 14 mU/L, with a mean level of 2.3±1.7 mU/L. Free T3 measurements ranged from 0.6 ng/L to 4.8 ng/L, with a mean level of 3.0±0.5 ng/L. Free T4 measurements ranged from 5.5 ng/L to 17.8 ng/L, with a mean level of 11.7±1.8 ng/L (Table 1).

The distribution of subjects based on ACR levels was as follows: 47.4% (n=110) had ACR <30 mg/g, 25.4% (n=59) had ACR ranging from 30 to 300 mg/g, and 27.1% (n=63) had ACR >300 mg/g.

The comparison of demographic and laboratory parameters among the ACR1, ACR2, and ACR3 groups is presented in Table 2. Gender distribution, mean age, height, weight, and BMI values did not exhibit any significant

differences among the ACR1, ACR2, and ACR3 groups (p>0.05). Similarly, the mean levels of PTH, calcium, phosphorus, ferritin, and vitamin D did not vary substantially across the groups (p>0.05). However, mean values for hemoglobin and HCT were significantly higher in the ACR1 and ACR2 groups compared to those of the ACR3 group (p<0.05). No significant difference in mean hemoglobin and HCT values was observed between the ACR1 and ACR2 groups (p>0.05) (Table 2).

Table 3 illustrates the correlations among GFR, serum albumin, urinary ACR, and various demographic and laboratory parameters. A significant negative correlation was identified between mean GFR and mean age, urea, creatinine, CRP, PTH, and phosphorus levels (p<0.05). Conversely, a significant positive correlation was detected between mean GFR and mean AST, ALT, HDL, free T3, hemoglobin, HCT (p<0.05). No significant correlation was observed between mean GFR and other demographic and laboratory parameters (p>0.05).

The mean serum albumin level exhibited a significant positive correlation with mean height, AST, ALT, calcium, vitamin D, hemoglobin, and HCT levels (p<0.05). Conversely, a significant negative correlation was found between mean serum albumin and mean urea, CRP, PTH, and phosphorus levels (p<0.05). There was no significant correlation with other demographic and laboratory findings (p>0.05).

Furthermore, a significant positive correlation was identified between median urine ACR and mean fasting blood glucose, urea, creatinine, PTH, and phosphorus levels (p<0.05). Conversely, a significant negative correlation was found between median urine ACR and mean GFR, AST, ALT, HDL, free T3, calcium, vitamin D, hemoglobin, and HCT levels (p<0.05). No significant correlation was detected with the other demographic and laboratory findings (p>0.05) (Table 3).

Table 1. Demographic characteristics and laboratory findings of patients with CKD

Characteristics		**n**	**%**		
Gender	**Female**	**129**	**(55.6)**		
	Male	**103**	**(44.4)**		
		Min.-max.		**Median**	**Mean ± SD**
Age (years)		19.0-65.0		54.0	51.6±10.3
Height (cm)		140.0-195.0		164.0	163.7±10.1
Weight (kg)		37.0-132.0		79.5	81.3±15.8
BMI (kg/m^2)		16.4-55.0		29.4	30.4±5.7
Fasting BG (mg/dL)		11.0-391.0		107.0	123.2±50.9
Urea (mg/dL)		12.5-326.0		35.7	45.2±32.5
Creatinine (mg/dL)		0.4-10.4		1.1	1.4±1.2
GFR (mL/min./1.73 m^2)		7.8-136.8		69.0	69.9±29.1
AST (U/L)		4.0-107.0		18.0	20.0±10.3
ALT (U/L)		4.0-75.0		18.0	20.2±11.6
Total cholesterol (mg/dL)		89.0-1858.0		192.0	205.8±146.4
Triglyceride (mg/dL)		22.0-886.0		152.0	170.5±105.5
HDL (mg/dL)		13.0-134.0		43.0	46.2±14.3
LDL (mg/dL)		26.0-400.0		113.0	119.4±58.9
CRP (mg/dL)		0.3-105.2		3.5	7.0±12.9
TSH (mU/L)		0.3-14.0		1.9	2.3±1.7
Free T4 (ng/L)		5.5-17.8		11.7	11.7±1.8
Free T3 (ng/L)		0.6-4.8		2.9	3.0±0.5
Free albumin (g/L)		16.2-53.7		45.7	44.9±4.7
Urine ACR (mg/g)		1.0-10260.0		39.0	485.7±1250.9
PTH (ng/L)		9.0-507.4		51.2	69.2±65.1
Calcium (mg/dL)		1.0-10.8		9.5	9.4±0.8
Phosphor (mg/dL)		1.9-6.5		3.6	3.6±0.7
Ferritin (µg/L)		3.4-715.7		70.9	108.3±115.8
Vitamin-D (µg/L)		3.0-70.5		15.2	18.2±12.4
Hb (g/dL)		7.6-17.9		13.2	13.0±1.9

CKD: Chronic kidney disease, min.: Minimum, max.: Maximum, SD: Standard deviation, BMI: Body mass index, BG: Blood glucose, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, ACR: Albumin/creatinine ratio, PTH: Parathyroid hormone, Hb: Hemoglobin

Table 2. Comparison of demographic and laboratory parameters of patients according to ACR1 (n=110), ACR2 (n=59) and ACR3 (n=63) groups

		ACR1 <30 mg/g	ACR2 30-300 mg/g	ACR3 >300 mg/g	p-value
Gender	Female, n (%)	67 (60.9)	29 (49.2)	33 (52.4)	0.285[X²]
	Male, n (%)	43 (39.1)	30 (50.8)	30 (47.6)	
Age (years)	Mean ± SD	52.4±9.7	50.8±11.5	51.1±10.4	0.585[K]
	Median	54.0	53.0	52.0	
Height (cm)	Mean ± SD	163.5±10.0	164.8±10.3	163.0±10.4	0.463[K]
	Median	164.0	166.0	162.0	
Weight (kg)	Mean ± SD	82.4±15.9	80.1±17.0	80.5±14.5	0.326[K]
	Median	80.0	78.0	79.0	
BMI (kg/m²)	Mean ± SD	30.8±5.4	29.6±6.3	30.5±5.6	0.055[K]
	Median	29.8	28.6	29.1	
Fasting BG (mg/dL)	Mean ± SD	113.1±34.4	132.1±58.4	132.5±63.6	0.054[K]
	Median	103.5	112.0	109.0	
Urea (mg/dL)	Mean ± SD	36.1±14.3	40.7±20.5	65.5±50.9	0.156[K]
	Median	33.0	37.0	49.7	
Creatinine (mg/dL)	Mean ± SD	1.1±0.9	1.3±1.4	1.8±1.4	0.436[K]
	Median	1.0	1.1	1.2	
GFR (mL/d/m²)	Mean ± SD	73.5±23.1	72.1±28.4	61.4±36.9	0.711[K]
	Median	70.2	68.4	58.8	
AST (U/L)	Mean ± SD	20.7±9.4	20.3±12.8	18.5±9.3	0.458[K]
	Median	18.0	19.0	17.0	
ALT (U/L)	Mean ± SD	20.6±10.5	20.9±12.6	19.1±12.7	0.730[K]
	Median	18.0	18.0	15.0	
Total cholesterol (mg/dL)	Mean ± SD	219.0±204.9	184.3±42.1	203.0±60.1	0.302[K]
	Median	191.0	189.0	200.0	
Triglyceride (mg/dL)	Mean ± SD	165.3±111.2	163.5±66.6	186.0±123.3	0.408[K]
	Median	141.0	151.0	162.0	
HDL (mg/dL)	Mean ± SD	47.6±13.4	44.2±12.5	45.5±17.2	0.053[K]
	Median	46.0	41.0	42.0	
LDL (mg/dL)	Mean ± SD	117.4±56.2	108.2±36.5	133.4±76.1	0.556[K]
	Median	111.5	111.0	119.0	
CRP (mg/dL)	Mean ± SD	5.5±8.7	8.9±12.8	8.1±18.0	0.264[K]
	Median	3.3	4.0	3.9	
TSH (mU/L)	Mean ± SD	2.1±1.2	2.3±1.6	2.7±2.5	0.928[K]
	Median	2.0	1.8	1.9	
Free T4 (ng/L)	Mean ± SD	11.8±1.8	12.0±1.9	11.3±1.6	0.109[A]
	Median	11.6	12.1	11.5	
Free T3 (ng/L)	Mean ± SD	3.1±0.5	2.9±0.6	2.8±0.5	0.082[K]
	Median	3.0	2.9	2.8	
Serum albumin (g/L)	Mean ± SD	46.0±3.8	46.5±3.1	41.7±5.9	0.522[K]
	Median	46.5	46.4	42.5	
Urine ACR (mg/g)	Mean ± SD	9.6±6.8	97.5±56.3	1680.7±1957.1	**0.001**[K]
	Median	7.5[2,3]	85.0[3]	870.0	
PTH (ng/L)	Mean ± SD	52.1±24.9	64.3±66.5	103.8±93.9	0.523[K]
	Median	47.6	48.6	66.7	
Calcium (mg/dL)	Mean ± SD	9.6±0.5	9.6±0.5	9.1±1.2	0.630[K]
	Median	9.6	9.6	9.2	
Phosphorus (mg/dL)	Mean ± SD	3.4±0.6	3.5±0.6	3.9±0.9	0.637[K]
	Median	3.4	3.5	3.9	
Ferritin (µg/L)	Mean ± SD	98.2±100.6	119.1±137.1	116.0±119.4	0.427[K]
	Median	70.4	78.1	65.6	
Vitamin D (µg/L)	Mean ± SD	20.9±13.6	19.3±12.2	12.6±7.9	0.642[K]
	Median	18.4	16.3	9.9	
Hb (g/dL)	Mean ± SD	13.4±1.7	13.2±1.9	12.3±2.2	**0.001**[A]
	Median	13.6[3]	13.4[3]	11.8	
Hct (%)	Mean ± SD	40.6±4.7	40.0±5.6	37.7±6.3	**0.002**[A]
	Median	41.1[3]	40.3[3]	36.6	

[K]Kruskal-Wallis (Mann-Whitney U test)/[X²] Chi-squared test/[A]ANOVA, [2]Difference with ACR2 group p<0.05, [3]Difference from ACR3 group p<0.05. ACR: Albumin/creatinine ratio, BMI: Body mass index, BG: Blood glucose, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, PTH: Parathyroid hormone, Hb: Hemoglobin, Hct: Hematocrit

Table 3. Correlation between the glomerular filtration rate, serum albumin, and urinary albumin/creatinine ratio; and the demographics and other laboratory parameters

	GFR		Serum albumin		Urine ACR	
	r	p	r	p	r	p
Age (years)	-0.335	**0.001**	0.056	0.396	-0.028	0.667
Height (cm)	0.058	0.377	0.187	**0.004**	-0.038	0.560
Weight (kg)	0.011	0.866	0.081	0.222	-0.061	0.358
BMI (kg/m^2)	-0.037	0.573	-0.031	0.635	-0.039	0.554
Fasting BG (mg/dL)	-0.062	0.345	-0.057	0.390	0.170	**0.009**
Urea (mg/dL)	-0.794	**0.001**	-0.169	**0.010**	0.285	**0.001**
Creatinine (mg/dL)	-0.929	**0.001**	-0.057	0.390	0.185	**0.005**
GFR (mL/d/m^2)					-0.186	**0.005**
AST (U/L)	0.180	**0.006**	0.164	**0.012**	-0.187	**0.004**
ALT (U/L)	0.310	**0.001**	0.254	**0.001**	-0.182	**0.005**
Total cholesterol (mg/dL)	0.046	0.486	-0.048	0.468	0.041	0.535
Triglyceride (mg/dL)	-0.112	0.088	0.014	0.835	0.113	0.085
HDL (mg/dL)	0.186	**0.004**	0.022	0.742	-0.149	**0.023**
LDL (mg/dL)	0.022	0.740	-0.035	0.592	0.044	0.504
CRP (mg/dL)	-0.199	**0.002**	-0.247	**0.001**	0.126	0.055
TSH (mU/L)	-0.033	0.612	-0.021	0.750	0.098	0.136
Free T4 (ng/L)	0.008	0.907	0.074	0.260	-0.035	0.595
Free T3 (ng/L)	0.395	**0.001**	0.119	0.072	-0.264	**0.001**
PTH (ng/L)	-0.428	**0.001**	-0.245	**0.001**	0.265	**0.001**
Calcium (mg/dL)	0.106	0.109	0.545	**0.001**	-0.280	**0.001**
Phosphorus (mg/dL)	-0.204	**0.002**	-0.248	**0.001**	0.239	**0.001**
Ferritin (µg/L)	-0.128	0.052	0.110	0.095	0.021	0.749
Vitamin D (µg/L)	0.153	0.099	0.287	**0.002**	-0.293	**0.001**
Hb (g/dL)	0.396	**0.001**	0.419	**0.001**	-0.253	**0.001**
Hct (%)	0.396	**0.001**	0.407	**0.001**	-0.239	**0.001**

GFR: Glomerular filtration rate, ACR: Albumin/creatinine ratio, BMI: Body mass index, BG: Blood glucose, AST: Aspartate Aminotransferase, ALT: alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, TSH: Thyroid-stimulating hormone, T4: Thyroxine, T3: Triiodothyronine, PTH: Parathyroid hormone, Hb: Hemoglobin, Hct: Hematocrit

Discussion

This study elucidated the relationship between albuminuria and thyroid function tests among patients with CKD. We found that the mean GFR exhibited significant negative correlations with several demographic and laboratory parameters, including age, urea, creatinine, CRP, PTH, and phosphorus levels. Conversely, a positive correlation was demonstrated between the mean GFR and AST, ALT, HDL, free T3, hemoglobin, and HCT. These findings highlight the intricate relationship between renal function and thyroid function, suggesting potential bidirectional influences.

