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Relationship Between Low Gait Speed and Geriatric Syndromes: Mortality in a University Geriatric Outpatients in Türkiye

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ABSTRACT

Introduction: Usual gait speed is a fundamental component of sarcopenia and frailty. The current study aimed to assess the correlation between low gait speed (LGS), geriatric syndrome, and mortality.

Methods: Of the 2,020 patients who attended the outpatient department of our university hospital between April 2012 and April 2023, a total of 661 participants with accessible gait speed data who were over 60 years of age were included in the study. LGS was defined as a gait speed of 0.8 m/s or less, whereas probable sarcopenia was assessed based on two different measurements: hand grip strength (HGS) and the chair stand test (CST). The cut-off values for HGS were 27 kg for women and 16 kg for men. For the CST, measurements of >15s or an inability to complete the test were considered indicators of probable sarcopenia.

Results: The median age of the participants was 73 (60-96) years, and 455 (68.8%) were women. Among the participants, 56 (27.3%) died during the study period. Univarite analysis revealed no significant association between LGS and mortality, whereas regression analysis suggested that LGS was statistically associated with age, sex, congestive heart failure, frailty, malnutrition, and probable sarcopenia assessed by CST.

Conclusion: In the presence of LGS, screening for malnutrition, frailty, and probable sarcopenia by CST was feasible.

Keywords: Low gait speed, comorbidities, geriatric syndromes, mortality

Introduction

In Türkiye, as in the rest of the world, the proportion of over-65s in the population is steadily increasing (1), and it is projected that by 2043, the number of over-65s in the population will equal those aged 0-14 years (2). The ability of older adults to maintain functional independence with advancing age is crucial both for themselves and for the community (3-5) and for the independent performance of daily and instrumental life activities (6). Declines in functional capacity in older adults can lead to dependency on others for daily and instrumental life activities, increasing also the risk of falls, frailty, sarcopenia, disability, institutionalization, and mortality (5-11).

Usual gait speed (UGS) is frequently used to assess functional capacity in older adults and is a non-invasive, fast, reliable, and practical measurement approach (7). UGS was determined by recording how long it took the patient to walk a 4 meter (m) course, which was recorded on a chronometer (seconds) (7). The European Working Group on Sarcopenia in Older People (EWGSOP2) suggested that a gait speed threshold of less than 0.8 m/s is necessary (7). When considering the presence of sarcopenia and frailty, UGS is clinically recognized as the sixth vital sign (12) and as a crucial parameter that can support clinical care, improve functional independence, and mitigate unfavorable clinical outcomes (3-10). Although several studies have suggested that a low gait speed may be indicative of all-cause mortality, many do not suggest a precise cut-off value for the prediction of mortality (3,6,7,8-13), while other studies report no association between gait speed and mortality, and more claim the relationship is dependent on sex. In some studies, the relationship is assessed without adjusting for confounding factors, while others are based on insufficient information (14-17).

There is an apparent need for regional studies to determine whether the conflicting data regarding UGS stems from chronic comorbid conditions or race-specific variations in gait speed cut-off values. With this in mind, the present study was designed to assess geriatric outpatients in our community with the goal of identifying potential relationships between low UGS and comorbidities, geriatric syndromes, and all-cause mortality.

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This study was presented as a poster at the 19th EuGMS congress in Helsinki on 22 September 2023.

Methods

The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki, and it was conducted after obtaining approval from the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (approval number: 15, date: 21.07.2023). The study began with a retrospective review of 2,020 patients aged 60 years who were followed up in the geriatric outpatient clinic of a university hospital from April 2012 to April 2023. Patients aged 60 years or older with a general medical condition appropriate for comprehensive geriatric assessment and performance evaluations were included in the study; those below 60 years of age and those with compromised general medical conditions (such as poor overall health, active cancer, acute illnesses, advanced organ failure, severe dementia, significant osteoarthritis, neuropathy, or stroke sequelae) that rendered them unsuitable for geriatric assessment were excluded. The final study population comprised 661 participants whose age, sex, specific diseases, medication count, probable sarcopenia, falls, frailty, malnutrition, urinary incontinence, sleep disorders, and functional status were recorded. Patient mortality data were accessed from the Ministry of Health's information system. The Katz Index of Independence in activities of daily living (ADL) was used to record activities on a scale of 0-6, while instrumental ADL were evaluated on a scale of 0-8 using the Lawton Instrumental Activities of Daily Living Scale (18,19). Height and weight were measured and recorded, and body mass index (BMI) was calculated by dividing weight by height squared (20). A UGS below 0.8 m/s was considered to indicate reduced gait speed (7). Probable sarcopenia was identified using two distinct measurement approaches: the hand grip strength (HGS) test and the chair stand test (CST). The cut-off value for the HGS test was set at 27 kg for women and 16 kg for men (7), and the cut-off value for the CST was set at 15s or an inability to complete the test. The UGS, HGS, and CST tests were conducted according to the recommendations provided in the EWGSOP2 guidelines (7). Falls data was garnered by asking patients about any falls within the previous year. The FRAIL scale was used to assess frailty, with a score of 3 indicating frailty (21). The Mini Nutritional Assessment-Short Form (MNA-SF) was used to screen for malnutrition, with an MNA-SF score of 7 being considered indicative of malnutrition (22). Urinary incontinence was evaluated by asking patients about any incident of involuntary urinary leakage within the last 3 months. The patients were screened for sleep disorders by asking about experiences of excessive sleepiness or insomnia. Polypharmacy was defined as the consumption of four or more medications (23).

Statistical Analysis

This study's data distribution evaluated with a Kolmogorov-Smirnov test. The association between low UGS and related factors was evaluated using the chi-square, Mann-Whitney U test, and independent samples t-tests in univariate analyses. Before conducting the multivariate analysis, the factors demonstrating significant associations in the univariate analysis were evaluated. For variables included in the multiple logistic regression analysis, the backward elimination method was used. The independent variables in the multiple logistic regression analysis were age, sex, congestive heart failure, probable sarcopenia, (low HGS), probable sarcopenia (CST), frailty, and undernutrition. In the multivariate analyses, the multiple logistic regression method was used to examine the associations between the presence of low UGS and related factors, for which odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results

Among the 661 participants, the median age was 73 years (60-96 years), and 455 of the sample (68.8%) were female. Of the total sample, 56 participants (27.3%) did not survive within the first 73 months. In the univariate analysis, age ($p<0.001$), sex ($p<0.001$), height ($p=0.017$), weight ($p<0.001$), BMI ($p=0.009$), hypertension ($p=0.035$), congestive heart failure ($p=0.011$), chronic renal failure ($p=0.010$), osteoporosis ($p<0.001$), dementia ($p<0.001$), depression ($p<0.001$), probable sarcopenia based on both HGS ($p<0.001$), and CST measurements ($p<0.001$), falls ($p<0.001$), frailty ($p<0.001$), malnutrition ($p<0.001$), urinary incontinence ($p<0.001$), polypharmacy ($p<0.001$), number of chronic diseases ($p<0.001$), ADL ($p<0.001$), and instrumental ADL ($p<0.001$), were identified as factors with a significant association with low UGS, while paired analyses revealed no significant association between low UGS and mortality (Table 1).

Prior to performing the regression analysis of the factors demonstrating significant associations in the univariate analysis, multicollinearity was evaluated. For variables included in the multiple logistic regression analysis, the backward elimination method was used. The independent variables in the multiple logistic regression analysis were age, sex, congestive heart failure, probable sarcopenia, (low HGS), probable sarcopenia (abnormal CST), falls, frailty, and undernutrition.

In the multivariate analysis, age ($p<0.001$, OR: 1,122, 95% CI: 1.080-1,166), sex ($p<0.001$, OR: 3,444, 95% CI: 1,188-6,283), congestive heart failure ($p=0.045$, OR: 2,543, 95% CI: 1,022-6,325), probable sarcopenia based on CST measurement ($p<0.001$, OR: 5,724, 95% CI: 3,397-9,644), falls ($p<0.001$, OR: 1,705, 95% CI: 1,067-2,725), frailty ($p<0.001$, OR: 2,848, 95% CI: 1,588-5,108), and malnutrition ($p=0.006$, OR: 20,747, 95% CI: 2,412-178,437) were identified as factors associated with low UGS in the multiple logistic regression analysis, while no statistically significant association was observed between low UGS and probable sarcopenia (based on HGS measurement) (Table 2).

Discussion

In the present study, age, sex, congestive heart failure, malnutrition, frailty, and probable sarcopenia diagnosed by the CST method were identified as factors associated with LGS among geriatric outpatients, whereas no significant association was observed between LGS and all-cause mortality within 73 months.

In a study by Taekema et al. (14), 9% of the 599 respondents who were aged 85 years or older recorded a gait speed below 0.8 m/sec, and after adjusting for the relevant confounders using this cut-off value, no significant association was observed between LGS and mortality.

Table 1. Univariate analysis results showing the relationship between low gait speed and factors

	Low UGS, (n=170) (25.7%)	Normal UGS, (n=491) (74.3%)	Total, (n=661) (100%)	p-value
Age*	78 (62-96)	72 (60-93)	73 (60-96)	**<0.001Θ**
Sex (n, %)				
Male	33 (19.4%)	173 (35.2%)	206 (31.2%)	**<0.001Θ**
Female	137 (80.6%)	318 (64.8%)	455 (68.8%)	
Height (mt)*	1.52 (1.35-1.73)	1.56 (1.40-1.83)	1.55 (1.35-1.83)	**<0.001Θ**
Weight (kg)*	70.7 (38.8-117.6)	73.2 (39.0-128.8)	73 (38.8-128.8)	**0.034Θ**
BMI (kg/m²)*	31.4 (16.7-48.9)	29.3 (16-58.7)	29.8 (16-58.7)	**0.018Θ**
Chronic disease (n, %)				
Hypertension	134 (78.8%)	340 (69.2%)	474 (71.7%)	**0.017Θ**
Diabetes mellitus	59 (34.7%)	168 (34.2%)	227 (34.3%)	**0.908**
Congestive heart failure[x]	21 (12.4%)	17 (3.5%)	38 (5.8%)	**<0.001Θ**
COPD	12 (7.1%)	28 (5.7%)	40 (6.1%)	**0.523**
Chronic liver disease	3 (1.8%)	5 (1%)	8 (1.2%)	**0.443**
Chronic kidney disease	12 (7.1%)	13 (2.6%)	25 (3.8%)	**0.009Θ**
Osteoporosis	36 (21.2%)	70 (14.3%)	106 (16.1%)	**0.035Θ**
Dementia	24 (14.1%)	37 (7.7%)	61 (9.2%)	**0.011Θ**
Depression	42 (24.7%)	78 (15.9%)	120 (18.2)	**0.010Θ**
Geriatric syndromes (n, %)				
Probable sarcopenia (low HGS)	42 (24.7%)	33 (6.7%)	75 (11.3%)	**<0.001Θ**
Probable sarcopenia (abnormal CST)	94 (55.3%)	42 (8.6%)	136 (20.6%)	**<0.001Θ**
Falls	86 (50.6%)	155 (31.6%)	241 (36.5%)	**<0.001Θ**
Frailty (FRAIL scale ≥3)[⊥]	71 (42%)	40 (8.2%)	111 (16.9%)	**<0.001Θ**
Malnutrition (MNA-SF)	14 (8.2%)	1 (0.2%)	15 (2.3%)	**<0.001Θ**
Urinary incontinence	94 (55.3%)	168 (34.2%)	262 (39.6%)	**<0.001Θ**
Sleep disorders	73 (43%)	174 (35.4%)	247 (37.4%)	**0.219**
Polypharmacy (n, %)	141 (83.4%)	340 (69.7%)	481 (72.8%)	**<0.001Θ**
Number of chronic drugs*	6 (0-21)	5 (0-17)	5 (0-21)	**<0.001Θ**
Number of chronic diseases	4 (0-8)	3 (0-10)	3 (0-10)	**<0.001Θ**
ADL*	6 (1-6)	6 (1-6)	6 (1-6)	**<0.001Θ**
IADL*	8 (0-8)	8 (0-8)	8 (0-8)	**<0.001Θ**
Mortality (n, %)	56 (32.9%)	48 (9.8%)	104 (15.8%)	**0.632**

ADL: Activities of daily living, BMI: Body mass index, CST: Chair stand test, COPD: Chronic obstructive pulmonary disease, HGS: Hand grip strength, IADL: Instrumental activities of daily living, MNA-SF: Mini Nutritional Test-Short Form, UGS: Usual gait speed, *Given data as median, ΘSignificant p-values , ⊥Marked data includes 657 participants, [x]Marked data includes 660 participants

Table 2. Univariate and multivariate regression results for low gait speed

	Univariate analysis				Multivariate analysis			
	p	OR	95% Cl Lower upper		p	OR	95% Cl Lower upper	
Age	<0.001Θ	1,122	1,080	1,166	<0.001Θ	1,122	1,080	1,166
Sex	<0.001Θ	3,490	1,913	6,367	<0.001Θ	3,444	1,888	6,283
Congestive heart failure	0.044Θ	2,550	1,024	6,351	0.045Θ	2,543	1,022	6,325
Probable sarcopenia (low HGS)	0.051	2,056	0.998	4,235	0.052	2,049	0.995	4,219
Probable sarcopenia (abnormal CST)	<0.001Θ	5,775	3,428	9,729	<0.001Θ	5,724	3,397	9,644
Falls	0.025Θ	1,708	1,069	2,729	0.026Θ	1,705	1,067	2,725
Frailty (FRAIL scale ≥3)	<0.001Θ	2,874	1,604	5,150	<0.001Θ	2,848	1,588	5,108
Malnutrition (MNA-SF)	0.006Θ	20,747	2,412	178,437	0.006Θ	20,706	2,409	177,956

CI: Confidence Interval, HGS: Hand grip strength, MNA-SF: Mini Nutritional Test-Short Form, OR: Odds ratio, ΘSignificant p-values

In a review of five studies involving a total of 14,692 participants, Cooper et al. (16) identified no significant association between gait speed and all-cause mortality after adjusting for confounding factors, and the results of this study align closely with ours regarding the outcomes associated with mortality.

In a 2009 consensus report, based on a review by the International Academy on Nutrition and Aging Task Force of 27 studies, LGS was identified as a risk factor for disability, cognitive impairment, hospitalization, falls, and mortality (24). In their study of 4,298 respondents aged 65 years or older, Doi et al. (25) reported an association between gait speed, stride length, and mortality, while a contrasting review of nine prospective studies involving a total of 12,901 participants aged 65 years or older by Liu et al. (11) reported an association between LGS and mortality among the male participants, but no significant association among the female participants. Similarly, in a study involving 1,348 older people living in a rural location in South Korea utilizing the 4 m walk test, Jung et al. (8) noted an inverse correlation between gait speed and frailty in both sexes, but when the sex-specific quartiles were considered, different statistical results were observed in the association between gait speed, mortality, institutionalization, and the prevalence of geriatric syndromes. In a study of 2,105 adults aged 65 years or older, Zhao et al. (15) reported an association between LGS and mortality in male participants. The above studies differ in terms of the outcomes related to mortality, which may be attributed to the absence of age, race, and sex-specific cut-off values in their analyses (8-11,24,25). The present findings could be validated by future studies that take into account sex-specific disparities or utilize different cutoff values in an investigation of the association between UGS and mortality (8,11,15).

In their study, Jung et al. (8) reported an association between frailty assessed using the K-FRAIL questionnaire and UGS, whereas a meta-analysis of 20 studies involving a total of 13,527 participants aged 60 years, consistent with the present study, reported a relationship between frailty and UGS (26).

Ramsey et al. (27) screened 286 outpatients with malnutrition using the Short Nutritional Assessment Questionnaire and observed a relationship between malnutrition and gait speed. A meta-analysis of 45 studies involving 16,911 adults aged 60 years reported a significant relationship between malnutrition and gait speed (28). In this regard, the results of the present study related to malnutrition are consistent with the literature.

In our study, we reported a significant relationship between CST score and low UGS in a geriatric outpatient sample (29). Similarly, a prospective study by Alcazar et al. (30) involving 1,844 older adults aged 67 years or older reported a significant relationship between CST scores and low UGS, which is consistent with the results of the present study.

The strength of this study lies in its status as the first to explore factors related to low gait speed among older adults in Türkiye, coupled with its inclusion of comprehensive data from a substantial number of patients.

Study Limitations

One limitation of this study is its retrospective design.

Conclusion

The current study identified an association between LGS and factors such as age, sex, malnutrition, frailty, and probable sarcopenia evaluated through CST among older adults in Türkiye.

Ethics Committee Approval: The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki, and it was conducted after obtaining approval from the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (approval number: 15, date: 21.07.2023).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices - M.E.B.; C.K.; Concept - M.E.B., M.A.K.; Design - M.E.B., M.A.K.; Data Collection or Processing - C.K.; Analysis or Interpretation - M.E.B.; Literature Search - M.E.B., C.K., G.B., M.A.K.; Writing - M.E.B., C.K., G.B., M.A.K.

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Preoperative Pulmonary Artery Systolic Pressure and Survival in Patients Undergoing Valve Replacement for Mitral Stenosis

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ABSTRACT

Introduction: High pulmonary artery pressure (PAP) is a critical survival parameter in patients with severe mitral stenosis. We investigated changes in PAP and their impact on survival in patients undergoing mitral valve replacement for severe mitral stenosis.

Methods: We retrospectively analyzed 42 patients who underwent mitral valve replacement for severe mitral stenosis between January 2020 and January 2022. Changes in systolic pulmonary artery pressure (sPAP) assessed by echocardiography and survival outcomes were analyzed.

Results: The mean age of the patients was 56.05±14.21 years. Among the patients, 71.4% were female and 28.6% were male. The median postoperative sPAP was 29 mmHg, which was significantly lower than the preoperative value ($p<0.001$). In the subgroup analysis according to preoperative sPAP value, the postoperative sPAP change was 17.87% in <50 mmHg group and 41.61% in ≥50 mmHg group, which indicated a statistically significant difference ($p=0.003$). In the patient group with preoperative sPAP <50 mmHg, the expected 3-year survival rate was 85.2% compared with 75.8% in the patient group with sPAP ≥50 mmHg, and the differences were insignificant ($p=0.510$).