Furthermore, significant correlations were observed between serum albumin levels and various demographic and laboratory parameters, including height, AST, ALT, calcium, vitamin D, hemoglobin, and HCT. Moreover, mean serum albumin was significantly negatively correlated with urea, CRP, PTH, and phosphorus levels. In addition, our study revealed significant correlations between urinary ACR and several metabolic parameters, including fasting blood glucose, urea, creatinine, PTH, and phosphorus levels. Conversely, a negative correlation was identified between urinary ACR and GFR, AST, ALT, HDL, free T3, calcium, vitamin D, hemoglobin, and HCT. These findings suggest a potential role of albuminuria in modulating thyroid function and vice versa, highlighting an intricate interplay among albuminuria, renal function, and metabolic parameters in patients with CKD.

Several studies have explored the connection between proteinuria and thyroid function in patients with normal renal function (14-18). A study involving 20 young patients (aged 12-50 years) with nephrotic syndrome and high proteinuria levels (mean: 5.2±1.2 g/day) revealed elevated TSH levels (5.9-2.9 mIU/m^2) alongside decreased levels of T4 and T3. In a retrospective analysis by Yang et al. (19), which included 211 patients with an average albuminuria of 2.1±2.0 g/day, a negative association was observed between free T4 levels and albumin excretion, whereas TSH levels remained unchanged. However, this study did not provide information on TBG and free T3 concentrations, nor did it include thyroid antibody status. It is worth noting that the mean levels of proteinuria in the aforementioned studies were higher than those measured in our study. Nevertheless, our study revealed a negative correlation solely between free T3 levels and ACR.

A study conducted by a Chinese group (20) investigated 581 individuals with albuminuria, categorizing patients into three subdivisions of albuminuria similar to our study. They observed a positive correlation between higher serum T4 and fT4 levels in the subgroup with albuminuria >300 mg. However, in the group with albuminuria >300 mg, only a mean of 996±843 mg/g creatinine was measured. TSH, T3, and free T3 levels did not exhibit significant variations among the albuminuria subsets. The study did not provide data on the number of patients in the true nephrotic range (>3 g/day) or TPO-Ab status. The authors attributed the differences between their findings and those of other studies partially to racial distinctions (20). Similarly, in line with previously reported studies, we observed that TSH and free T3 and T4 levels did not differ significantly among the albuminuria groups. However, contrary to previous findings, we discovered a negative correlation between the levels of free T3 and albuminuria. This discrepancy may stem from the fact that our study was single-centered and included patients with CKD in the early stages, without representation from diverse racial groups.

Thyroid hormones within normal levels can directly influence kidney function by impacting both glomerular and tubular functions, as well as indirectly through prerenal effects on cardiovascular hemodynamics and renal blood flow (21). Elevated levels of TSH within the normal range have been associated with reduced estimated glomerular filtration rate (eGFR) (22-24). However, the association between the related levels of T3 and T4 and kidney function remains controversial (13,23,25). The diagnosis of kidney disorders may also be linked to thyroid dysfunction, either due to the leakage of TSH, free T4, and relevant binding proteins into the urine or due to non-thyroidal illness (21,26,27).

A recent study demonstrated a directional association between hypothyroidism and increased TSH, but not free T4, and decreased eGFR using cystatin C and increased CKD (28). Our study further substantiates the significant association between GFR and thyroid function markers. Specifically, we observed a negative correlation between the mean GFR and several demographic and laboratory parameters, including age, urea, creatinine, CRP, PTH, and phosphorus levels. Conversely, a positive correlation was found between the mean GFR and AST, ALT, HDL, hemoglobin, and HCT. The correlations between GFR decline and increased PTH and phosphorus levels and decreased hemoglobin and HCT levels are significant as secondary signs of CKD. Notably, among thyroid function markers, only free T3 levels were positively correlated with GFR. These findings highlight the intricate relationship between renal function and thyroid function, suggesting potential bidirectional influences.

In a prospective study, Reinhardt et al. (11) examined the association between thyroid and kidney function in individuals without thyroid antibodies across all stages of CKD. They observed a negative association between serum albumin levels, and age and CRP, while a positive association was found with T3, T4, fT3. However, no significant correlation was observed between serum albumin and TSH and fT4 (11). Consistent with these findings, our study indicated that TSH and free T4 levels were unaffected by albumin excretion, whereas free T3 showed a significant negative correlation with urinary albumin excretion. Furthermore, we observed significant correlations between serum albumin levels and various demographic and laboratory parameters, including height, AST, ALT, calcium, vitamin D, hemoglobin, and HCT. These findings suggest a potential role for albuminuria in modulating thyroid function and vice versa.

In a study involving 1624 adult patients at stage 3-5 CKD and 200 normal control subjects, it was found that 98.6% of CKD patients had insufficient levels of 25-hydroxyvitamin D [25(OH)D], compared with only 48% of normal subjects (29). Similarly, in our study, serum levels of vitamin D showed a significant negative correlation with ACR. Another report, comprising 9,162 participants from the Dong-gu study's baseline survey conducted in Korea between 2007 and 2010, revealed that higher ACR levels were associated with elevated PTH and lower 25(OH)D levels (30). Consistent with this finding, we found a positive correlation between urine ACR and PTH and phosphorus levels, whereas urine ACR exhibited a significant negative correlation with GFR, calcium, and vitamin D levels. However, our study did not detect any correlation between urine ACR and PTH, GFR, creatinine, calcium, phosphorus, or vitamin D levels.

In a study conducted from 1996 to 1998, which recruited 5801 participants with available hemoglobin measurements from the ARIC study, anemia prevalence was stratified according to ACR. The study revealed an anemia prevalence of 8.1% in attendees with ACR <10 mg/g, 10.7% in those with ACR 10 to 29 mg/g, and 13.3% in those with ACR ≥30 mg/g (31). Furthermore, a retrospective analysis conducted using data from the Clinical Laboratory of the University Hospital of Verona between May 2007 and May 2009 examined ACR and hemoglobin levels in the entire cohort. Within the comprehensive outpatient cohort, an accelerating decline in hemoglobin and an increased prevalence of anemia were observed in patients with microalbuminuria (24%) and macroalbuminuria (32%) compared with those with normoalbuminuria (15%) (32).

In a cross-sectional study by Inker et al. (33), an association between albuminuria stages and laboratory abnormalities (PTH, GFR, creatinine, calcium, phosphorus) was generally lacking or minimal in both CKD cohorts and those representing the general population or at high risk. In addition, they reported little or no association between stages of albuminuria and hemoglobin levels in both CKD cohorts and cohorts representing the general population or individuals at elevated risk. However, increased albuminuria was linked to slightly reduced hemoglobin levels in CKD cohorts (34). Similarly, in our study, a negative correlation was observed between albuminuria and hemoglobin levels. Additionally, significantly lower albuminuria was detected in the ACR3 group than in the ACR1 and ACR2 groups. Furthermore, we found a significant negative correlation between urinary ACR and hemoglobin and HCT levels, which aligns with findings in the existing literature.

Study Limitations

The limitations of our study are the small sample size from a single center, absence of measurement of anti-thyroid peroxidase antibody, and absence of results of total T3 and T4 of patients.

Conclusion

In summary, our study offers valuable insights into the interplay between albuminuria, thyroid function, and renal function in patients

with CKD. This suggests that albuminuria may contribute to a decline in free T3 concentrations in patients with CKD. Additionally, clinicians should remain vigilant regarding the potential for abnormal thyroid function tests in patients with CKD with high albuminuria. Further research encompassing a broader range of parameters and a larger cohort of patients is warranted to fully elucidate the underlying mechanisms and clinical implications of these associations. Such investigations have the potential to inform the development of targeted therapeutic strategies for managing CKD and associated thyroid dysfunction, ultimately improving patient outcomes.

Ethics Committee Approval: This study protocol received approval from the Local Ethical Committee of Non-invasive Clinical Research at University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 392, date: 23.12.2022).

Informed Consent: Retrospective study.

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Comparison of Postoperative Anxiety, Depression, Somatization, and Somatosensory Perception Levels of Patients After Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery

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ABSTRACT

Introduction: This study investigated the effect of coronary artery bypass grafting surgery performed using either the on-pump or off-pump technique on the levels of postoperative anxiety, depression, somatization, and somatosensory amplification in patients.

Methods: There were 100 participants in this cross-sectional study who completed the "Sociodemographic Data Form", the "Hospital Anxiety and Depression Scale", the "Somatization Scale (SS)", and the "Somatosensory Amplification Scale".

Results: Compared with the off-pump group, the on-pump group had a higher mean SS score.

Conclusion: Because the mean SS score was lower in patients after off-pump surgery, it may be more advantageous to perform off-pump surgeries in the future. Before the superiority of the off-pump over the on-pump can be definitively established, however, data from large, randomized trials are required.

Keywords: Coronary artery bypass graft surgery, off-pump, on-pump, CABG, depression, anxiety, somatization

Introduction

Even with advances for treating cardiovascular diseases, these diseases continue to be the leading cause of death worldwide (1). For treating coronary artery disease (CAD), the most commonly used method is coronary artery bypass grafting (CABG). In most health centers, cardiac surgery is performed with very low mortality due to rapid technological advancements, knowledge, and experience (2). Essentially, CABG provides continuity of circulation by creating an alternative route between the proximal and distal parts of the occluded coronary artery. The use of this procedure reduces mortality in patients with extensive CAD (3).

There are two main ways of performing CABG: CABG with the use of a cardiopulmonary bypass machine (CPBM) (on-pump) and CABG without the use of a CPBM (off-pump). The surgeon begins both methods by preparing blood vessels from the leg, chest, or arm to be used as grafts for the revascularization procedure. With on-pump CABG surgery, blood flow to the body is provided via CPBM, which allows for blood revascularization in a bloodless and stable state. The following revascularization, the heart is restarted once the body is removed from the CPBM (4,5). On the other hand, on-pump CABG is associated with an inflammatory response of the whole body, leading to postoperative complications such as systemic inflammatory response syndrome (6), neurocognitive dysfunction, renal failure, myocardial depression, and bleeding (3,7,8).

During off-pump CABG, the heart is left unconnected to the CPBM while performing systole and diastole as usual. Studies have demonstrated definite benefits in patients with extensive atherosclerotic disease of the aorta, renal insufficiency, or prior cerebrovascular disease, as well as providing a less invasive approach to surgical revascularization of the heart (3,9). While there is disagreement regarding the long-term efficacy of off-pump CABG, studies indicate that it reduces operative duration as well as the length of hospitalization in intensive care units (ICUs), blood transfusion rates, and early morbidity (10).

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As a dominant and persistent mood disorder, depression is experienced internally and negatively affects one's behavior and perception of the world. Anxiety is characterized by a persistent, unpleasant, and vague sense of negativity. Everyone is susceptible to this condition, which is often accompanied by autonomic symptoms. Symptoms of anxiety can vary and differ from person to person (11).

Somatization disorder is a psychiatric condition characterized by unexplained physical or somatic symptoms. Rather than a well-defined diagnostic class or disorder, somatization refers to a comprehensive clinical assessment. Thus, patients with somatization represent a very heterogeneous group. In addition to the length and severity of somatization, the extent and severity of the mood component, as well as the ability of individuals to recognize and describe their emotions, vary greatly between individuals (12,13). In general, somatization refers to the manifestation of emotions through the body rather than verbal expression (14). The concept of somatosensory amplification refers to the tendency to perceive ordinary somatic sensations as severe, intense, disturbing, and harmful (15). In people with somatic complaints, the tendency to amplify somatic sensations is prominent (16).

Cardiovascular diseases continue to be one of the leading causes of mortality and morbidity worldwide. Although there are various methods of treating this disease, including lifestyle changes and medical treatments, surgical methods play a crucial role as a last resort. Similar to other surgical procedures, cardiovascular surgery may result in a number of complications. The CABG procedure causes significant metabolic, physical, and psychological stress in patients (17,18). A high level of anxiety has also been reported to be associated with a high level of postoperative pain in patients undergoing CABG surgery (19). Additionally, patients with high levels of postoperative anxiety have poorer long-term psychological outcomes (17,18).

Although there are studies that examine anxiety, depression, somatization, and somatosensory amplification in patients undergoing CABG, the number of studies that compare these parameters based on the technique used in surgery (on-pump, off-pump) is quite limited. Accordingly, the purpose of this study was to investigate the effects of CABG surgery performed using on-pump or off-pump techniques on postoperative anxiety, depression, somatization, and somatosensory amplification levels in patients.

Methods

Design and Participants

The population of this cross-sectional study consisted of 140 patients who underwent CABG surgery with an on-pump or off-pump technique in the cardiovascular surgery clinic of a hospital in the eastern region of Turkey between December 2021 and February 2023.

A total of 100 patients were included in the study who were willing to participate between the specified dates, had no communication difficulties, had no history of cerebrovascular events, and had no mental illness diagnosis, and planned to undergo CABG with either an on-pump or an off-pump technique. Fifty of these patients underwent CABG surgery using the On-Pump technique, and the remaining 50 underwent CABG surgery using the off-pump technique.