Conclusion: Patients with severe mitral stenosis and high sPAP can undergo surgery with acceptable survival expectancy. However, the decrease in pulmonary pressure in the early postoperative period alone cannot adequately predict survival.

Keywords: Mitral stenosis, mitral valve, pulmonary artery, survival rate

Introduction

Mitral stenosis is a heart valve disease that develops on a rheumatic or degenerative basis, is associated with high mortality rates when left untreated, and remains a significant problem in developing countries (1). When the stenosis in the mitral valve orifice drops below 1.5 cm^2, the passage of blood from the left atrium to the left ventricle becomes difficult during diastole, leading to an increase in the transmitral pressure gradient (2). Because of increased pressure in the left atrium and pulmonary circulation, permanent or reversible changes may occur in the pulmonary vascular bed. When the disease is left untreated, symptoms such as palpitations, shortness of breath, weakness, and peripheral edema may emerge because of increased pulmonary pressure.

Medical treatment alone is insufficient for mitral stenosis, which is a mechanical problem. Percutaneous mitral commissurotomy (PMC) and mitral valve replacement are treatment strategies aimed at increasing the valve area. PMC is a less invasive method; however, because of limitations in its applicability, mitral valve replacement remains the primary treatment option for severe mitral stenosis (3).

In patients with mitral stenosis, left ventricular function is usually preserved, whereas systolic pulmonary artery pressures (sPAP) are generally high. An sPAP >50 mmHg is considered a heightened risk of increased hemodynamic decompensation (4). Surgery is particularly indicated for patients at high risk of hemodynamic decompensation (3). However, this situation raises concerns among surgeons because of the decrease in survival expectancy (5). Despite these concerns, there is limited evidence regarding the impact of preoperative elevation in sPAP on survival.

The aim of this study was to investigate the effect of preoperative elevation of sPAP on survival in patients undergoing mitral valve replacement due to severe mitral stenosis.

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Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board for Non-Interventional Clinical Research of Aydın Adnan Menderes University Faculty of Medicine (approval number: 2022/126, date: 04.08.2022). Digital and manual patient records were retrospectively reviewed at the Department of Cardiovascular Surgery, Aydın Adnan Menderes University Faculty of Medicine.

The study included all patients who underwent surgery between January 2020 and January 2022, with the primary indication being severe mitral stenosis. Emergency surgeries, redo surgeries, patients who underwent surgery because of infective endocarditis, and patients who underwent concomitant aortic valve surgery were excluded from the study. The surgical decision was made by the university's cardiac specialists, considering the current guidelines.

The echocardiographic parameters of the patients were measured preoperatively and after 3 months postoperatively, and the changes between the two groups were analyzed. The echocardiographic parameters analyzed were sPAP, mean mitral valve gradient, mitral valve area, and left ventricular ejection fraction.

Tricuspid regurgitation was localized using Doppler color flow imaging. The peak flow velocity of the transtricuspid jet was measured using continuous-wave Doppler spectroscopy, and the pressure gradient between the right ventricle and right atrium was calculated using the modified Bernoulli equation. sPAP was estimated by adding the clinically determined mean jugular venous pressure.

The demographic and preoperative data of the patients included age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, end-stage renal failure, and atrial fibrillation. Information on length of hospital stay, time of discharge, a type of valve used, and mortality was obtained from the university's digital record system.

The surgeries were performed under general anesthesia via a median sternotomy incision using classic cardiopulmonary bypass techniques and antegrade cold-blood cardioplegia. The aortic cross-clamping and cardiopulmonary bypass durations were recorded. All surgeries included mitral valve replacement, with additional procedures including coronary artery bypass graft and tricuspid valve surgery. Operations are conducted by different teams; standard and similar protocols are applied in terms of technique and strategy.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate the conformity of the data to the normal distribution. Normally distributed data were expressed as mean and standard deviation, whereas non-normally distributed data were expressed as median and quartiles. Frequency and percentage were used to present categorical data. In the comparison of preoperative and postoperative continuous variables, the paired samples t-test was used for normally distributed data, and the Wilcoxon signed-rank test was used for non-normally distributed data. The Kaplan-Meier method was used for survival analysis. A $p<0.05$ was set as statistically significant in all analyses.

Results

The mean age of the 42 patients evaluated in the study was 56.05±14.21 years. Of the patients, 30 (71.4%) were female and 12 (28.6%) were male. The demographic characteristics and comorbidities of the patients are presented in Table 1. There were no significant differences in comorbidities between the groups of patients who died and those who did not. The median preoperative sPAP was 44 mmHg, and 14 (33.3%) patients had sPAP values ≥50 mmHg. The median left ventricular ejection fraction was 60.29. The mean gradient detected by echocardiography for the mitral valve was 9 mmHg, and the mean valve area was 1.39±0.38 cm^2.

Isolated mitral valve replacement was performed in 25 patients (59.52%). Two patients underwent coronary artery bypass grafting during the same session because of concomitant coronary artery disease. Fifteen patients underwent concomitant surgical treatment due to tricuspid regurgitation (Table 2). For mitral valve replacement, mechanical valves were preferred in 32 patients (76.2%), whereas bioprosthetic valves were

Table 1. Patient characteristics and comorbidities

	Total (n=42)	Survivor (n=34)	Non-survivor (n=8)	p-value
Age (mean ± SD)	56.05±14.21	53.71±13.85	67±11.73	0.027*
Sex, n (%)				0.589 (+)
Male	12 (28.6)	10 (39.4)	2 (25)	
Female	30 (71.4)	24 (70.6)	6 (75)	
Atrial fibrillation, n (%)	29 (69)	22 (64.7)	7 (87.5)	0.398 (+)
Diabetes mellitus, n (%)	8 (19)	6 (17.6)	2 (25)	0.482 (+)
Hyperlipidemia, n (%)	11 (26.2)	10 (29.4)	1 (12.5)	0.312 (+)
Hypertension, n (%)	19 (45.2)	14 (41.2)	5 (62.5)	0.243 (+)
Coronary artery disease, n (%)	7 (16.7)	4 (11.8)	3 (37.5)	0.113 (+)
Chronic renal failure, n (%)	4 (9.5)	2 (5.9)	2 (25)	0.158 (+)
Smoking frequency, n (%)	8 (19)	7 (20.6)	1 (12.5)	0.518 (+)

SD: Standard deviation, *: Mann-Whitney U test, (+): Chi-squared test.

preferred in 10 patients (23.8%). The median cardiopulmonary bypass duration was 152.5 min, whereas the median cross-clamp duration was 100.5 min. The median length of hospital stay in the intensive care unit was 4 days, whereas the median length of hospital stay until discharge was 7 days.

The median postoperative sPAP was 29 mmHg, which was significantly lower than the preoperative sPAP (p<0.001). Other echocardiographic parameters and their comparisons with the preoperative period are presented in Table 3.

In the subgroup analysis based on preoperative sPAP values, the postoperative change in sPAP was 17.87% in patients with sPAP <50 mmHg and 41.61% in those with sPAP ≥50 mmHg. A significant difference was observed between the two groups in terms of postoperative sPAP change (p=0.003) (Figure 1).

The median follow-up period was 35.6 months, and mortality was observed in 8 (19%) patients. The expected 1-year and 3-year survival rates were 88.1% and 81.6%, respectively. In the patient group with preoperative sPAP <50 mmHg, the expected 1-year and 3-year survival rates were 88.9% and 85.2%, respectively. In the patient group with preoperative sPAP value ≥50 mmHg, the expected 1-year and 3-year survival rates were 86.7% and 75.8%, respectively. There was no statistically significant difference between the two groups in terms of survival expectancy (p=0.510) (Figure 2).

Discussion

In this study involving patients who underwent mitral valve replacement due to severe mitral stenosis, two important findings were noted regarding the change in sPAP. First, a significant decrease in sPAP was observed in the early period. The pressure decrease was more pronounced in patients with preoperative sPAP values above the haemodynamic decompensation threshold of 50 mmHg compared with the group with values <50 mmHg. Second, no significant difference in midterm survival outcomes was observed between the two patient groups.