Data Collection

The Sociodemographic Data Form, Hospital Anxiety and Depression Scale (HADS), Somatization Scale (SS), and Somatosensory Amplification Scale (SSAS) were administered to the patients after their verbal/written consent was obtained. During the preoperative period, patients were asked to complete a "Sociodemographic Data Form." A face-to-face interview was performed in approximately 15-20 minutes to collect "HADS", "SS" and "SSAS" data at the 1st month postoperatively.

Data Collection Tools

Sociodemographic Data Form: The information form, which was prepared by the researchers in line with the literature, consisted of questions about the descriptive characteristics of the patients.

Hospital Anxiety and Depression Scale: This self-assessment tool was designed to assess the risk of anxiety and depression in patients with physical diseases, as well as those applying for primary health care services, and to measure the level and change in severity of symptoms (20). It was adapted into Turkish by Aydemir (20), and a validity and reliability study was conducted. The scale had subscales for anxiety and depression. A Cronbach's alpha value of 0.85 was found for the anxiety subscale, and 0.77 was found for the depression subscale. The item total score correlation coefficients ranged between 0.81 and 0.85 for the anxiety subscale and 0.73 to 0.77 for the depression subscale. The two-half reliability was found to be r=0.85 for the anxiety subscale and 0.80 for the depression subscale (20). In this study, the Cronbach's alpha value of the scale was found to be 0.86.

Somatization Scale: The SS was created from the items related to Somatization Disorder of the Minnesota Multiphasic Personality Inventory created by Hathaway and McKinley (21). The scale included 33 questions that could be answered as true or false. Participants received 1 point for each "true" answer and 0 point for each "false" answer when responding to positively scored questions. The participants scored 0 when they left the question blank. The items numbered 2, 3, 8, 9, 12, 13, 14, 14, 15, 16, 17, 18, 24, 25, 28, 29, 30, and 31 in the scale were scored reversely. The total score obtained from the scale was ranging from 0 to 33. Because of the validity and reliability study of the scale conducted by Dülgerler (22), Cronbach's alpha value was found to be 0.83. In this study, the Cronbach's alpha value of the scale was found to be 0.84. This value indicates that the scale is highly reliable.

Somatosensory Amplification Scale: Barsky and Wyshak (23) developed a scale to measure the mechanisms used by individuals during somatization. As part of the dependent validity test, participants were asked to evaluate 10 different somatosensory expressions, most of which did not reflect disease or problems under normal conditions, on a scale between "1- Not at all true" and "5-Extremely true". Because of summing the scores obtained from the items, the amplification score was calculated, which provided information regarding the tendency of individuals toward somatization. A test-retest reliability of the original version of the scale, which was validated for Turkish validity and reliability by Güleç et al. (24), was reported to be 0.73, and Cronbach's alpha was 0.76 in the patient group. Based on the results of this study, the Cronbach's alpha value for the scale was 0.74.

Data Collection Process

Ethical Aspects of the Study

A clinical research ethics committee approval from the Clinical Research Ethics Committee of the Erzincan Binali Yıldırım University Clinical Research Ethics Committee where the study was conducted as well as institutional permission from the relevant hospital were obtained in order to conduct this study in accordance with ethical principles (approval number: 15/06, date: 21.02.2022). The participants who volunteered to participate in the study were informed about the study and informed consent was obtained from them. Informed patients were assured that their personal information would remain confidential.

Statistical Analysis

The data was analyzed using IBM SPSS Statistics 21 (IBM Corporation, Armonk, New York, USA). The descriptive statistics used were frequency, percentage, median (interquartile range), mean, and standard deviation. To evaluate the conformity of the numerical data to a normal distribution, Skewness-Kurtosis (+3 and -3) was applied. Student's t-tests were used to compare numerical variables with normal distribution, and Mann-Whitney U tests were used to compare variables comparing two independent groups that did not fit the normal distribution. The categorical variables were compared using the chi-square test. The variables affecting the numerical data were determined using comparative correlation analyses (Pearson, Spearman). Cronbach's alpha coefficient was calculated for reliability analysis of the scales. At a confidence interval of 95%, the results were interpreted at a level of significance of $p<0.05$.

Results

The distribution of patients according to their descriptive characteristics is presented in Table 1. The on-pump group consisted of 52% female patients with a mean age of 60.77±10.87 years and a body mass index (BMI) of 29.45±5.52 kg/m^2. In the same group, 48% were male patients with an average age of 57.21±12.01 years and a BMI of 30.97±3.58 kg/m^2. In the off-pump group, 44% were female patients with an average age of 67.59±7.04 years and a BMI of 29.05±5.73 kg/m^2, and 56% were male patients with an average age of 66.64±8.35 years and a BMI of 28.36±2.39 kg/m^2.

In the on-pump group, 66% lived in the city, 70% were married, 30% were university graduates, 72% had a moderate economic status, 46% smoked and 14% used alcohol, 38% were retired, 58% had a known chronic disease, 58% had a family history of psychiatric disease, and 44% had two coronary artery revascularizations. In the off-pump group, 68% lived in the city, 76% were married, 26% were primary school graduates, 68% had a medium economic status, 46% smoked, 22% used alcohol, 50% were retired, 76% had a known chronic disease, 68% had a diagnosis of psychiatric disease in their family history, and 38% had two coronary artery revascularizations.

The mean scores of HADS-Anx, HADS-Dep, SS, and SSAS after CABG are presented in Table 2. Therefore, the mean scores of HADS-Anx, HADS-Dep, and SSAS did not differ between the groups; however, the mean score of SS was statistically significantly higher in the on-pump patient group (p=0.02).

After the off-pump operation, the mean scores of HADS-Anx, SS, and SSAS were significantly higher in females than in males (p=0.00, p=0.04, p=0.00, respectively). The mean SS scale scores of non-smokers were significantly higher than those of smokers (p=0.00). The mean scores of those with a diagnosed chronic disease were significantly higher than those without a diagnosed chronic disease (p=0.01).

After the on-pump operation, it was observed that females had significantly higher mean scores on the SSAS than males (p=0.01). The mean SSAS scores of non-smokers were significantly higher than those of smokers (p=0.00).

When compared in terms of gender, the mean scores of HADS-Anx, HADS-Dep, and SSAS were significantly higher in females (p=0.00, p=0.03, p=0.00, respectively). The mean scores of HADS-Anx and SS were significantly higher in non-alcohol users (p=0.022, p=0.003, respectively). Similarly, the mean SSAS scores were significantly higher in non-smokers (p=0.001).

Table 1. Comparison of sociodemographic characteristics of the on-pump and off-pump groups

	On-pump (n=50)		Off-pump (n=50)	
	Number (n)	%	Number (n)	%
Female	26	52	22	44
Male	24	48	28	56
	Age		Age	
	Avg. ± SS		Avg. ± SS	
Female	60.77±10.87		67.59±7.04	
Male	57.21±12.01		66.64±8.35	
	BMI		BMI	
	Avg. ± SS		Avg. ± SS	
Female	29.45±5.52		29.05±5.73	
Male	30.97±3.58		28.36±2.39	

SS: Somatization Scale, BMI: Body mass index, Avg.: Average

Table 2. Comparison of the mean scores of HADS-Anx, HADS-Dep, SS, and SSAS between the on-pump and off-pump groups

	HADS-Anx Avg. ± SS	HADS-Dep Avg. ± SS	SS Avg. ± SS	SSAS Avg. ± SS
Off-pump	10.14±3.79	8.64±3.49	**32.86±2.52**	31.34±8.31
On-pump	10.90±4.93	9.74±5.02	**34.04±2.57**	28.78±8.82
p	0.39	0.20	**0.02**	0.13

HADS: Hospital Anxiety and Depression Scale, SS: Somatization Scale, SSAS: Somatosensory Amplification, Avg.: Average.

Table 2. Continued

	Off-pump				On-pump			
	HADS-Anx	**HADS-Dep**	**SS**	**SSAS**	**HADS-Anx**	**HADS-Dep**	**SS**	**SSAS**
Gender								
Female	**11.73±3.62**	9.45±3.00	**33.68±2.37**	**34.95±6.47**	11.81±3.69	10.73±4.32	34.00±2.53	**31.73±8.08**
Male	**8.89±3.48**	8.00±3.77	**32.21±2.48**	**28.50±8.59**	9.92±5.91	8.67±5.58	34.08±2.68	**25.58±8.61**
p	**0.00**	0.14	**0.04**	**0.00**	0.18	0.14	0.91	**0.01**
Smoking								
Yes	10.26±4.37	8.91±3.80	**31.87±2.07**	29.61±8.83	10.48±4.98	9.65±4.87	34.52±2.53	**24.57±7.21**
No	10.04±3.29	8.41±3.27	**33.70±2.59**	32.81±7.69	11.26±4.95	9.81±5.24	33.63±2.58	**32.37±8.57**
p	0.83	0.61	**0.00**	0.17	0.58	0.91	0.22	**0.00**
Diagnosed as a chronic disease								
Yes	10.47±3.84	8.97±3.02	**33.37±2.36**	**31.89±8.64**	12.00±4.87	10.76±5.13	33.62±2.61	30.41±9.01
No	9.08±3.57	7.58±4.69	**31.25±2.41**	**29.58±7.20**	9.38±4.70	8.33±4.63	34.62±2.47	26.52±8.22
p	0.27	0.35	**0.01**	**0.01**	0.06	0.09	0.17	0.12
Alcohol use								
Yes	8.82±3.15	7.36±3.64	**30.45±1.63**	32.18±5.58	7.71±4.88	7.57±4.57	34.00±2.58	**21.86±8.49**
No	7.36±3.64	9.00±3.41	**33.54±2.31**	31.10±8.97	11.42±4.79	10.09±5.05	34.05±2.60	**29.91±8.43**
p	0.19	0.17	**0.00**	0.70	0.06	0.22	0.96	**0.02**

HADS: Hospital Anxiety and Depression Scale, SS: Somatization Scale, SSAS: Somatosensory Amplification Scale

Table 3. Comparison of the mean scores of HADS-Anx, HADS-Dep, SS, and SSAS according to age

	HADS-Anx	**HADS-Dep**	**SS**	**SSAS**
Age	R :0.084 P: 0.406	R: -0.036 P: 0.719	**R: -0.133** **P: 0.018**	**R: 0.268** **P: 0.007**
HADS-Anx	*	**R: 0.742** **P: 0.00**	R: 0.097 P: 0.339	**R: 0.380** **P: 0.00**
HADS-Dep	**R: 0.742** **P: 0.00**	*	R: 0.115 P: 0.253	**R: 0.282** **P: 0.004**
SS	R: 0.097 P: 0.339	R: 0.115 P: 0.253	*	R: -0.056 P: 0.580
SSAS	**R: 0.380** **P: 0.00**	**R: 0.282** **P: 0.004**	R: -0.056 P: 0.580	*

HADS: Hospital Anxiety and Depression Scale, SS: Somatization Scale, SSAS: Somatosensory Amplification Scale

According to Table 3, there was a significant correlation between the patient's age and the mean scores on the HADS-Anx, HADS-Dep, SS, and SSAS. The correlation between age and SS was negative, whereas the correlation between age and SSAS was positive. HADS-Anx was positively correlated with HADS-Dep and SSAS. The correlation between HADS-Dep and SSAS was positive.

A comparison of off-pump and on-pump in terms of gender is presented in Table 4. As a result, there was no difference between the off-pump and on-pump in females in this context. In terms of males, the mean SS score was significantly higher in the on-pump group.

Discussion

According to our knowledge, this is the first study to investigate the effects of CABG surgery performed using two different techniques, on-pump and off-pump, on patients' anxiety, depression, somatization, and somatosensory perception.

It is no longer sufficient to consider surgery the only safe or effective method for treating cardiovascular disease because of technological advancements in this field. The length of hospital stay, level of pain, speed of recovery after surgery, and severity of postoperative complications are also critical factors for both patients and their relatives.

Although CABG surgery significantly reduces mortality rates, it remains a significant life event with significant psycho-emotional implications (25,26). Furthermore, CABG is one of the surgical interventions most associated with postoperative depression and anxiety, in addition to spinal surgery, cholecystectomy, and hysterectomy (27).

In the study, although there was no significant difference in terms of the technique used, it was observed that the patients experienced moderate anxiety and depression in the postoperative period. CABG is a traumatic procedure, and patients' depression and anxiety levels increase in the postoperative period. Although there is a relationship between CABG and depression, its onset is not clear (28,29). Patients feel anxious and

Table 4. Comparison of mean scores of HADS-Anx, HADS-Dep, SS, and SSAS according to gender

Gender	Female		Male	
	Off-pump	On-pump	Off-pump	On-pump
HADS-Anx	11.73±3.62	11.81±3.69	8.89±3.48	9.92±5.91
	p=0.94		p=0.44	
HADS-Dep	9.45±3.00	10.73±4.32	8.00±3.77	8.67±5.58
	p=0.23		p=0.61	
SS	33.68±2.37	34.00±2.53	**32.21±2.48**	**34.08±2.68**
	p=0.65		p=0.01	
SSAS	34.95±6.47	31.73±8.08	28.50±8.59	25.58±8.62
	p=0.13		p=0.22	

HADS: Hospital Anxiety and Depression Scale, SS: Somatization Scale, SSAS: Somatosensory Amplification Scale

depressed in the postoperative period because they are isolated from their families, friends, and work life and face a series of problems such as pain, sleep disorders, loss of status, sexual and social ability, inability to adapt to treatment, and fear of death (27-29). The results of our study indicate that patients undergoing CABG surgery today experience mood disorders at a significant level. The vital importance of the heart as well as the patient's fear of death because the individual's heart will be operated upon increases the risk of postoperative depression and anxiety (30,31). Therefore, it is essential for patients undergoing CABG surgery to receive psychological support before and after surgery.

According to our study, there was no significant difference in anxiety or depression between male and female patients treated with on-pump or off-pump techniques. The issue of gender has remained controversial in the CABG literature. Although female gender seemed to be a risk factor for postoperative depression, it was observed in a systematic review by McKenzie et al. (32) examining postoperative depression and anxiety in individuals undergoing CABG surgery found no significant difference between males and females in terms of depression. Furthermore, in the same study, it was found that gender was not a determining factor in postoperative anxiety (32). A subsequent study conducted by Vaccarino et al. (33) reported that females had a more difficult recovery after CABG than males. In comparison to male patients, female patients experienced more complications and depressive symptoms and were almost twice as likely to be readmitted to the hospital (33,34). Because of the different social roles between males and females and the fact that females had greater domestic responsibilities and expectations, it is possible to suggest that females had more fatigue, insomnia, and depressive symptoms (33).

Although some theories have been proposed, the evidence regarding the effects of gender on postoperative anxiety and depression remains unclear (32,33,35). Different characteristics of the sample groups included in the studies may explain this difference.

Comparing the mean SSAS scores between the groups did not reveal any significant differences in this study. Although CABG surgery is intended to alleviate or eliminate some symptoms associated with CAD, complications may occur in the postoperative period (36,37). Accordingly, patients with these complications were more sensitive to their somatosensory perceptions and tended to amplify them (38,39).

In comparison with the off-pump group, the on-pump group scored higher on the SS. Several studies have highlighted the advantages of off-pump surgery in terms of reducing renal damage, respiratory complications, perioperative bleeding, postoperative ventilation time, ICU stay, and mortality (40-43). Patients may have developed somatization disorders because of these negative outcomes following an on-pump procedure.

The correlation between HADS-Anx, HADS-Dep, and SSAS was positive. The most common somatic symptoms of depression include pain, weakness, fatigue, dizziness, shortness of breath, palpitations, weight loss, and others involving almost every organ system (13,44). In the same way as with depression, somatization is clearly related to anxiety disorders (45). The prevalence of somatic symptoms is higher among patients with anxiety disorders than among healthy individuals. Shortness of breath, chest pain, dizziness, palpitations, and sweating are examples of somatic symptoms associated with anxiety (13,45,46). Those who suffer from depression or high anxiety tend to catastrophize their somatic symptoms and attribute them to serious physical disorders. Therefore, by increasing their interest in and attention to the body, they can amplify and externalize their pre-existing fears and anxieties. Previous studies support our findings (38).

When the age of the patients was compared to the mean scores of HADS-Anx, HADS-Dep, SS, and SSAS, it was noted that there was a negative correlation between age and SS and a positive correlation between age and SSAS. This study concluded that age had no significant effect on postoperative depression and anxiety in patients. However, different findings were found when the literature was reviewed. Based on the findings of Koivula et al. (47) and Redeker (48), young patients experienced higher levels of anxiety during the postoperative period due to concerns about their ability to return to their preoperative independence (47,48). It was determined in a study conducted by McCrone et al. (30) that participants aged 70 years experienced lower levels of depression and anxiety than participants aged 60 to 70 years. Considering the differences in age classifications among the studies, these findings were not surprising.

The level of somatic symptoms in the postoperative period decreased with increasing age in this study. This result may be attributed to the

individual's gradual adjustment to the disease and changes in life associated with aging. There was also an increase in the amplification of somatic symptoms with age (49). The findings of this study support the recommendation for psychosocial support for CABG patients both during the disease and before surgery to facilitate their recovery following surgery.

Study Limitations

There were some limitations to this study. Most importantly, there was a limited number of patients. The use of self-report scales for determining anxiety, depression, and somatization, as well as the absence of a structured clinical interview, were also limitations of this study.

Another limitation of the study was that participants were not interviewed for an extended period following surgery. Our findings were limited by these limitations, which prevented them from being generalized. There is a need for further studies to be conducted in large sample groups with a much larger number of participants.

Conclusion

CABG surgery is an anxiety-provoking procedure for patients. The low score on the SS scale in this study, especially among patients who underwent off-pump surgery, i.e., surgery without stopping the heart, suggests that future CABG surgeries may benefit from off-pump surgery. However, large, randomized trials are necessary before definitive conclusions can be drawn regarding the superiority of off-pump treatment over on-pump treatment.

In this study, the off-pump CABG group experienced fewer postoperative somatic reactions than the on-pump group. Multiple evaluations at different time points (1, 3, 6, and 12-months) may be recommended in studies with larger sample sizes to confirm this finding.

From the moment CABG is determined as a treatment option, it is essential that patients receive training and counseling to support their mental health throughout their hospital stay, postoperative period, and after discharge, as well as assistance from mental health professionals.

Ethics Committee Approval: The study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval number: 15/06, date: 21.02.2022).

Informed Consent: The participants who volunteered to participate in the study were informed about the study and informed consent was obtained from them.

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Etiological Evaluation and Mortality of Patients with Renal Artery Stenosis: A Single-Center Experience

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ABSTRACT

Introduction: Renal artery stenosis (RAS) is a clinical picture that is evaluated as a renovascular disorder and includes many diseases in its etiology. The primary purpose of the present study was to reveal the etiology of cases followed up in the nephrology outpatient clinic due to RAS; to describe their demographic, clinical, and radiological features; and investigate their treatment and prognosis. The second aim of the study was to investigate the relationship between isolated RAS cases that cannot be attributed to any etiological cause and Takayasu's arteritis.

Methods: Patients were included in retrospectively examining all patient files that were registered between January 1996 and 2018. Demographic data of the patients, date of diagnosis, initial physical examination findings, comorbid diseases, imaging findings, interventional and medical treatments, need for kidney replacement therapy, and time to hemodialysis/transplantation were recorded.

Results: Out of the 17427 (8800 M/8627 F) patients, a total of 134 (70 M/64 F) patients aged over 18 years with RAS were included in the study; 60 (55%) patients had atherosclerotic RAS, whereas 23 (21.1%) patients were diagnosed with vasculitis. In total, 16 patients (13.5%) died with a mean of 6±3.4 years after admission. It was found that advanced age, low GFR at diagnosis, and small kidneys are significant and poor prognostic factors.

Conclusion: A more systematic approach model can be developed in terms of applying "maximal medical treatment", which is our approach that we can currently describe as incomplete in cases of RAS with an early atherosclerotic process.

Keywords: Renal artery stenosis, atherosclerosis, Takayasu's arteritis, hypertension, prognosis

Introduction

Renal artery stenosis (RAS) is a clinical picture that is evaluated as a renovascular disorder and includes many diseases in its etiology (1-3). RAS, which constitutes the group of renovascular diseases together with ischemic nephropathy and renovascular hypertension (HT), includes conditions in which more than 60% of the luminal diameter of the renal artery is affected (1-3).

The most common cause at the age of 40 years and below was Takayasu's arteritis (with 60.5%), while the primary etiology above the age of 40 years was atherosclerosis (with 94.7%) (3,4). Atherosclerotic RAS, the most common type, is seen especially in the elderly population and mainly occurs in patients with comorbid diseases (1-5). This population appears to have more left ventricular hypertrophy, ischemic heart disease, and renal failure (6). Atherosclerotic RAS usually involves the ostium and the middle 1/3, and it can also be seen at the level of the proximal renal artery, especially in normotensive patients aged 60 years or over (1-5).

Takayasu's arteritis, which can cause vascular involvement and may also involve the renal artery, appears as vasculitis that can result in HT, renal failure, and early death; particularly in the second or third decades, females are predominantly encountered (7). Fibromuscular dysplasia (FMD), on the other hand, is predominantly seen between the ages of 30 and 50 and exhibits a 3- to 4-fold female dominance. It is an idiopathic, non-inflammatory, and non-atherosclerotic process. It progresses bilaterally in 40% of cases, especially in the right renal artery. In conventional angiographic imaging, it is defined as "string-of-beads". Apart from the most common medial type, there are intimal and adventitial types; the medial type especially involves the distal 2/3 of the renal artery and is bilateral in 60% of cases (7,8).

RAS arises because of various etiologies, but prognostic studies supported by clinical and radiological data showing the etiologies followed from one center are limited. The primary purpose of the present study was to reveal the etiology of cases followed up in the nephrology outpatient

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clinic due to RAS; to describe their demographic, clinical, and radiological features; and investigate their treatment and prognosis. The second aim of the study was to investigate the relationship between isolated RAS cases that cannot be attributed to any etiological cause and Takayasu's arteritis.

Methods

Patients who met the inclusion criteria were included in the study by retrospectively examining all patient files that were registered between January 1996 and January 2018 in the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Nephrology Outpatient Clinic.

The study protocol was approved by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 83088843-604.01.01-379993, date: 11.10.2017). This study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013. The form of consent was not obtained because the data were analyzed anonymously. The ethics committee waived the requirement for informed consent.

Inclusion Criteria

- Age ≥18 years,

- Having been diagnosed with RAS using any of the defined imaging methods,

Exclusion Criteria

- Age <18 years,

- Incomplete or inaccessible diagnosis and follow-up information,

- Previous kidney transplant before admission to the clinic,

- RAS involves only a segmental renal artery branch,

- Diagnosed with RAS before admission.

Demographic data of the patients (date of birth, gender), date of diagnosis, initial physical examination findings (blood pressure measured at the time of admission, fundus examination), comorbid diseases, imaging findings, interventional and medical treatments (antihypertensive and immunosuppressive drugs), need for kidney replacement therapy (hemodialysis and renal transplantation), and time to hemodialysis/transplantation were recorded. Although the patients were excluded from our hospital follow-up, the causes and dates of death were recorded using the national patient follow-up system and included in the analysis. The cause of death and date of death of the patients who came out of the hospital follow-up were obtained and recorded using the national patient follow-up system.

Comorbidities

They were classified as HT, hyperlipidemia (HL), diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), and malignancies. Inflammatory comorbidities were grouped as vasculitides [Takayasu's arteritis, Behçet's syndrome, other vasculitides (defined as suspicious or undifferentiated)] and other inflammatory diseases (rheumatoid arthritis, ankylosing spondylitis, familial Mediterranean fever, gout, mixed connective tissue disease). All patients were diagnosed with Takayasu's arteritis by rheumatologists using the 1990 American College of Rheumatology criteria (9).

Resistant HT is defined as above-goal elevated blood pressure in patients despite concurrent use of three antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system, and a diuretic. Antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. It also includes patients whose blood pressure achieves target values on ≥4 antihypertensive agents (10).

Laboratory

The laboratory results included urea, creatinine, sodium, potassium, uric acid, calcium phosphate, calcium × phosphate, parathormone, leukocyte, neutrophil, hemoglobin, platelet, C-reactive protein, and 1st-hour sedimentation value. The 24-hourly urine findings included glomerular filtration rate (GFR), proteinuria, and albuminuria. The estimated GFR was calculated using the formulas of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) (11,12) in patients who could not collect 24-h urine.

Imaging

Doppler ultrasonography (USG) findings were recorded using the following parameters:

If measured, the renal/aortic ratio separately for the right and left renal arteries: It was determined by proportioning the renal artery systolic flow velocity and the aortic systolic flow velocity. When the ratio between renal artery peak systolic velocity (PSV) and aortic PSV is >3.5, it indicates a 60% stenosis (13,14). Patients whose renal arteries could not be visualized with Doppler USG were categorized as unsuccessful.

In addition, computed tomographic (CT) angiography or magnetic resonance (MR) angiography results, if available, and conventional angiography results, if performed, were recorded.

Interventional procedures applied to the patients during the follow-up period were grouped under three headings: stent application, balloon angioplasty, and bypass.

Statistical Analysis

The mean, standard deviation, and minimum and maximum values were used in the data analysis to generate statistics for the continuous structure. The frequency and percentage values were used to define categorical variables. The Kaplan-Meier method was used to estimate the overall survival curves. The log-rank test was used to determine differences according to risk factors. The statistical significance of the data was taken as $p<0.05$. SPSS 18.0 (SPSS Inc, USA) was used in the study.

Results

Demographic and Clinical Characteristics and Follow-Up

Out of the 17427 (8800M/8627F) patients registered at the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Clinic of Nephrology Outpatient between January 1996 and January 2018, a total of 134 (70 M/64 F) patients aged over 18 years with RAS were included in the study.

Twenty-five (12 M/13 F) patients (18.6%) were excluded from the study because of the limited follow-up duration of one visit and lack of data. The files of the remaining 109 patients (58 M/51 F) were scanned retrospectively using a standardized study form (Figure 1).

The demographic and clinical characteristics of the patients are shown in Table 1. Patients were usually middle-aged (median: 55; range: 18 to 87 years), and male gender (53%) was more prominent.

The most common comorbidities accompanying RAS were HT (96.3%), followed by CAD (23.9%), DM (22.9%), CVA (8.3%), HL (4.6%), COPD (3.7%), CHF (3.6%), and malignancies (2.8%).