Table 2. Surgical treatments performed

	(n=42)
	n (%)
Isolated mitral valve replacement	25 (59.52)
Mitral valve replacement + Coronary artery bypass grafting	2 (4.76)
Mitral valve replacement + De Vega annuloplasty	8 (19.05)
Mitral valve replacement + Tricuspid ring annuloplasty	4 (9.52)
Mitral valve replacement + Tricuspid valve replacement	3 (7.14)

The incidence of rheumatic heart disease is gradually decreasing with the widespread adoption of treatment for acute rheumatic fever. However, mitral stenosis and its related complications remain significant health concerns, particularly in developing countries. Every year, approximately

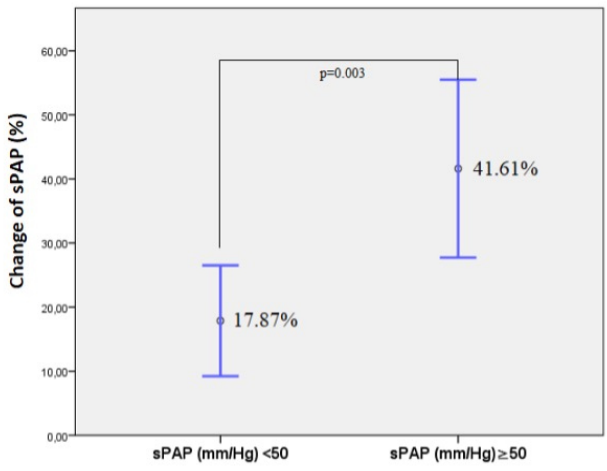

Figure 1. Comparison of postoperative sPAP changes between sPAP <50 and ≥50 mmHg groups
sPAP: Systolic pulmonary artery pressure

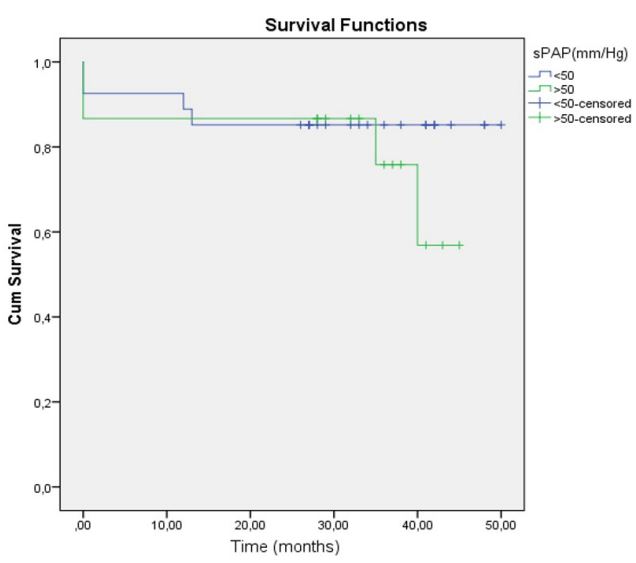

Figure 2. Kaplan-Meier method showing the survival expectancy of sPAP <50 and ≥50 mmHg groups
sPAP: Systolic pulmonary artery pressure

Table 3. Comparison of preoperative and postoperative echocardiographic variables

	(n=42)		
	Preoperative value	Postoperative value	p-value
sPAP (mmHg), median (IQR)	44 (23)	29 (15)	<0.001*
Left ventricular ejection fraction (%), median (IQR)	65 (5)	60 (5)	0.006*
Mean gradient (mmHg) and median (IQR)	9 (5)	4 (2)	<0.001*
Valve area (cm^2), mean ± SD	1.39±0.38	2.74±0.45	<0.001 (+)

IQR: Interquartile range, sPAP: Systolic pulmonary arterial pressure, SD: Standard deviation, *: Wilcoxon signed-rank test, (+): Paired samples t-test

4.8 out of 100,000 individuals die because of these diseases (6). Mitral valve replacement, one of the most effective treatment methods for preventing complications and mortality, aims to reduce the valve gradient to prevent congestion in the pulmonary circulation and periphery. When exposed to high pressures for prolonged periods, pulmonary vascular bed hypertrophy and vasoconstriction can develop, leading to persistent pulmonary hypertension that may not adequately respond to surgical treatment (7). The elevation of sPAP because of mitral stenosis can be concerning for cardiac surgeons during decision-making for surgery, as it may negatively impact both short-term and long-term survival (5). This concern arises from the possible lack of sufficient improvement in sPAP values despite normalization of postoperative left atrial pressures in patients with mitral stenosis, which could decrease survival expectations. The calculation of sPAP using noninvasive echocardiography and its insufficiency on it's own in evaluating the pulmonary vascular bed further exacerbate this concern (8).

In a retrospective descriptive study by Briongos Figuero et al. (7) involving 111 patients, preoperative high sPAP could persist after mitral valve replacement. In another study conducted by Walls et al. (9), pulmonary pressures decreased after mitral valve replacement and physiological repair, regardless of the surgical type. Consistent with these reports, sPAP values decreased significantly in the early postoperative period compared with preoperative values in the present study. The primary reason for the decrease in sPAP in the early postoperative period is the reduction in left atrial pressure because of the resolution of the mechanical problem. In the present study, although the percentage decrease in postoperative sPAP values was higher among patients with preoperative sPAP values >50 mmHg, this result did not significantly impact survival. This indicates that sPAP values alone are not sufficient to evaluate the pulmonary vascular bed and that postoperative decreases in sPAP are not sufficient to predict survival.

The risks associated with high pulmonary pressure in patients undergoing mitral valve replacement are unclear. In the study conducted by Cámara et al. (10) with 88 patients and an average follow-up duration of 44 months, the 5-year expected survival rate was 86%. In this study, survival analysis was conducted without classifying the PAP values. In a retrospective study conducted by Vincens et al. (11) involving 43 patients, the 5-year expected survival rate was 80%. In this study, all patients had sPAP values >60 mmHg, and survival analysis was performed by grouping patients according to their ages. In a retrospective study conducted by Yang et al. (5) involving 317 patients, postoperative long-term survival was significantly reduced in patients with mitral stenosis and higher pulmonary pressures compared with those with lower pressures. In the present study, the 3-year expected survival rate was 81.6%, and a lower survival rate was observed in the group with sPAP values >50 mmHg. Consistent with the study of Yang et al. (5), midterm follow-up revealed that survival rates were lower in patients with high pulmonary pressure. However, no significant difference was observed.

Study Limitations

There are certain limitations to this study. The study was conducted at a single center, and the sample size was relatively small. Symptomatic evaluation could not be performed in the two groups due to insufficient data on the change in functional capacity of the patients. The necessary data to calculate preoperative surgical risk scores were not obtained. The use of different valve brands was considered a limitation of the study. Echocardiographic assessment of pulmonary pressure and lack of invasive confirmation is another limitation of the study.

Conclusion

In severe mitral stenosis, preoperative high sPAP values can be reduced by achieving an appropriate valve area through valve replacement, and acceptable survival rates can be achieved. However, a decrease in sPAP alone in the early period is not sufficient to evaluate midterm survival.

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board for Non-Interventional Clinical Research of Aydın Adnan Menderes University Faculty of Medicine (approval number: 2022/126, date: 04.08.2022).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices - S.D.; Concept - Ö.F.R.; Design - Ö.F.R.; Data Collection or Processing - F.A.; Analysis or Interpretation - Ö.F.R.; Literature Search - F.A.; Writing - F.A.

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

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Impact of Ultrasonography-Guided Transversus Abdominis Plane Block and Local Anesthetic Infiltration in the Surgical Field on Postoperative Analgesic Requirements for Laparoscopic Cholecystectomy Procedures

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ABSTRACT

Introduction: This study aimed to assess the impact of intraperitoneal local anesthetic infiltration and ultrasonography-guided transversus abdominis plane (TAP) block on postoperative pain intensity and opioid usage within the first 24 hours after laparoscopic cholecystectomy.

Methods: Sixty patients classified under the American Society of Anesthesiologists 1-2-3 risk groups participated in this prospective, controlled, and randomized study and were divided. into three groups. The TAP group (n=20) underwent bilateral TAP blocks with 20 mL of 0.25% bupivacaine. prior to surgical incision. The following gallbladder removal by the surgical team, the intraperitoneal group (n=20) received 10 mL of 0.5% bupivacaine infiltration into the bladder bed. The control group (n=20) did not receive local anesthesia via TAP block or intraperitoneally. Postoperative pain scores on the Numeric Rating Scale [(NRS) 0-10] were recorded at 1, 2, 4, 8, and 24 hours. Additionally, the total tramadol dosage (mg) consumed at the 24th postoperative hour and the frequency of additional analgesic use were documented in the case report form.

Results: The postoperative NRS scores of both the TAP block and intraperitoneal groups were significantly lower than those of the control group ($p<0.05$). Moreover, there was no notable difference between the TAP block and intraperitoneal groups concerning NRS scores ($p>0.05$). Similarly, no significant variance was observed in the total tramadol dosage among the TAP block, intraperitoneal, and control groups ($p>0.05$).

Conclusion: The analgesic efficiencies of TAP block and intraperitoneal local anesthesia infiltration were similar, and both groups provided more effective analgesia than the control group.

Keywords: Intraperitoneal local anesthesia infiltration, pain, transversus abdominis plane block

Introduction

In recent years, laparoscopic cholecystectomy has become the gold standard for the treatment of cholelithiasis. The primary advantages of this approach include rapid patient mobilization and reduced postoperative pain compared with other surgical methods. Although pain after laparoscopic cholecystectomy is generally less than that after open cholecystectomy, it remains a common issue during recovery. Unlike pain from the abdominal wall after laparotomy, pain from post-laparoscopic cholecystectomy involves visceral, parietal, and shoulder (somatic) components, which may manifest at varying times and intensities (1).

Transversus abdominis plane (TAP) block is one of the commonly employed regional blocks for postoperative analgesia following abdominal procedures (2,3). This study aimed to compare two frequently utilized methods-intraperitoneal local anesthetic infiltration and ultrasonography (USG)-guided TAP block-both of which have demonstrated efficacy in postoperative analgesia in prior research. The comparison focuses on the assessment of postoperative analgesia efficacy and opioid consumption.