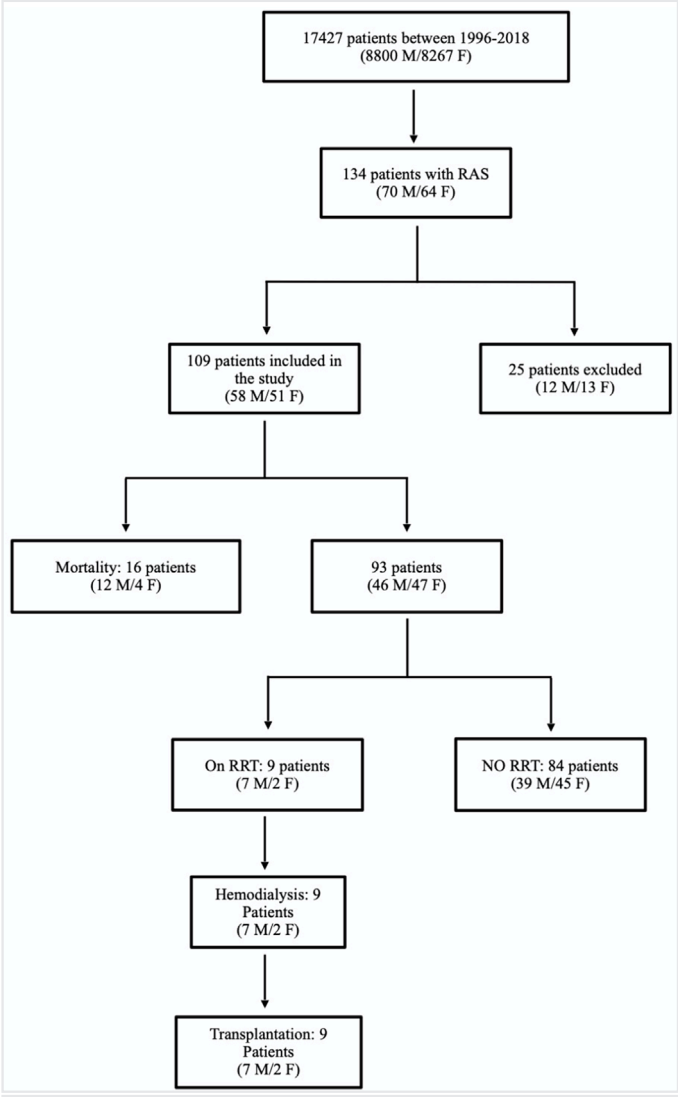

Figure 1. Patients' flow chart
M: Male, F: Female, RAS: Renal artery stenosis

While 60 (55%) patients were diagnosed with RAS due to atherosclerosis, 18 (16.6%) patients had a diagnosis of FMD.

Thirty-one (28.4%) patients with inflammatory disease were identified. It was observed that there were 23 patients (21.1%) in total with vasculitis. Fourteen patients (12.8%) were diagnosed with Takayasu arteritis. There were 2 patients with Behçet's disease (1.8%) and 7 patients (6.4%) with undifferentiated vasculitis. There were 8 patients under the title of other inflammatory disorders (6.4%). Of this patient group, 2 had rheumatoid arthritis (1.8%), 2 had ankylosing spondylitis (1.8%), 1 had familial Mediterranean fever (0.9%), 2 had crystal arthropathy (1.8%), and 1 had mixed connective tissue disease (0.9%).

The mean age of the patients diagnosed with Takayasu's arteritis was 29 (median: 27, range: 18-55).

Initial Laboratory Findings

On-admission laboratory data of the patients are shown in Table 2.

The mean leukocyte count was 7976.3±2463.7/mm^3, platelet count 261385.6±80652.4/mm^3, hemoglobin 13.2±1.9 g/dL, serum urea 45.9±32.1 mg/dL, and creatinine was 1.5±1.1 mg/dL.

Table 1. Demographic and clinical characteristics of all patients

Characteristics	All patients (n=109)
Gender, n (%)	
Female	51 (47%)
Male	58 (53%)
Age, years	49±17
Female	50±17
Male	51±17
Comorbidities	
Hypertension	105 (96.3)
CAD	26 (23.9)
DM	25 (22.9)
CVA	9 (8.3)
Hyperlipidemia	5 (4.6)
CHF	4 (3.7)
COPD	4 (3.7)
Malignancy	3 (2.8)
Inflammatory comorbidities	31 (28.4)
- Vasculitis	23 (21.1)
Takayasu	14 (12.8)
Behcet's disease	2 (1.8)
Vasculitis, other	7 (6.4)
- Other inflammatory disorders	8 (7.3)
Follow-up duration (years)	4.74±3.8
Mortality	16 (14.6)
Overall survival (years)	6±3.4

CAD: Coronary artery disease, DM: Diabetes mellitus, CVA: Cerebrovascular accident, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease.
Data are expressed as mean ± standard deviation for quantitative parameters and n (%) for nominal parameters

Table 2. Laboratory findings of all patients

Parameters	All patients (n=109)
Urea (mg/dL)	45.9±32.1
Creatinine (mg/dL)	1.5±1.1
Na (mEq/L)	140±3.2
K (mEq/L)	4.5±0.6
Uric acid (mg/dL)	6.1±1.9
Ca (mg/dL)	9.4±0.5
P (mg/dL)	3.6±0.7
CaxP (mg^2/dL^2)	33.5±6.5
Parathormone (pg/mL)	91.9±86.4
WBC (/mm^3)	7976.3±2463.7
Neutrophil (/mm^3)	5109.2±2042
Hemoglobin (gr/dL)	13.2±1.9
Thrombocyte (/mm^3)	261385.6±80652.4
CRP (mg/L)	13.1±35.2
Sedimentation (mm/h)	26.6±23.7
GFR in 24-hours urine (mL/min/1.73 m^2)	70.4±40.2
Protein in 24-hours urine (mg/day)	574.1±1026.1
Albumin in 24-h urine (mg/day)	288.2±813.7
CKD-EPI eGFR (mL/min/1.73 m^2)	67.7±33.6
MDRD eGFR (mL/min/1.73 m^2)	65.7±34.4

Data are expressed as mean ± standard deviation. Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphate, CAxP: Calcium x phosphate, WBC: White blood cell, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, MDRD: Modification of Diet in Renal Disease

In the 24-h urine measurements, the mean GFR was 70.4±40.2 mL/min/1.73 m^2. The mean GFR was 67.7±33.6 mL/min/1.73 m^2 according to the CKD-EPI formula. It was calculated as 65.7±34.4 mL/min/1.73 m^2 using the MDRD formula. Most of the patients had a GFR value of 30 and had stage I, II, and III chronic kidney disease.

Initial Examination Findings

The mean arterial blood pressure was 145±26 mmHg at the first visit, and the mean diastolic blood pressure was 87±18 mmHg. Fundus examination results were available for 76 patients (69.7%). Grade 1-2 hypertensive retinopathy was found in 33 (30.2%) patients, grade 3-4 hypertensive retinopathy in 2 (1.8%), and diabetic retinopathy in 6 (5.5%). The remaining 35 pa-tients (32.1%) had normal fundus results.

Imaging Results

A total of 109 patients were diagnosed with RAS using at least one imaging method. Among these methods, the most commonly used were Doppler USG (n=92) (84.4%) and conventional angiography (n=70) (64.2%). These were followed by MR angiography (n=29) (26.6%) and CT angiography (n=23) (21.1%). Fourteen patients were diagnosed using MR angiography (n=4), CT angiography (n=5), or conventional angiography (n=5), when Doppler USG was unsuccessful. All four imaging modalities were used in two patients. The total number of patients with bilateral RAS detected by any imaging method was 40 (36.7%).

The rate of detecting stenosis in the right renal artery in Doppler USG was more prominent [right renal artery in 43 (39.4%) patients, left renal artery in 33 (30.3%) patients]. Doppler USG findings of the patients are shown in Table 3.

Interventional Procedures

We found that 33 (30.3%) renal stenting was the most frequently applied interventional procedure. In 11 patients, a stent was inserted into the right renal artery (10.1%) and in 15 (13.8%) patients into the left renal artery. Seven (6.4%) patients underwent bilateral stenting. Eight (7.3%) patients underwent balloon angioplasty in the right renal artery. Eleven patients (10.1%) underwent balloon angioplasty in the left renal artery; 4 (3.7%) patients underwent bilateral balloon angioplasty. Five patients (4.6%) underwent a bypass.

Interventional treatment was performed in 5 of 14 patients with Takayasu's arteritis: Balloon angioplasty was performed in 3 patients, bypass in 1 patient after balloon angioplasty, and a unilateral stent was performed in 1 patient.

Renal Replacement Therapy

Hemodialysis was initiated in 9 patients (8.3%). The mean time between admission and hemodialysis was 37.7±33.7 months in the total population. Transplantation was performed in 4 patients (3.7%). The mean time to transplantation was 96.2±62.5 months.

Following Status

The mean follow-up period was 4.74±3.8 years. Among the survivors, 40 (36.7%) patients used alpha receptor blockers, 36 (33%) angiotensin-converting enzyme inhibitors (ACEI), 17 (15.6%) diuretics, 17 (15.6%) calcium channel blockers, and 5 (4.6%) nitrite-based antihypertensives. The number of patients who met the definition of resistant HT in the survivor group was 12 (11%) in total. Six of the resistant HT patients were controlled after interventional therapy, two after both interventional therapy and immunosuppressive therapy, and two only after immunosuppressive therapy (Table 4).

All patients with Takayasu's arteritis received immunosuppressive therapy, 1 patient underwent hemodialysis and then renal transplantation, and no death was observed in any patient.

Table 3. Doppler USG findings of the patients

Parameters	n=76 (%)
Renal/aortic ratio <3.5, right, n (%)	57 (52.3)
Renal/aortic ratio ≥3.5, right, n (%)	32 (29.3)
Renal/aortic ratio <3.5, left, n (%)	51 (46.7)
Renal/aortic ratio ≥3.5, left, n (%)	39 (35.7)
Undetectable renal artery, right, n (%)	3 (2.8)
Undetectable renal artery, left, n (%)	2 (1.8)
Size of kidney, (mm)	103.6±17.6
Size of kidney, (mm)	100.5±19.7

Data are expressed as mean ± standard deviation for quantitative parameters and n (%) for nominal parameters. USG: Ultrasonography

Table 4. Patients with resistant hypertension	
Resistant hypertension, n (%)	12 (11)
Controlled resistant hypertension after interventional therapy	6 (5.5)
Resistant hypertension with inflammatory comorbidities	5 (4.6)
Resistant hypertension with inflammatory comorbidities treated with interventional therapy and immunosuppressive	3 (2.8)
Resistant hypertension with inflammatory comorbidities treated with immunosuppressive agents	2 (1.8)
Controlled resistant hypertension with inflammatory comorbidities treated with interventional therapy and/or immunosuppressive therapy	4 (3.7)

Among the survivors, 5 patients (4.6%) had ischemic CVA, 1 patient (0.9%) had hemorrhagic CVA, and 5 patients (4.6%) had myocardial infarction and required coronary arterial intervention.

Mortality

In total, 16 patients (13.5%) died with a mean of 6±3.4 years after admission. Six deaths were due to myocardial infarction, 4 due to CVA, and two due to sepsis in the males. Two of the females died due to a CVA and 2 due to myocardial infarction.

The 5-year survival estimate was 82% (M: 78%, F: 87%), whereas the 15-year survival rate was 68% (M: 59%, F: 87%). In the first 7.5 years following admission, mortality was similar between males and females, after which it increased significantly in males. Figure 2 shows the Kaplan-Meier survival curves a and b. All patients were shown in Figure 2a., comparison of gender subgroups was shown in Figure 2b.

We found that advanced age, low GFR at the time of diagnosis, and small kidneys are significant, poor prognostic factors ($p<0.01$, for all).

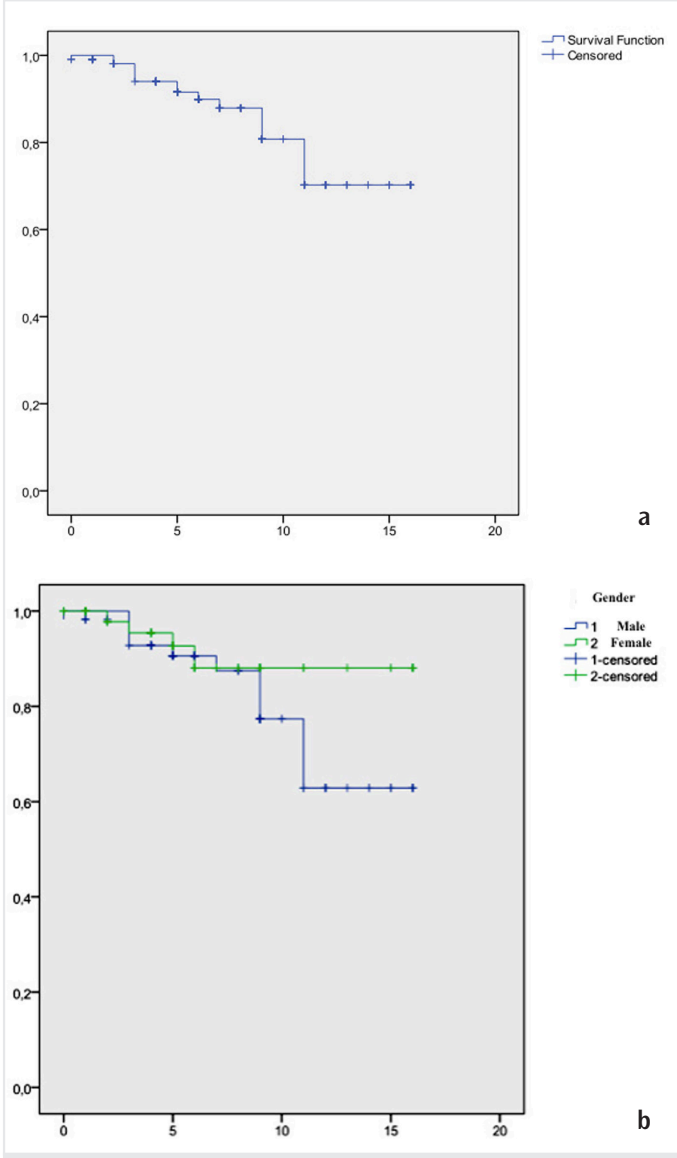

Figure 2. (a) Kaplan-Meier curves: All patients, (b) Kaplan-Meier curves: Comparison of gender subgroups

Discussion

RAS is a clinical picture that is evaluated as a renovascular disease, but many diseases are involved in its etiology. Although there are many studies examining the causes in the etiology, it should be noted that there is limited information about the follow-up of patients diagnosed with RAS, the treatments applied during the follow-up period, and the mortality of the patients. In our study, 60 (55%) patients had atherosclerotic RAS, whereas 23 (21.1%) patients were diagnosed with vasculitis. In total, 16 patients (13.5%) died with a mean of 6±3.4 years after admission. In the first 7.5 years following admission, mortality was similar between gender subgroups, after which it increased significantly in males. It was found that advanced age, low GFR at diagnosis, and small kidneys are significant and poor prognostic factors.