Methods

We enrolled a total of 60 male and female patients aged 18 to 70 who were scheduled for laparoscopic cholecystectomy at the general surgery

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department of a tertiary level training and research hospital between July and December 2019. Approval for the study was granted by the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 2019/1912, date: 26.07.2019). The sample size was determined with an 80% confidence level and a 5% margin of error, yielding (n=16). Each of the three groups comprised 20 patients. Prior to commencement, patients underwent comprehensive procedures and provided signed informed consent. Patients were allocated to groups based on their sequence of arrival to the operating room: Patient group 1 received a TAP block (group TAP), patient group 2 underwent local anesthesia infiltration into the Gallbladder Bed (Group Intraperitoneal), and patient group 3 served as the control group.

Patients were instructed. to rate their pain intensity using the Numeric Rating Scale (NRS) before the operation, which ranges from 1 to 10, with 10 representing the highest pain level (comparable to normal labor pain, kidney stone, or toothache). Additionally, they were trained on how to use the patient-controlled analgesia (PCA) device to enable postoperative pain measurement.

The exclusion criteria were patients undergoing open cholecystectomy, those with allergies to anesthetic drugs, individuals with infections at the site of TAP block application, patients with chronic pain and/or undergoing pain treatment, individuals with bleeding disorders, those with mental health disorders, emergency cases, pregnant women, patients classified as ASA 3-4, individuals with surgical durations exceeding 2 hours for various reasons, patients requiring conversion to open surgery, and those unable to use the PCA device due to nausea or device-related issues.

All patients underwent endotracheal intubation following intravenous (i.v.) administration of 1 mg/kg lidocaine, 5 mg/kg thiopental sodium, 2 µg/kg fentanyl and 0.5 mg/kg following routine ASA monitoring. Anesthesia maintenance was achieved using a combination of 50% oxygen and 50% nitrous oxide along with 2% sevoflurane.

In the TAP block group, the Petit points (defined as the anterior wall of the Petit's triangle, comprised of the external oblique muscle; the posterior wall, by the latissimus dorsi; and the lower border, by the iliac crest) were identified and prepared before the initiation of surgery following orotracheal intubation. A high-frequency linear ultrasound probe (GE Healthcare, LOGIQ 200 PRO, USA) was placed on the mid-axillary line in the transverse plane on the abdominal wall between the costal margin and the iliac crest. To ensure optimal imaging quality, necessary adjustments were made in USG, and the probe was positioned to visualize the skin-subcutaneous layer, external oblique muscle, internal oblique muscle, transversus abdominis muscle, and peritoneal membrane from top to bottom. The insertion of a 21-gauge, 100 mm block needle (StimuplexR A, Braun, Insulated Needle, USA) using an in-plane technique between the internal oblique and transversus abdominis muscles was confirmed with 1% lidocaine.

20 mL of 0.25 % bupivacaine. (Bustesin® 0.5 %, Vem, Türkiye). was administered under real-time visualization. The procedure was performed bilaterally.

The intraperitoneal group, patients received 10 mL of 0.5% bupivacaine administered by the general surgical team following gallbladder removal. The drain was closed until the procedure was completed. Conversely, no local anesthetic was administered to patients in the control group.

Intraoperatively, all participants received i.v. tramadol (1 mg/kg) following cholecystectomy. Upon completion of surgery, the patient was extubated with 0.015 mg/kg of atropine antagonized with 0.04 mg of neostigmine.

Statistical Analysis

Postoperatively, a PCA device was affixed to all patients. The PCA device used was the CADD Legacy Patient Control Analgesia device Model 6300 Ambulatory Infusion (Pump smith Medical ASD, Inc. St. Paul, MN 55112 USA), delivering 300 mg tramadol/100 cc mediflex with a bolus dose of 10 mg and a lockout interval of 15 minutes.

Postoperative pain scores on the NRS (0-10) were documented at the 1st, 2nd, 4th, 8th, and 24th hours. The total dosage of tramadol (in milligrams) administered within the first 24 hours postoperatively, as well as the frequency of supplementary analgesic use, was documented in the case report form.

Results

Table 1 presents the comparative data within the study. Table 2 illustrates that there were no significant differences between age, body mass index, total tramadol dosage, or additional analgesic use among the TAP block, intraperitoneal, and control groups ($p>0.05$). NRS values were significantly lower in the TAP block and intraperitoneal groups compared with the control group ($p<0.05$), as depicted in Table 3. There were no. significant differences in NRS values between the TAP block and intraperitoneal groups ($p>0.05$).

Within the intraperitoneal group, NRS values at the 4th, 8th, and 24th hours exhibited a significant decrease compared with the 1st hour ($p<0.05$). Similarly, in the TAP block and control groups, NRS values at the 2nd, 4th, 8th, and 24th hours demonstrated a significant decrease compared with the 1st hour ($p<0.05$) (Table 3). Furthermore, the decrease in NRS

Table 1. Data compared within the scope of the study

	Min.-max.	Median	Mean ± SD, (n %)
Age	26-63	48	45.1±10.2
BMI	20-43	29	29.3±4.9
Total tramadol	10-300	100	112.8±72.5
NRS			
1st hour	0.0-10.0	5.0	5.0±2.4
2nd hour	0.0-8.0	4.0	3.8±1.6
4th hour	0.0-7.0	3.0	3.1±1.4
8th hour	0.0-7.0	2.0	2.7±1.4
24th hour	0.0-5.0	2.0	2.3±1.0
Using supplemental analgesics		7	12%
Not using additional analgesics		53	88%

Min.: Minimum, max.: Maximum, SD: Standard deviation, NRS: Numerical rating scale, BMI: Body mass index

values at the 2nd hour was significantly higher in the TAP block and control groups than in the intraperitoneal group ($p<0.05$). There was no significant. difference in the decrease in NRS values between the TAP block and control groups at the 2nd hour ($p>0.05$). Moreover, there were no significant decreases in NRS values at the 4th, 8th, and 24th hours among the TAP block, control, and intraperitoneal groups ($p>0.05$) (Table 3).

There was no significant difference in the 4th hour NRS value compared to the 2nd hour, 8th hour NRS value compared to the 4th hour, and 24-hour NRS value compared to the 8th hour in the TAP block, intraperitoneal, and control groups ($p>0.05$) (Table 3). The changes in NRS values over time in the three groups determined for the study are depicted in Figure 1.

Discussion

Acute postoperative pain following laparoscopic cholecystectomy manifests in three distinct types: Incisional (somatic), visceral, and shoulder pain. The intensity and duration of pain following laparoscopic cholecystectomy can vary significantly among individuals and are often unpredictable. Typically, pain reaches its peak on the day of the operation and the following day, gradually subsiding over the course of 3-4 days. However, it is worth noting that approximately 13% of patients may experience persistent severe pain during the first week after surgery (4).

Given the multifaceted nature of pain during laparoscopic procedures, multimodal analgesia is essential. In clinical practice, alongside oral cyclooxygenase-2 inhibitors and non-steroidal anti- inflammatory drugs, various approaches, such as PCA, opioids, local anesthetic infiltration at the surgical trocar entry site (PSI), intraperitoneal local anesthetic infiltration, rectus sheath block, TAP block, or their combinations, are recommended (5-8). In this study, we aimed to compare the effectiveness of two analgesic protocols routinely utilized by our surgical and anesthesia teams, which are integral components of our multimodal analgesic regimen in our clinical setting.

Ongoing studies are investigating whether preoperative analgesic administration contributes to postoperative pain relief (7). In our study, the TAP block was administered following anesthesia induction and before surgical incision.

The literature extensively explores the effects of intraperitoneal local anesthetic administration on postoperative pain; however, conclusive information regarding optimal dosage and timing remains elusive (9-12). Although some studies have indicated that intraperitoneal use of local anesthetics reduces postoperative pain and analgesic consumption, others have suggested inadequacies in its efficacy.

Several studies in the literature explore the impact of administration timing on postoperative pain following intraperitoneal injection of

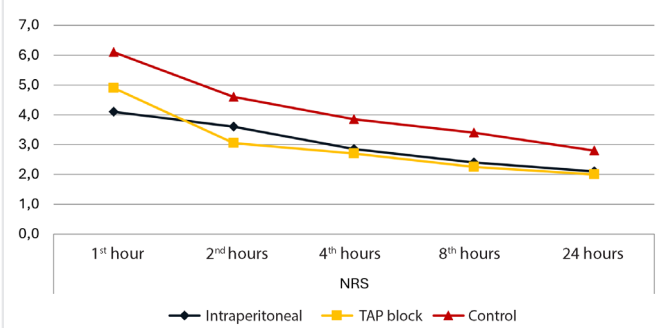

Figure 1. Change in NRS values between groups
NRS: Numerical rating scale, TAP: Transversus abdominis plane

Table 2. Demographic data and additional analgesia usage rates

	Intraperitoneal		TAP block		Control		p
	Mean ± SD, (n %)	Median	Mean ± SD, (n %)	Median	Mean ± SD, (n %)	Median	
Age	47.3±9.0	48.5	43.0±10.8	43.5	45.2±10.9	49.5	0.482[K]
BMI	30.4±4.5	29.0	29.9±4.4	29.0	28.4±5.8	28.0	0.414[K]
Tramadol	106.5±79.6	85.0	98.5±63.3	100.0	133.5±72.6	100.0	0.316[K]
Use of additional analgesics							
Not used	18	90%	19	95%	16	80%	0.322[K]
Used	2	10%	1	5%	4	20%	

[m]Mann-Whitney U test, [χ²]Chi-square test, [K]Kruskal-Wallis test. BMI: Body mass index; TAP: Transversus abdominis plane, Min.: Minimum, max.: Maximum, SD: Standard deviation

Table 3. Comparison of NRS between groups

	Intraperitoneal		TAP block		Control		p
	Mean ± SD, (n %)	Median	Mean ± SD, (n %)	Median	Mean ± SD, (n %)	Median	
NRS							
1st hour	4.1±2.1	4.0	4.9±2.8	5.0	6.1±1.9	6.0	0.021[K]
2nd hour	3.6±1.5	3.5	3.1±1.2	3.0	4.6±1.8	4.5	0.005[K]
4th hour	2.9±1.0	3.0	2.7±1.2	3.0	3.9±1.7	4.0	0.023[K]
8th hour	2.4±0.8	2.0	2.3±1.3	2.0	3.4±1.6	3.0	0.034[K]
24th hour	2.1±0.7	2.0	2.0±1.0	2.0	2.8±1.2	3.0	0.034[K]

[m]Mann-Whitney U test, [w]Wilcoxon test, [K]Kruskal-Wallis test, NRS: Numerical rating scale, TAP: Transversus abdominis plane

local anesthetic (11,13). In our study, the TAP block was conducted pre-incision, with local anesthetic applied to the exit site of the gallbladder bed.