In our study, the mean age of patients was 49±17 years old, male gender (53%) was more prominent. The most common accompanying comorbidity was HT, whereas the most common cause of RAS was atherosclerosis. The J-RAS study from Japan (15) was a prospective, multi-center study with 168 patients to assess the clinical outcome of RAS for up to 1-year-old patients with atherosclerotic RAS. The mean patient age was 72.7±8.5 years old, 82.6% of patients (123/149), and the most common accompanying clinical characteristic was HT (81.2%). Looking at the literature data, atherosclerosis is the primary cause and accounts for >90% of all cases with RAS, and FMD is the second most common cause (13,14,16). In our study, the second most common cause was vasculitides in 23 patients (21.1%) and, in parallel with the literature (13,14,17), Takayasu's arteritis constitutes an essential part of it.

Among the methods that can be used for RAS imaging, treatment, or diagnosis, plasma renin activity, the captopril challenge test, bilateral renal vein renin measurement, captopril renography, color Doppler USG, CT, or MR angiography could be used. Conventional angiography has emerged as the gold standard method (18). In our study, the most frequently used imaging method was Doppler USG. While conventional angiography followed Doppler USG, other non-invasive imaging methods were less preferred. In the J-RAS study (15), the most frequently used method was 100% conventional angiography. In the literature,

compared with the gold standard method, the sensitivities of Doppler USG, CT angiography, and MR angiography were 84 to 92%, 59 to 96%, and 90 to 100%; while the specificities were 64 to 99%, 82 to 99%, and 76 to 94%, respectively (19). In a study conducted in 2017, MR angiography using contrast material and non-contrast MR angiography were compared with conventional angiography as a reference. Non-contrast MR angiography is better, especially in application and motion artefacts, and it is safer in the patient group with a low filtration rate (18). In addition, false-positive MR angiography and false high measurement of the stenosis grade are also highlighted. In our study and the major studies from the literature (15,19,20), MR and CT angiography are in the back row.

Interventional therapy is one of the most important discussion topics in the current literature. Particularly with resistant HT (under a minimum of 3 antihypertensive drugs used at the maximum dose), progressive renal failure [progressive increase in serum creatinine, progressive decrease in GFR under ACEI or angiotensin receptor blockade (ARB)], or acute coronary syndrome independent of pulmonary edema, "revascularization" is recommended in patients with refractory CHF and bilateral RAS (21-23). In our study, a total of 33 patients underwent stenting (30.3%), 23 (21.1%) underwent balloon angioplasty, and 5 (4.6%) underwent a bypass. In the J-RAS study (15), 126 patients (84.6%) underwent interventional treatment for a single lesion, and 23 patients (15.4%) were treated for bilateral RAS. While the positive effect of renal arterial stenting on renal functions was shown to be inappropriate for patient selection in this study, in two other major studies, CORAL (20) and ASTRAL (21), no clinical benefit was demonstrated.

Permanent renal replacement therapy was 0.6% in the J-RAS (14), 0.7% in CORAL (20), and percentage in the ASTRAL (21) study, whereas it was 8.3% (9/109) of all patient groups in our study. Transplantation was performed in 4 patients (3.7%). The mean time to transplantation was 96.2±62.5 months. In our study, among the survivors, the most commonly used antihypertensive therapies were alpha-receptor blockers [40 patients (36.7%)] and ACEI [36 patients (33%)]. Calcium channel blockers and ARB were the most frequently used agents in other major studies related to RAS (15,20,21,24). Another important feature of our study was the resistant HT-related results. Six resistant HT patients were controlled after interventional therapy, two after both interventional and immunosuppressive therapy, and two only after immunosuppressive therapy. This result has not been previously defined in terms of inflammatory pathologies, renal artery involvement, and antihypertensive effect. While the most important causes of mortality in our study were cardiovascular and cerebrovascular events, in these studies (15,20,21,24), they were renal and cardiovascular events.

The CORAL study (20) provided prognostic information on RAS and its course. Nine hundred forty-seven patients were followed up for a mean of 43 months, with cardiovascular or renal events as the primary endpoint. A low baseline urinary albumin-creatinine ratio is a good prognostic feature, especially in the follow-up of HT and treatment response after stenting. Basal blood pressure and severity were not associated with post-stent response. In our study, advanced age, low GFR at the time of diagnosis, and small kidneys were found to be significant and poor prognostic factors.

In a study by Chen et al. (17), it was revealed that patients with Takayasu's arteritis with renal artery involvement were younger than those without renal involvement. In a study of 246 patients with renal artery involvement due to Takayasu's arthritis (25), the primary endpoints were chronic renal failure, refractory HT (blood pressure above 140/90 mmHg under 2 different maximum doses of antihypertensive used), and death. Of the 246 Takayasu patients included in that study, 62 had renal artery involvement, and 11 had undergone renal artery intervention; it was observed that these patients were aged 35 or below and predominantly male. In the same study, bilateral arterial involvement was riskier in terms of cardiovascular complications, such as CHF, than unilateral involvement (25). In a Chinese cohort (26), 567 patients with Takayasu were included, and RAS was confirmed in 172/567 (30.3%) patients. Revascularization was performed in 46 of 172 (26.7%) patients. Although this study showed that revascularization is beneficial in patients with Takayasu-associated RAS and uncontrolled or worsening renal function, the prognosis appears to be poorer for patients with renal insufficiency at presentation, bilateral artery involvement, and severe stenosis (26). In our study, interventional treatment was performed in 5 of 14 patients; all patients received immunosuppressive therapy. There was no mortal course in patients with Takayasu.

Study Limitations

There are several limitations to our study. First, our patient population was limited compared with other studies. Data collection was challenging because of the difficulty of accessing past records. In particular, it was impossible to access the imaging methods' data completely retrospectively. Another important feature was that it contained only single-center data.

Conclusion

The most common cause of RAS in our study was atherosclerosis. A total of 23 (21.1%) patients were diagnosed with vasculitis. Mortality was 13.5%, with 16 patients with a mean of 6±3.4 years after admission. Advanced age, low GFR at the time of diagnosis, and small kidneys are significant prognostic factors for mortality. In future study plans, RAS could be screened for with appropriate imaging methods to be selected in patients followed up with HT, and inflammatory etiologies in these cases can be investigated. In addition, a more systematic approach model can be developed in terms of applying "maximal medical treatment", which is our approach that we can currently describe as incomplete in cases of RAS with an early atherosclerotic process.

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Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 83088843-604.01.01-379993, date: 11.10.2017).

Informed Consent: Retrospective study.

Authorship Contributions: Concept - İ.S., S.T., N.S.; Design - İ.S., S.T., N.S.; Data Collection or Processing - İ.S.; Analysis or Interpretation - İ.S.; Literature Search - İ.S.; Writing - İ.S.

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Ketamine as a Supplementary Analgosedative in COVID-19 Patients on Mechanical Ventilation: A Single-Center Observational Study

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ABSTRACT

Introduction: Sedation of coronavirus disease-2019 (COVID-19) acute respiratory distress syndrome (ARDS) patients on mechanical ventilation (MV) has lately become a concern. The purpose of this study was to report the sedation strategy used in COVID-19 ARDS patients who were mechanically ventilated at a single institution.

Methods: In this study, we performed a retrospective review of the sedation strategy in mechanically ventilated COVID-19 ARDS patients in our 37-bed intensive care unit. All mechanically ventilated COVID-19 ARDS patients who were sedated and hospitalized between March 2020 and September 2021 were included in this study. Patients reported using sedatives and analgesics as well as suffering from delirium.

Results: This study involved 100 patients with COVID-19 ARDS who were both eligible to participate. In all patients, a triple sedation regimen was required. Ketamine attitudes reduced patients' opioid and benzodiazepine needs ($p<0.05$). Furthermore, the following ketamine administration, the need for vasopressors was significantly reduced ($p<0.05$). There were no drug interactions documented.

Conclusion: We showed that extremely high sedative doses were required in this group of patients with COVID-19 ARDS who needed MV. However, our findings suggest that when ketamine infusion was introduced, benzodiazepine, opiate, and vasopressor doses were reduced without adverse pharmacological effects. Further research will be required to determine appropriate dosing regimens.

Keywords: Ketamine, sedation, ARDS, COVID-19, mechanical ventilation

Introduction

About 5% of coronavirus disease-2019 (COVID-19) infections progress to acute respiratory distress syndrome (ARDS), which frequently necessitates intubation and invasive mechanical ventilation (MV) (1). Unusually high doses of sedative and analgesic drugs are often used in patients with COVID-19 ARDS to alleviate anxiety, reduce excessive oxygen use, and enhance treatment (2). Although routinely used sedatives and analgesics are beneficial for many patients, they are associated with several side effects, including opioid-induced constipation and hemodynamic instability associated with propofol and dexmetatomidine (3,4).

To the best of our knowledge, only a few trials have been undertaken to target sedation in COVID-19 ARDS patients. Wongtangman et al. (2) reported that ARDS patients with COVID had a much higher need for analgosedation based on a sedative burden index. Furthermore, Kapp et al. (5) showed a link between deep sedation and death in mechanically ventilated COVID-ARDS patients.

Ketamine, a non-competitive NMDA receptor antagonist, induces sleepiness, amnesia, and analgesia while preserving pulmonary compliance and lowering airway resistance (6-8). Thus, ketamine provides an additional sedative option in COVID-19-induced ARDS patients. We anticipated in this study that continuous ketamine infusion would minimize sedative and analgesic consumption and the prevalence of delirium in COVID-19-induced ARDS patients.

Methods

Study Design and Setting

This is a single-center, retrospective observational study conducted in a 37-bed multidisciplinary academic intensive care unit (ICU) that serves between 900 and 950 inpatients each year. The study protocol was evaluated and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2390, date: 29.05.2020). Our unit has a physician-driven

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institutional strategy, aiming for a sedation state of 2 to +1 on the Richmond Agitation Sedation Scale (9).

We used a first-line sedation approach comprising continuous infusion of an opioid (fentanyl, starting dosage 0.7 mcg/kg/h), a benzodiazepine (midazolam, starting dose 0.03 mg/kg/h), or a combination of both, depending on the clinical features of the patients and the projected illness course. When high opioid and benzodiazepine dosages (e.g., fentanyl 3 mcg/kg/h, midazolam 0.1 mg/kg/h) failed to provide appropriate analgosedation, ketamine was delivered as a continuous infusion at a dose of 10 mg/kg/min. Daily, bedside nurses employed the confusion assessment technique for ICU (CAM-ICU) to track the occurrence of delirium (10).

Study Population

We included all patients who had positive severe acute respiratory syndrome-coronavirus-2 polymerase chain reaction results and required invasive MV for ARDS between March 2020 and September 2021. Patients who were pregnant or breastfeeding, had psychosis as defined by the DSM-IV, were given a concomitant neuromuscular blocker, regularly used opiates, or were administered ketamine on the first day of MV were excluded from the study. Patients were treated for COVID-19 as per local guidelines.

Data Collection

A retrospective query of the institutional electronic system and medical documents was conducted to collect data for this study. The following variables were gathered: 1) demographic information such as age, gender, and weight; 2) clinical baseline features such as comorbidities, Acute Physiologic and Chronic Health Evaluation II Score, and Sequential Organ Failure Assessment score; 3) ICU stay metrics such as MV duration, ICU length of stay, and 28-day mortality; 4) nature and dosages of concurrent continuous infusions of analgesics, sedatives, and vasopressor medications. 5) Any occurrence of withdrawal syndrome or delirium that occurred throughout the ICU stay (delirium in the ICU was recorded through the daily routine assessment of the CAM-ICU evaluation reports), 6) any adverse event (AE) that occurred during ketamine infusion.

Outcome Measures

In our study, ketamine was considered useful as an adjuvant for troublesome sedation if no changes in the doses of other analgesics and sedatives were necessary within 72 h following ketamine infusion. Finally, the safety profile of ketamine was assessed as a secondary goal, with a focus on hypertension, tachycardia, laryngospasm, hypersalivation, emesis, nystagmus, anaphylaxis, and erythema.

Statistical Analysis

There was no statistical power analysis performed before this retrospective investigation. The current investigation is looking back. The data was analyzed using the Statistical Package for the Social Sciences for Windows version 26.0 software package (SPSS, Chicago, IL). The normality of the distribution was determined using the Shapiro-Wilk test. The quantitative data displayed are the mean ± standard deviation and median (interquartile range). The Wilcoxon signed-rank test was used to compare hemodynamic parameters, sedative and analgesic use, and vasopressor usage before and after ketamine infusion. $P<0.05$ was found to be statistically significant.