Johns et al. (14) conducted a meta-analysis in 2012 involving nine studies with 413 patients to evaluate the analgesic effects of TAP block following abdominal surgery. The analysis demonstrated the efficacy and safety of the TAP block, resulting in a significant reduction in morphine requirement by - 23.71 mg ($p<0.002$) and 38.08 mg ($p<0.0001$) at 24 and 48 hours postoperatively, respectively. Notably, no significant differences were observed in postoperative nausea and vomiting. or pain scores (14).

In our study, tramadol consumption was 106.5 mg ($p>0.005$) in the group receiving bupivacaine at the gallbladder bed, 98.5 mg ($p>0.005$) in the TAP block group, and 133.5 mg ($p>0.005$) in the control group. These findings indicate comparable tramadol consumption between the TAP block and bupivacaine at the gallbladder bed groups. Moreover, compared with the control group, both groups exhibited decreased narcotic consumption.

TAP block has the potential to provide analgesia to the abdominal wall; nevertheless, achieving visceral analgesia may necessitate a broader dispersion of local anesthetics. Magnetic resonance imaging investigations have indicated substantial paravertebral spread. extending from T5 to L1 with posterior approach TAP blocks, whereas such spread was absent with subcostal TAP blocks (15). In our study, we opted for the posterior TAP block approach, anticipating that it would offer visceral analgesia, and administered bilateral posterior TAP blocks to our patients.

Concerns arose regarding the efficacy of TAP block in upper abdominal surgery. However, consistent with findings by Bisgaard, there was no discernible distinction in analgesic usage between patients undergoing TAP block and those receiving local anesthetic application to the gallbladder bed in the Fowler position within our study cohort.

Study Limitations

The limitations of our study. include its single-center nature and the small number of samples. Multicenter studies with more patients are needed.

Conclusion

In this study, we assessed the effectiveness of ultrasound-guided TAP block. and intraperitoneal local anesthetic administration in patients undergoing laparoscopic cholecystectomy under general anesthesia. We compared the postoperative pain levels, opioid consumption, and additional analgesic requirements among the three groups. NRS pain scores at all assessment time points were comparable between the TAP block and intraperitoneal local anesthesia groups, but were significantly lower than those of the control group. The analysis of total tramadol consumption revealed that the control group had the highest tramadol consumption, although no significant intergroup differences were observed. The variability in individual tramadol utilization likely contributed to the high standard deviation values. Our findings indicate that both TAP block and intraperitoneal local anesthesia offer similar analgesic efficacy, exceeding that of the control group.

In conclusion, US-guided TAP block and intraperitoneal local anesthesia application significantly improved postoperative pain scores.

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 2019/1912, date: 26.07.2019).

Informed Consent: Prior to commencement, patients underwent comprehensive procedures and provided signed informed consent.

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Relationship of Neoadjuvant Chemotherapy Efficacy with Histopathologic Molecular Subtypes in Breast Cancer Patients

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ABSTRACT

Introduction: Breast cancer is the most common malignancy in women, and it is the second leading cause of malignancy-related mortality in women after lung cancer. Locally advanced breast cancer is a clinically heterogeneous group with a broad spectrum. Neoadjuvant chemotherapy (NAC) is the standard treatment at this stage. The present study aimed to evaluate the efficacy of NAC in terms of histopathologic molecular subtypes.

Methods: The study included 183 patients receiving NAC. Patients were studied in three groups: Luminal tumors, human epidermal growth factor receptor-2 (HER-2)-positive tumors, and triple-negative tumors based on the expressed receptor status. In our retrospective review, we only examined pathological complete response (pCR) based on breast tumor shrinkage before and after chemotherapy. In this study, we evaluated factors affecting pathologic complete response in patients receiving NAC.

Results: According to breast cancer subtypes based on biopsy results, pCR developed in 8 of 20 patients with triple-negative tumors (40%), 24 of 61 patients with HER-2-positive tumors (39.3%), and 22 of 102 patients with luminal tumors (21.5%) (p=0.030). The pCR rate was available in 5 of 40 patients with lymphovascular invasion (LVI) (12.5%) and 49 of 143 patients without LVI (34.2%) (p=0.008). pCR was available in 1 of 16 patients with perineural invasion (PNI) (6.6%) and 53 of 168 patients without PNI (31.5%) (p=0.043). PCR was available in 2 of 25 patients with extracapsular lymph node invasion (8%) and in 52 of 158 patients without extracapsular lymph node invasion (32.9%) (p=0.011).

Conclusion: The NAC pCR rate of hormone-positive tumors was lower than that of hormone-negative tumors in breast cancer. This finding was related to the biological response of the tumor in heterogeneous breast cancer.

Keywords: Breast cancer, neoadjuvant chemotherapy, molecular subtype, pathological response

Introduction

The main risk factor for breast cancer is female sex, as the lifetime risk of developing breast cancer is 1 in 8 for women (12%) compared with 1 in 833 for men (0.12%) (1). It is the most common malignancy and the second most common cause of malignancy-related mortality in women (2). Breast cancer is a multifactorial disease (3). The etiopathogenesis of the disease is influenced by demographic factors, such as sex, age, and race, and hereditary factors, such as family history and genetic mutations. Moreover, reproductive factors such as early menarche-late menopause, age at first pregnancy, breastfeeding, use of combined oral contraceptives, hormone replacement therapy, body mass index, physical activity, and medical risk factors such as smoking, alcohol, radiation, and benign diseases of the breast.

Neoadjuvant chemotherapy (NAC) is increasingly being used for locally advanced breast cancer. This is because NAC evaluates tumor response before surgery and provides information about tumor biology; furthermore, NAC reduces tumor size and allows for smaller-scale surgery in the breast and axilla. NAC provides a cosmetically better appearance and reduces post-operative complications, such as lymphedema (4-6). Therefore, NAC has become a standard treatment for locally advanced breast cancer. Pathological complete response (pCR) has been recognized as an important marker of NAC and a prognostic marker in many studies (7). In other studies, clinicopathological parameters such as hormone receptor status, human epidermal growth factor receptor-2 (HER-2) status, histological grade, proliferation index, tumor size, age, and laboratory values that may predict pCR have been studied. However,

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in various studies evaluating these factors that may predict pCR, it has been reported that a single factor is not sufficient to predict the efficacy of NAC because of the different pCR rates obtained (8).

Locally advanced breast cancer is a clinically heterogeneous group with a broad spectrum. The 8th edition of the American Joint Committee on Cancer staging system with prognostic data, such as tumor size, lymph node positivity, presence of distant metastasis, hormone receptor [estrogen receptor (ER), progesterone receptor (PR)] and HER-2 can be used by clinicians. Pre-operative treatment should be considered when planning the systemic treatment of stage 3A, 3B, 3C, and inoperable stage 2B T3N0 tumors, except for operable stage 2B tumors. This is because systemic treatments have many benefits for this group of patients. This group includes T3 tumors >5 cm in diameter, T4 tumors that are fixed to the chest wall, cause edema or ulceration of the breast skin, or have satellite skin nodules, and N2 and N3 tumors with ipsilateral supraclavicular, infraclavicular, internal mammary, or fissile axillary lymph node involvement (9). Inflammatory breast cancer is also classified as locally advanced.

In this study, we aimed to investigate in patients with breast cancer treated with NAC the relationship between the efficacy of this treatment and histopathologic molecular subtypes, prognostic factors, and factors affecting pCR.

Methods

Patients

In our two-center study, 183 patients treated with NAC between February 2012 and July 2021 were retrospectively analyzed. Pre- and post-operative tumor diameters were evaluated using various methods, including ultrasound, mammography, and contrast-enhanced magnetic resonance imaging (MRI). Because the number of lymph nodes was not evaluated quantitatively before NAC, no post-operative comparison could be made. Patients underwent breast biopsy to determine histological subtype, hormone receptor, and HER-2 status before NAC.

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki and patient right regulations. The ethics committee approved the study by the Ethics Committee of the Gaziantep University Faculty of Medicine and the Gaziantep Provincial Directorate of Health (approval number: 2021/81, date: 01.09.2021).

Chemotherapy Regimens

Various chemotherapy protocols were used when NAC regimes were reviewed. This may be due to the histologic subgroup effect, as well as the effect of the clinician's choice of treatment as it is a heterogeneous disease. One hundred and one patients (55.4%) received AC-T, i.e. 4 cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks, followed by paclitaxel 80 mg/m^2 weekly for 12 weeks. Thirty-three patients (17.9%) received AC-taxane-trastuzumab, 14 patients (7.6%) received only AC, and 10 patients (5.4%) received AC-taxane-trastuzumab-pertuzumab (Table 1).

Surgical Method

Surgical methods and axillary procedures performed in patients after NAC were analyzed. A total of 165 patients (90.16%) underwent modified radical mastectomy, 4 patients (2.18%) underwent mastectomy + sentinel lymph node dissection (SLND), 12 patients (6.55%) underwent breast-conserving surgery (BCS) + axillary lymph node dissection, and 2 patients (1.09%) underwent BCS + SLND (Table 2).

Pathological Examination

Tumors were classified according to the standard criteria of the World Health Organization. ER and PR status was examined immunohistochemically and considered positive in cases of a positive value >10%. HER-2 status was assessed using immunohistochemistry and grading the intensity of membrane staining. Tumors graded as strong HER-2 homogeneous staining +3 were considered positive. Either fluorescence *in situ* hybridization or silver *in situ* hybridization was used to determine amplification in case of a moderately homogeneous staining +2. In microscopic examinations of the resection sample, regardless of carcinomas in situ, only the absence of invasive carcinoma

Table 1. Types of neoadjuvant chemotherapy

Neoadjuvant chemotherapy regimens	n	%
AC→T	101	55.4
AC→T→trastuzumab	33	17.9
AC	14	7.6
AC→T→trastuzumab-pertuzumab	10	5.4
TCH	10	5.4
TAC	7	3.8
AC→T→carboplatin	2	1.08
TCH→AC	2	1.08
TC	1	0.54
EC	1	0.54
CMF	1	0.54
FEC→T	1	0.54
Total	183	100

AC: Doxorubicin + cyclophosphamide, T: Taxane (paclitaxel or docetaxel), H: Trastuzumab, TAC: Dosexel + doxorubucin + cyclophosphamide, TC: Docetaxel + cyclophosphamide, EC: Epirubicin + cyclophosphamide, CMF: Cyclophosphamide + methotrexate + 5-FU, FEC: 5-FU + epirubicin + cyclophosphamide

Table 2. Surgical methods and axillary lymph node dissection procedures following neoadjuvant chemotherapy

		n	%
The type of operation	MRM	165	90.16
	Mastectomy + SLND	4	2.18
	BCS + ALND	12	6.55
	BCS + SLND	2	1.09
	Total	183	100
Lymph node dissection	ALND	177	96.72
	SLND	6	3.27
	Total	183	100

MRM: Modified radical mastectomy, ALND: Axillary lymph node dissection, BCS: Breast-conserving surgery, SLND: Sternal lymph node dissection

in the breast was considered as pCR because sufficient pre- and post-operative information on the axilla was not available.

Statistical Analysis

The Shaphiro-Wilk test was used to analyze whether the numerical variables were normally distributed. To compare variables that were not normally distributed, the Mann-Whitney U test was used to compare variables in two groups, and the Kruskal-Wallis and Dunn's tests were used to compare variables in three groups. Relationships between categorical variables were tested using the chi-square and Bonferroni multiple comparison tests. A multinomial logistic regression analysis was used to estimate the variables that influenced the response outcome. The SPSS 22.0 Windows version package program was used in the analysis. $P<0.05$ is considered significant.

Results

The characteristics according to breast cancer subtype are presented in Table 3. The median age of the patients was 48 years (29-78). Fifty-seven of 102 patients (55.8%) in the luminal group, 19 of 61 patients (31.15%) in the HER-2 group, and 11 of 20 patients (55%) in the triple negative group

Table 3. Characteristics of breast cancer subtypes

Variables		Subtypes of breast cancer								p
		Luminal		HER-2-positive		Triple negative		Total		
		n	%	n	%	n	%	n		
Age (years)	≤48	45	44.12	42	68.85	9	45.00	96	183	**0.007**
	>48	57	55.88	19	31.15	11	55.00	87		
Pathological cancer	Invasive ductal	97	95.10	61	100.00	18	90.00	176	183	0.090
	Non-invasive ductal	5	4.90	0	0.00	2	10.00	7		
Pre-operative tumor diameter	T1-T2	83	81.37	47	77.05	14	70.00	144	183	0.488
	T3-T4	19	18.63	14	22.95	6	30.00	39		
Grade	1-2	35	74.47	10	37.04	0	0.00	45	183	**0.001**
	3	12	25.53	17	62.96	3	100.00	31		
	Unknown	55		34		17		107		
Ki-67 status (%)	≤20	45	52.94	22	46.81	2	11.76	69	183	**0.008**
	>20	40	47.06	25	53.19	15	88.24	80		
	Unknown	17		14		3		34		
Pre-operative lymph node metastasis	Present	75	73.53	52	85.25	16	80.00	143	183	0.211
	Absent	27	26.47	9	14.75	4	20.00	40		
The type of surgery	MRM	91	89.22	56	91.80	18	90.00	165	183	0.686
	Mastectomy + SLND	1	0.98	2	3.28	1	5.00	4		
	BCS + ALDN	8	7.84	3	4.92	1	5.00	12		
	BCS + SLND	2	1.96	0	0.00	0	0.00	2		
Lymph node dissection	Axillary dissection	99	97.06	59	96.72	19	95.00	177	183	0.894
	Sentinel dissection	3	2.94	2	3.28	1	5.00	6		
Laterality	Right	49	48.04	33	54.10	13	65.00	95	183	0.350
	Left	53	51.96	28	45.90	7	35.00	88		
Localization	Top-exterior	58	56.86	33	54.10	12	60.00	103	183	0.710
	Top-interior	7	6.86	7	11.48	2	10.00	16		
	Bottom-exterior	25	24.51	10	16.39	3	15.00	38		
	Bottom-interior	8	7.84	9	14.75	3	15.00	20		
	All	4	3.92	2	3.28	0	0.00	6		
Multifocality	Present	26	25.49	14	22.95	5	25.00	45	183	0.935
	Absent	76	74.51	47	77.05	15	75.00	138		
LVI	Present	27	26.47	12	19.67	1	5.00	40	183	0.092
	Absent	75	73.53	49	80.33	19	95.00	143		
PNI	Present	12	11.76	3	4.92	0	0.00	15	183	0.112
	Absent	90	88.24	58	95.08	20	100.00	168		
Lymph node extracapsular invasion	Present	20	19.61	3	4.92	2	10.00	25	183	**0.027**
	Absent	82	80.39	58	95.08	18	90.00	158		

Table 3. Continued

Variables		Subtypes of breast cancer								p
		Luminal		HER-2-positive		Triple negative		Total		
		n	%	n	%	n	%	n		
Surgical margin	Negative	97	95.10	58	95.08	20	100.00	175	183	0.599
	Positive	5	4.90	3	4.92	0	0.00	8		
Skin invasion	Present	12	11.76	9	14.75	1	5.00	22	183	0.504
	Absent	90	88.24	52	85.25	19	95.00	161		
In situ carcinoma	Present	14	13.73	5	8.20	1	5.00	20	183	0.366
	Absent	88	86.27	56	91.80	19	95.00	163		

P<0.05. HER-2: Human epidermal growth factor receptor-2, MRM: Modified radical mastectomy, SLND: Sternal lymph node dissection, BCS: Breast-conserving surgery, ALND: Axillary lymph node dissection, LVI: Lymphovascular invasion, PNI: Perineural invasion

were >48 years of age, which was statistically significant (p=0.007). One hundred and seventy-six patients (96.17%) had a pathological type, the majority of which was invasive ductal carcinoma. Pre-operative tumor diameters calculated according to the TNM staging system were analyzed in two subgroups as T1-T2 and T3-T4. The grade was not specified in 107 patients (58.46%), and the remaining patients were analyzed in two subgroups as grade 1-2 and grade 3 patients. The grade was unknown in 55 patients and 12 of the remaining 47 patients (25.53%) had grade 3 tumors in the luminal group; the grade was unknown in 34 patients and 17 of the remaining 27 patients (63.96%) had grade 3 tumors in the HER-2-positive group, and the grade was unknown in 17 patients and available only for 3 patients and 3 patients had grade 3 tumors (100%) in the triple negative group, and grades according to subgroups were statistically significant (p=0.001). The percentage of patients with Ki-67 was not recorded in the pathology reports of 34 of 183 patients (18.57%). The percentage of Ki-67 was unknown in 17 patients and 40 of 85 patients (47.06%) had Ki-67 >20 in the luminal group; the percentage of Ki-67 was unknown in 14 patients and 25 of 47 patients (53.19%) had Ki-67 >20 in the HER-2-positive group, and the percentage of Ki-67 was unknown in 3 patients and 15 of 17 patients (88.24%) had Ki-67 >20 in the triple negative group. Therefore, the high percentage of Ki-67 was higher and statistically significant in the HER-2-positive and triple-negative groups (p=0.008). The lymph node extracapsular invasion was significantly negative in all subtypes, and percentages were negative in 82 of 112 patients (80.39%) in the luminal group, 58 of 61 patients (95.08%) in the HER-2-positive group, and 18 of 20 patients (90%) in the triple negative group, respectively (p=0.027).