Results

We identified 125 (of 830 patients who admitted to the unit and mechanically ventilated) mechanically ventilated COVID-19 ARDS patients who satisfied the inclusion criteria during the assessment period. Twenty patients were excluded; 13 of them were administered neuromuscular blockers, 5 patients received ketamine infusions for less than 24 h, and 2 patients had incomplete documentation. The 100 participants in the research were largely men with an average age of 67.1±14.4 years (Table 1).

Adjunctive analgesics and sedatives were reduced without the use of alternative sedatives. After ketamine administration, fentanyl use was significantly reduced at 24 h [4.25±1.56 vs. 2.71±1.56 µg/kg/hour, ($p<0.001$)], 48 h [4.25±1.56 vs. 1.50±1.62 µg/kg/hour, ($p<0.001$)] and 72 h [4.25±1.56 vs. 0.72±1.11 µg/kg/hour, ($p<0.001$)] (Table 2). Midazolam dose was similarly reduced at 24 h [0.21±0.71 vs. 0.14±0.59 mg/kg/hour, ($p=0.007$)], 48 h [0.21±0.71 vs. 0.10±0.47 mg/kg/hour, ($p<0.001$)], 72 h

Table 1. Baseline characteristics and treatment outcomes of patients[a,b]

Variable	All patients (n=100)
Age, years	67.1±14.4
Male, n (%)	70 (70%)
Body mass index, n (%)	
Underweight	2 (2%)
Normal	30 (30%)
Overweight	35 (35%)
Obese	29 (29 %)
Morbid obese	4 (4%)
Comorbidities, n (%)	
Hypertension	45 (45%)
Diabetes	14 (14%)
CHF	30 (30%)
CKD	20 (20%)
APACHE II score	18.3±7.6
SOFA score at ICU admission	7.2±2.9
P/F at ICU admission	170±35.9
Create CL. (mL/min) at ICU admission	79.6±35.9
Vasopressor used, n (%)	34 (34%)
Mechanical ventilation length median (IQR), days	11 (6-18)
ICU length of stay (days)	18.6±12.8
Delirium status, n (%)	15 (12%)
28-day mortality, n (%)	40 (40%)

[a]Data are presented as mean ± standard deviation unless otherwise indicated, [b]N = number of patients on continuous infusion, Body mass index is classified as <18.5 kg/m^2 underweight, 18.5-24.9 kg/m^2 normal weight, 25-29.9 kg/m^2 overweight, 30-39.9 kg/m^2 obese, and >40 kg/m^2 morbidly obese; CHF: Congestive heart failure, CKD: Chronic kidney diseases, PaO_2/FIO_2: Partial pressure of oxygen/fraction of inspired oxygen, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Orgailure Assessment, ICU: Intensive care unit, Create CL: Creatinine clearance, IQR: Interquartile range

[0.21±0.71 vs. 0.09±0.58 mg/kg/hour, (p<0.001)] compared to baseline before ketamine (Table 2).

Table 2 shows the patient's hemodynamic parameters. Heart rate and blood pressure did not considerably change during the experiment. Our study included 65 patients who required vasopressor treatment, 19 who continued to require vasopressors, and 46 who had vasopressors discontinued after 72 h. The norepinephrine dosage was substantially reduced after 24 hours of ketamine therapy [0.12±0.18 vs. 0.09±0.14 µg/kg/min, (p<0.001)], 48 h [0.12±0.18 vs. 0.06±0.17 µg/kg/min, (p<0.001)], 72 h [0.12±0.18 vs. 0.06±0.2 µg/kg/min, (p<0.001)] (Table 3).

Throughout the study, all patients received ketamine infusions at a rate of 10 µg/kg/min. In our patient cohort, we examined an AE that might have been caused by ketamine. There were no documented side effects, and no patients suffered hypersalivation that required atropine therapy.

Delirium in the ICU is associated with diagnostic issues since the patient was unable to engage in the CAM-ICU evaluation. During their ICU stay, 15 (12%) individuals tested positive for delirium.

Discussion

In this trial, patients received significantly lower benzodiazepine, opiate, and vasopressor doses when ketamine was used as part of a multimodal sedation regimen, with no adverse effects. To the best of our knowledge, this is the first trial to demonstrate the benefits of low-dose ketamine infusion in mechanically ventilated COVID-19 ARDS patients.

It has been discovered that obtaining and maintaining enough analgesia before sedation reduces the duration of mechanical breathing, which is generally performed with the use of opioids. In our group of patients, ketamine exhibited an opioid-sparing effect. Our findings are consistent with previous research on low-dose ketamine (11-14). Ketamine is an agonist of the µ, δ, and κ-opioid receptors and an antagonist of the NMDA receptor, which might explain the reduction in opioid consumption (15,16).

According to our findings, ketamine infusion in mechanically ventilated patients reduced not only opioid consumption but also benzodiazepine use without compromising proper sedation. Although no studies have been undertaken to evaluate its effectiveness in describing extreme sedation, ketamine's benzodiazepine-sparing effects are consistent with earlier work addressing moderate sedation techniques (17,18). This is crucial because long-term benzodiazepine infusions have been associated with delirium, long-term cognitive damage, and the need for additional MV time (19,20).

In addition to its positive respiratory dynamics profile, ketamine may have a chronotropic effect on the cardiovascular system via the sympathetic nervous system (15). We noticed a significant reduction in the demand for vasopressors in our patient group. This finding is consistent with a prior study on the use of low-dose ketamine in mechanically ventilated adult patients for moderate sedation (12).

Delirium is crucial in critically ill patients because it is related to diagnostic issues and therapeutic dilemmas, and each additional day

Table 2. Analgesic and sedative dosage needs for continuous infusion before and after ketamine administration[a,b]

Drug	Before Ketamine initiation	24 h after Ketamine initiation	48 h after Ketamine initiation	72 h after Ketamine initiation
Ketamine				
N	0	100	100	100
Dose (µg/kg/min)		10	10	10
Fentanyl				
N	100	100	100	100
Dose (µg/kg/h)	4.25±1.56	2.71±1.56*	1.50±1.62*	0.72±1.11*
Midazolam				
N	100	100	100	100
Dose (mg/kg/h)	0.21±0.71	0.14±0.59*	0.10±0.47*	0.09±0.58*

Wilcoxon signed-rank test was used to test the parameters. [a]Data are presented as mean ± standard deviation unless otherwise indicated, [b]N = number of patients on continuous infusion, *p<0.05 as a comparison of dosing at each specified time point with the original dosing at the time of ketamine initiation

Table 3. Comparison of hemodynamic parameters and vasopressor medications during the analyzed time frame[a,b]

Hemodynamic parameters and medications	Pre-ketamin	24 h after Ketamine initiation	48 h after Ketamine initiation	72 h after Ketamine initiation
SBP, mm Hg	114±18.64	116.00±21.63	106.48±41.86	90.85±58.05
DBP, mm Hg	58.15±11.4	59.61±13.58	54.57±21.06	53.56±24.44
HR, beats per minute	90.76±23.49	87.09±15.43	79±35.53	68±44.03
Noradrenaline				
N	65	30	24	19
Dose (mg/kg/min)	0.12±0.18	0.09±0.14*	0.06±0.17*	0.06±0.2*

HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Wilcoxon signed-rank test was used to test the parameters. [a]Data presented as mean ± standard deviation unless otherwise indicated, [b]N = number of patients on continuous infusion, *p<0.05 as a comprasion of dosing at each specified time point to the original dosing at time of ketamine initiation

of delirium is associated with a 10% increased risk of death (21,22). Dexmetatomidine appears to be producing positive results at the time; nevertheless, it is a more expensive chemical that can induce bradycardia, hypotension, hypertension, nausea, and atrial fibrillation (23,24). Furthermore, studies suggest that ketamine can be used for the treatment of delirium and depression because of its immune-regulatory effects on the peripheral and central nervous systems (25,26). Using the CAM-ICU, 15 patients (15%) tested positive for delirium throughout their ICU stay. This was substantially lower than predicted, given that the frequency of delirium in mechanically ventilated patients admitted to the ICU has been reported to be as high as 24.4% (23,24).

In recent studies, ketamine has been shown to have both proconvulsant and anticonvulsant effects (25). Convulsions were not detected in any of the participants taking ketamine in this trial. Furthermore, ketamine usage has been linked to hypersalivation, which is commonly treated with glycopyrrolate or atropine (26). None of the patients were given medication because of hypersalivation. Some studies highlighted possible adverse effects such as hypertension and tachyarrhythmias, which were not detected in any of the ketamine-treated patients. Lower ketamine doses (10 µg/kg/min) do not appear to produce the psychomimetic side effects observed at higher doses (12).

Study Limitations

The study was conducted at a single location and was retrospective, with no ability to manage treatments to impact analgesic and sedative requirements. However, prospective studies are required to verify these findings and determine the appropriate ketamine dosage in this circumstance.

Conclusion

This study shows that low-dose ketamine has a favorable safety profile, with no significant effects on hemodynamics or agitation. The initiation of ketamine infusion resulted in a significant reduction in the total fentanyl and midazolam requirements, indicating that ketamine as an analgosedative medication could be a viable alternative in mechanically ventilated patients.

Ethics Committee Approval: The study protocol was evaluated and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2390, date: 29.05.2020).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices - S.B., M.H., A.N.S.; Concept - S.B., M.H., A.N.S., V.E, M.T.; Design - S.B., M.H., A.N.S., V.E, M.T.; Data Collection or Processing - S.B., M.H., A.N.S.; Analysis or Interpretation - S.B., M.H., V.E, M.T.; Literature Search - S.B., M.H.; Writing - S.B., M.H., A.N.S., V.E, M.T.

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Can Preoperative Parameters of Inflammation be Used to Predict Acute Kidney Injury in Pediatric Liver Transplant Recipients? A Single-Center Retrospective Study

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ABSTRACT

Introduction: Inflammation is one of the factors involved in the occurrence and progression of acute kidney injury (AKI). We evaluated the relationship between preoperative systemic inflammatory markers and early postoperative AKI development in pediatric liver transplantation (LT) patients.

Methods: Data from 190 pediatric patients were retrospectively analyzed. The preoperative neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIV) levels were calculated. AKI was classified according to the Kidney Disease: Improving Global Outcomes staging. Patients who did not develop AKI in the early postoperative period were classified as group 0, patients with stage 1 AKI were classified as group 1, and patients with stage 2-3 AKI were classified as group 2. The relationship between the inflammatory parameters and AKI was evaluated.

Results: AKI developed in 20% of patients, and 16.31% of these patients had severe AKI. The NLR, SII, and PIV values were significantly higher in patients with severe AKI ($p<0.001$). Preoperative high PIV values were found to be an independent predictor of AKI development.

Conclusion: High preoperative PIV values may be used as a predictive factor for the development of early AKI in patients undergoing pediatric LT.

Keywords: Acute kidney injury, pediatric transplantation, systemic immune inflammation index, pan-immune-inflammation value

Introduction

Acute kidney injury (AKI) is a complication after liver transplantation (LT) that is associated with morbidity and mortality (1,2). It is clear that around 20-47% of paediatric LT patients experience AKI (3). The etiology of AKI is complex and multifactorial. Although the primary cause of AKI is ischemia, mounting evidence suggests that AKI may occur without signs of hypoperfusion and may be linked to immune and inflammatory responses. The pathogenesis of AKI in the early post-LT period is not fully understood. The cause of AKI in pediatric patients is likely to be multifactorial, with patient characteristics, pre-transplant organ function, donor components, intraoperative factors, and postoperative course potentially contributing to AKI (4,5).

Inflammation is a complex biological response required to eliminate microbial pathogens and repair tissue after injury. AKI is associated with intrarenal and systemic inflammation. The Systemic Immune-Inflammation Index (SII) has been linked to diseases accompanied by renal dysfunction (6,7). The neutrophil-to-lymphocyte ratio (NLR), SII, and pan-immune-inflammation value (PIV) are reliable markers of potential inflammation. These values are based on peripheral lymphocyte, neutrophil, and platelet counts. These parameters can be easily calculated from the hemogram without additional cost (8).

Our literature review revealed that no studies have evaluated the relationship between AKI and inflammatory parameters in pediatric patients undergoing LT. Our study aimed to determine whether an early post-LT AKI is associated with preoperative inflammatory parameters in pediatric patients.

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Methods

Study Population

This retrospective cohort study was conducted at the Liver Transplant Institute in İnönü University. The files of 216 patients aged 18 years who underwent elective LT between January 2018 and June 2022 were evaluated. Six patients with end-stage kidney disease, hepatorenal syndrome clinic and diagnosis and creatinine values elevation, 4 patients with retransplantation, 12 patients with massive blood transfusion, and 4 patients with missing information in the electronic data system were excluded. A total of 190 patients were included in our study.

Data Collection

Age, gender, weight, reason for LT, and duration of operation were recorded from the electronic data system of the hospital. Haemogram and biochemical parameters are routinely studied from blood samples taken from patients for preoperative preparation 1 day before the operation. Neutrophil (N) (10^9/L), lymphocyte (L) (10^9/L), platelet (P) (10^9/L), monocyte (M) (10^9/L), and creatinine values were recorded from the data system.

Preoperative inflammation parameters were calculated and recorded using the following formulae (8).

NLR: N/L,

SII: NxP/L,

PIV: Nx Px M/L,

The relationship among NLR, SII, PIV, and AKI development was evaluated.

Intraoperative data: The cold ischemia time (CIT) is the time that elapses between the clamping of the donor vessels and the graft being implanted into the abdominal cavity of the recipient. The warm ischemia time (WIT), on the other hand, is the time that elapses between the graft being removed from the ice and the anastomoses being opened for implantation. At our clinic, the operation time, WIT, and CIT operation time are routinely recorded on anesthesia forms. The relationship between operation time, CIT, WIT, and AKI development was evaluated.

Definition of acute kidney injury: AKI was evaluated in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (Table 1) (9). Postoperative laboratory data were collected, including creatinine values on postoperative days 1, 2, and 7 and urine output data recorded in the intensive care unit (ICU) in the first week.

Table 1. Acute kidney injury Kidney Disease: Improving Global Outcomes staging

Stage	Serum creatinine level	Amount of urine
1	1.5-1.9 times the basal value or >0.3 mg/dL increase	<0.5 mL/kg/h for 6 h
2	2.0-2.9 times increase from baseline	Across two 6-h blocks <0.5 mL/kg/h
3	A 3-fold increase from baseline or serum creatinine >4.0 mg/ initiation of dl or renal replacement therapy	<0.3 mL/kg/day for more than 24 h clock or anuria for ≥12 hours

Patient Grouping

Group 0: Patients not diagnosed with AKI,

Group 1: Patients diagnosed with stage 1 AKI,

Group 2: Patients diagnosed with grade 2 and 3-AKI (Table 1) (9).

In addition, the duration of postoperative ICU and hospital stays were also recorded. Mortality from transplantation to hospital discharge was recorded and considered as in-hospital mortality. The relationship between the development of AKI and in-hospital mortality and length of hospital stay was evaluated.

Anesthesia modality: Anaesthetic drugs used in LT management were standardized in our hospital. After the depth of anesthesia is achieved with pentothal (3-8 mg/kg) and fentanyl (1-2 µg/kg) as opioid agents during induction, rocuronium bromide is administered at a dose of 0.9-1.2 mg/kg. Anesthesia is maintained with an oxygen/air mixture and sevoflurane (1-1.5%).

Although the decision to use vasopressors is made by the anesthetist, norepinephrine is the first choice during surgery. During the postoperative period, patients are transferred to the ICU without extubation. When the general condition and vital signs of the patient stabilize, extubation is performed and the patient is transferred to the ward.

Surgical method: An L-shaped incision is made from above the umbilicus to the groin. After abdominal exploration, the liver is evaluated. Following the transplantation decision, the falciform ligament is released and dissection is performed up to the suprahepatic vena cava. The hepatic veins are isolated and the hepatic artery, portal vein, and common bile duct were prepared. All connections are cut, and the liver is removed. Implantation is completed by placing the graft into the abdomen, followed by vascular and biliary anastomoses. Bleeding is controlled, a drain is placed, and the abdomen is closed.

Compliance with Ethical Standards

Our study was conducted after approval by the Scientific Review Board and Ethics Committee of the İnönü University and in accordance with the principles of the Declaration of Helsinki (approval number: 2022/3909, date: 04.10.2022). Considering the retrospective nature of the study, patient consent was waived.

Statistical Analysis

The SPSS package program (version 23.0, IBM, USA) was used for statistical analysis. Continuous variables are reported as the mean ± standard deviation, whereas categorical variables are presented as numbers and percentages. Whether the data conformed to the normal distribution was evaluated using the Shapiro-Wilk test. One-Way ANOVA or Kruskal-Wallis test was used in the analysis of continuous variables. The Bonferroni test was used for post-hoc correction. The chi-square test was the appropriate statistical tool for analyzing the categorical variables. Pearson's or Spearman's tests were used according to the data type in the correlation analysis of the variables between the groups. We used multiple logistic regression analysis to identify the independent variables that predicted the occurrence of AKI and mortality. For the

univariate analysis, we conducted regression analysis on the variables with p-values <0.10, and we considered the results statistically significant if the p-values were <0.05.

Results

Retrospective analysis was performed on two hundred and sixteen LT patients. Twenty-six patients were excluded from the study because they did not meet the inclusion criteria, resulting in the inclusion of 190 patients. The mean age of our patients was 3.73±3.5 years, with the oldest being 14 years old. Among the patients, 76 were female and 114 were male. The average weight of the patients was 15.3±8.5 kg, with the lowest weight recorded at 3 kg and the highest at 48 kg. Demographic data were similar across all groups (Table 2). When evaluating etiological factors, biliary atresia was the most common (65.2%), followed by primary sclerosing cholangitis. A similar etiology was observed in all groups (p=0.658).

AKI was observed in 38 patients (20%), with severe AKI noted in 31 patients (16.31%) (Table 2). When evaluating the inflammation parameters of patients in the preoperative period, upon assessing NLR a clear and significant difference was observed between the groups (p<0.001; for all). When the patients were evaluated between the groups, similarities were observed between group 0 and group 1, whereas a statistically significant difference was observed between group 1 and group 2 and between group 0 and group 2 (p<0.001) (Table 3).

When the SII and PIV values of the patients were compared, a significant difference was observed for both parameters between the patients who developed AKI in the early period and those who did not develop AKI (p<0.001; for all. In the intergroup evaluation, PIV and SII values were significantly higher in the group of patients with severe AKI than in the group without AKI (p<0.001) (Table 3).

When intraoperative variables were evaluated, the length of the operation time and similarly, the duration of hot ischemia and cold ischemia were statistically significant between the groups. In the group of pediatric patients who developed severe AKI, it was observed that patients who did not develop AKI were significantly longer than those who did not develop AKI (p<0.001) (Table 4).

The mean length of stay in the ICU in the postoperative period was 25.2±29.9 days, and all groups were similar in this regard (p=0.153). When the mean length of hospital stay is evaluated was 48.7±41.1 days, there was a significant difference between the groups (p=0.154). It was observed that this period was significantly longer in group 0 compared to group 2 (Table 3). Mortality was observed in 13.68% of the patients. Mortality was observed in 50% of patients who developed severe AKI. There is a clear statistical difference between the groups (p<0.001) (Table 4).

The analysis of predictors of AKI revealed significant correlations between cold and WIT, operation time, and PIV. These findings were further validated by logistic regression analysis, which demonstrated a clear association between cold and WIT. and PIV were found to be independent predictors of AKI (Table 5).

Table 2. Demographic data of the groups and AKI

	Group 0, (n=152)	Group 1, (n=7)	Group 2, (n=31)	p-value
Age (years)	3.86±3.54	6.14±3.76	2.54±2.2	0.020
Weight (kg)	15.75±8.59	18.57±7.39	12.5±11.35	0.055
Gender (female, %)	64 (84.2)	2 (2.6)	10 (13.2)	0.657
Etiology Biliary atresia (n, %)	102/53.68	4/57.1	18/58.06	0.658

AKI: Acute kidney injury

Table 3. Evaluation of the relationship between preoperative data of the groups and AKI

	Group 0, (n=152)	Group 1, (n=7)	Group 2, (n=31)	p-value
NLR	2.03±2.22	6.77±7.34	4.73±8.73	<0.001$^{\beta,\Phi}$
SII	324.09±359.16	650.57±423.94	1293.68±2522.17	<0.001$^{\beta}$
PIV	259.93±325.40	576.31±452.72	848.47±1222.15	<0.001$^{\beta}$

$^{\alpha}$: p<0.05 in group 0 vs. group 1, $^{\beta}$: p<0.05 in group 0 vs. group 2, $^{\Phi}$: p<0.05 in group 1 vs. group 2, AKI: Acute kidney injury, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value

Table 4. Evaluation of the relationship between intraoperative variables and postoperative AKI data in the groups

	Group 0, (n=152)	Group 1, (n=7)	Group 2, (n=31)	p-value
Operation time (minute)	371.03±67.46	445.71±102.77	495.45±104.72	<0.001$^{\beta}$
CIT (minute)	60.34±20.52	78.42±19.99	94.63±34.75	<0.001$^{\beta}$
WIT (minute)	53.61±13.8	51±15.74	73.27±15.42	<0.001$^{\beta}$
ICU stay (days)	27.57±31.54	23.14±8.97	14.55±12.4	0.153
Hospital stay (days)	53.66±40.76	38±20.76	42.27±38.23	0.066
Mortality, (n, %)	12 (7.89)	0 (0)	14 (45.16)	<0.001$^{\beta,\Phi}$

$^{\alpha}$: p<0.05 in group 0 vs. group 1, $^{\beta}$: p<0.05 in group 0 vs. group 2, $^{\Phi}$: p<0.05 in group 1 vs. group 2, AKI: Acute kidney injury, CIT: Cold ischemia time, WIT: Warm ischemia time, ICU: Intensive care unit

Table 5. Predictors of AKI and mortality

Predictors of AKI						Predictors of mortality				
Parameters	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	r	p-value	OR	95% CI	p-value	r	p-value	OR	95% CI	p-value
CIT	0.384	<0.001	1.045	1.007-1.086	0.028	0.109	0.136			
WIT	0.430	<0.001	1.038	1.014-1.063	0.002	0.149	0.040	1.027	1.003-1.0381	0.023
Operation time	0.480	<0.001	1.017	1.007-1.027		0.155	0.032			
PIV	0.160	0.027	1.002	1.001-1.003	<0.001	0.183	0.012	1.001	1.000–1.002	0.002

AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval, CIT: Cold ischemia time, WIT: Warm ischemia time, PIV: Pan-immune-inflammation value

When analyzed for predictors of mortality, a significant correlation was observed between AKI and CIT, operation time, and PIV. In the logistic regression analysis, it was determined that CIT and PIV value were independent predictors of mortality (Table 5).

Discussion

This is the first study to investigate the relationship between inflammatory parameters and the risk of AKI development in the early postoperative period in pediatric patients undergoing LT. The study revealed a strong link between high NLR, SII, and PIV values before surgery and the risk of developing AKI. Elevated PIV levels before surgery also indicate a higher chance of AKI and in-hospital mortality.

AKI is a common and serious complication of LT, its incidence varies between 5% and 94%, and 11% to 17% of these are severe AKI (10). A study conducted in a paediatric patient group highlighted that AKI was seen in 46.2% of the patients, 20.5% had stage 2 AKI and 3.8% had stage 3 AKI (2). The wide range in these rates is due to the breadth of the parameters used in n to diagnose AKI. In our study, we used KDIGO staging to define early-stage AKI in the pediatric patient group (10). In our study, 20% of the patients developed AKI, with 16.31% experiencing severe AKI. We observed a lower rate of AKI development compared with other studies, whereas the rate of severe AKI development was similar to that reported in the literature. We believe that this difference is attributable to the exclusion of patients with preoperative renal dysfunction in our study.

To date, numerous studies have been conducted on the risk factors for early AKI after LT. These studies have emphasized that various factors, such as hypotension during the preoperative and intraoperative periods, cold and WIT, and immunosuppressive therapy, may contribute to AKI. However, there is still uncertainty regarding the factors that cause AKI, and early recognition and AKI remain difficult to treat. It is crucial to identify the risk factors for AKI (11-13).

There is an opinion that excessive activation of inflammatory mediators is an important mechanism in the development of AKI (14). It has been argued that the disruption of tissue oxygenation initiates the release of proinflammatory cytokines from damaged kidney cells, leading to subsequent renal dysfunction (15). Recently, NLR, SII, and PIV parameters have been used as inflammatory markers (16). Studies have reported that SII can predict postoperative AKI in patients with hepatocellular carcinoma after hepatectomy (17,18). Lu et al. (18) and Biyik et al. (19) emphasized that SII and AKI can be similarly predicted in their studies involving patients with acute pancreatitis (20). Lai et al. (21) emphasized that a high pre-procedural SII level is a significant and independent risk factor for post-procedure AKI in patients undergoing coronary angiography. Similarly, in our study, a significant relationship was observed between preoperative NLR, SII, PIV values, and AKI. It was also observed that high PIV values were independent predictors of AKI development.

It is emphasized that AKI causes death in the early period after LT (22,23). Similarly, in our study, it was observed that deaths due to AKI increased. A development in the ICU revealed an association between SII and mortality (24). Vasculitis-related deaths are similarly associated with SII (25). In our study, unlike the literature, high PIV values were determined to be a predictive factor for mortality in patients undergoing LT.

We believe that incorporating inflammatory hematological markers, in addition to the known risk factors, can be effective in predicting AKI and preventing its occurrence. This approach may contribute to early diagnosis and treatment, thereby helping to prevent or limit AKI and mitigate the potential short-term and long-term consequences, such as chronic kidney disease or end-stage kidney disease, associated with AKI.

Study Limitations

It should be acknowledged that the current study has certain limitations. First, I would like to make clear that this study is single-center and retrospective. It also did not evaluate other potential causes of AKI. Additionally, the effect of postoperative treatments and other intraoperative causes of AKI were excluded from the study because of lack of data. To reinforce these results, more comprehensive, multicenter prospective studies are required.

Conclusion

The PIV value, which can be calculated inexpensively and easily in the preoperative period, is associated with early AKI development in patients undergoing pediatric LT. We believe that PIV values in the preoperative evaluation may serve as a parameter for predicting AKI and in-hospital mortality. Multicenter prospective studies are required to further explore this association.

Ethics Committee Approval: Our study was conducted after approval by the Scientific Review Board and Ethics Committee of the İnönü University and in accordance with the principles of the Declaration of Helsinki (approval number: 2022/3909, date: 04.10.2022).

Informed Consent: Retrospective study.

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