Pathological Complete Response Rate

The factors influencing the response to NAC are presented in Table 4. Patients who did not have invasive carcinoma in the breast tumor size on pathological examination after neoadjuvant therapy were evaluated as having pCR, and the others were considered non-responders. The axillary pCR rate was not analyzed because it was not available in the pathological reports. Fifty four of 183 patients (29.5%) had pCR. According to subtypes, 22 of 102 patients (21.6%) in the luminal group, 24 of 61 patients (39.3%) in the HER-2-positive group, and 8 of 20 patients (40%) in the triple negative group had a pCR (p=0.030). Lymphovascular invasion (LVI) was absent in 49 of 54 patients with pCR (90.74%) and in 94 of 129 patients without pCR (72.87%) (p=0.008). Perineural invasion was absent in 53 of 54 patients with pCR (98.15%) and in 115 of 129 patients without pCR (89.15%) (p=0.043). Lymph node extracapsular invasion was absent in 52 of 54 patients with pCR (96.3%) and in 106 of 129 patients without pCR (82.17%) (p=0.011).

For the significant variables (p<0.05) influencing the response to NAC, a univariate regression analysis was first performed (Table 5). In the univariate analysis of the factors influencing the response to NAC, the luminal group was taken as a reference among breast cancer subtypes, and the HER-2-positive group and the triple negative group were found to have more responses (p-values were p=0.033 for luminal group, p=0.016 for HER-2-positive group and p=0.086 for triple negative group). Patients without LVI and those with lymph node extracapsular invasion had a better response (p-values of 0.011 and 0.022, respectively). Multivariate regression analysis was performed for the variables that were significant (p<0.05) in the univariate regression analysis, and it was found that only LVI tumors had an independent effect on pCR (p=0.048).

Discussion

Neoadjuvant therapies have been used more frequently in recent years for large tumors that are not suitable for surgery and in cases requiring extensive axillary resection. The routine use of chemotherapy in luminal group breast cancers is controversial because of its lower efficacy. Neoadjuvant therapy is used more frequently in HER-2-positive and triple-negative patients. In this study, we investigated the relationship between neoadjuvant therapy efficacy and molecular subtypes and other factors that contribute to pCR. For this purpose, we categorized the patients as luminal, HER-2-positive, and triple-negative. Rouzier et al. (10) also categorized patients in a similar way. In a study conducted by Galvez et al. (11) that included 435 patients who received NAC and evaluated the clinicopathological characteristics of patients according to molecular subtypes, it was found that the majority of luminal A cases (97%) were low grade, whereas luminal B, HER-2-positive, and triple negative type tumors were mostly high grade (61%, 69%, 72%, respectively). In our study, the majority of patients in the luminal group were grade 1-2 and the majority of patients in the HER-2 group were grade 3, which was consistent with the literature (p=0.001) (11,12). When the pCR was analyzed according to the breast cancer subtypes, it was observed in our study that the response rates were higher in HER-2-positive and triple-negative tumors compared with luminal type

Table 4. Factors influencing pathologic complete response

Variables		Pathological complete response					p
		Pathological complete response		Pathological complete response		Total	
		n	%	n	%	n	
Age (years)	≤48	31	57.41	65	50.39	96	183	0.386
	>48	23	42.59	64	49.61	87		
Histopathologic subtype	Invasive ductal	53	98.15	123	95.35	176	183	0.368
	Non-invasive ductal	1	1.85	6	4.65	7		
Pre-operative tumor diameter	T1-T2	42	77.78	102	79.07	144	183	0.846
	T3-T4	12	22.22	27	20.93	39		
Grade	1-2	13	72.22	32	54.24	45	183	0.175
	3	5	27.78	27	45.76	32		
	Unknown	36		70		106		
Ki-67 status (%)	≤20	21	47.73	48	45.71	69	183	0.822
	>20	23	52.27	57	54.29	80		
	Unknown	10		24		34		
Pre-operative lymph node metastasis	Present	43	79.63	100	77.52	143	183	0.753
	Absent	11	20.37	29	22.48	40		
Breast cancer subtype	Luminal	22	40.7	80	62	102	183	**0.030**
	HER-2-positive	24	44.4	37	28.7	61		
	Triple negative	8	14.8	12	9.3	20		
Laterality	Right	30	55.56	65	50.39	95	183	0.523
	Left	24	44.44	64	49.61	88		
Localization	Top-exterior	25	46.30	78	60.47	103	183	0.067
	Top-interior	7	12.96	9	6.98	16		
	Bottom-exterior	9	16.67	29	22.48	38		
	Bottom-interior	10	18.52	10	7.75	20		
	All	3	5.56	3	2.33	6		
Multifocality	Present	11	20.37	34	26.36	45	183	0.391
	Absent	43	79.63	95	73.64	138		
LVI	Present	5	9.26	35	27.13	40	183	**0.008**
	Absent	49	90.74	94	72.87	143		
PNI	Present	1	1.85	14	10.85	15	183	**0.043**
	Absent	53	98.15	115	89.15	168		
Lymph node extracapsular invasion	Present	2	3.70	23	17.83	25	183	**0.011**
	Absent	52	96.30	106	82.17	158		
Presence of *in situ* carcinoma	Present	4	7.41	16	12.40	20	183	0.323
	Absent	50	92.59	113	87.60	163		

P<0.05. HER-2: Human epidermal growth factor receptor-2, LVI: Lymphovascular invasion, PNI: Perineural invasion

Table 5. Univariate and multivariate analyses of pathological complete response

Variables		Univariate analysis			Multivariate analysis		
		OR	CI	p	OR	CI	p
Breast cancer subtype	Luminal (reference)			**0.033**			0.135
	HER-2-positive	**2,359**	**1,174-4,738**	**0.016**	2,103	0.979-4,140	0.057
	Triple negative	2,424	0.882-6,665	0.086	1,887	0.666-5,345	0.232
LVI		**3,649**	**1,344-9,906**	**0.011**	2,837	1,007-7,992	**0.048**
PNI		6,452	0.827-50,355	0.075			
Lymph node extracapsular invasion		**5,642**	**1,281-24,845**	**0.022**	3,634	0.792-16,672	0.097

P<0.05, LVI: Lymphovascular invasion, PNI: Perineural invasion, OR: Odds ratio, CI: Confidence interval

tumors. These results are in line with the literature (11-14). The Ki-67 cut-off value was set at 20 in accordance with the ESMO 2021 Guideline, and luminal groups were classified as luminal B in cases where Ki-67 was ≥20 and luminal A in cases where Ki-67 was <20. In both our study and the study by Rouzier et al. (10), patients with HER-2-positive and triple-negative tumors had a higher response to NAC than patients with luminal tumors. In a study by Kaufmann et al. (15), the pCR was higher in patients with a negative hormone profile than in those with a positive hormone profile. Osako et al. (14) designed a study in which the response status was evaluated based on the percentage of hormone receptor positivities. In their study, patients with ER positivity >30% and PR positivity >1% (p=0.0001) had a lower pCR rate. On the other hand, a pCR was 18.6 times more common in patients with a negative ER than in patients with a positive ER of ≥30% (14). In our study, similar to the findings of Kaufmann et al. (15), pCR was observed more frequently in patients with a negative hormone profile and in HER-2-positive patients, which was in line with the literature. Nishimura et al. (16) demonstrated a significant relationship between the Ki-67 percentage and pCR in a multivariate analysis. In our study, we investigated whether there was a relationship between the Ki-67 percentage and pCR. However, no statistically significant relationship was found. A study by Spring et al. (17) showed that the tumor grade was an independent predictive factor for pathological response. They reported that the neoadjuvant therapy response was higher, and a greater pathologic response was obtained in high-grade tumors (17). In our study, no relationship was found between tumor grade and pCR. This may be due to the fact that pathology reports did not specify grade information for all patients. A study by Uematsu et al. (18) showed that the absence of LVI in surgical specimens after NAC was associated with a pathological response. Another study showed that the degree of LVI was associated with tumor recurrence and tumor-related deaths (19). Therefore, it is important to evaluate LVI to predict the pathological response after NAC. In our study, LVI was an independent factor influencing pathological response (p=0.048).

Study Limitations

Our study is a retrospective study. The pathological data of some patients were obtained from other centers, and these could not be obtained. Finally, the follow-up time was short.

Conclusion

In the present study, although the complete response rate following neoadjuvant therapy was approximately 30%, it was noteworthy that the rate of BCS was approximately 10%. Mastectomy after neoadjuvant therapy is usually performed for inflammatory breast cancer and multicentric focal tumors, and this approach constituted the majority of our study cohort. High mastectomy rates may be due to patient insistence and clinician preference. Tumor marking before neoadjuvant therapy and similar imaging methods of pre-operative restaging (with breast MRI, if possible) will increase the rates of BCS, thereby providing better cosmetic results with less breast tissue loss.

In conclusion, both the treatment response and pCR rates of patients who received NAC for breast cancer were higher in patients with HER-2-positive and triple-negative breast cancers. Similar to other studies in the literature, we found that luminal tumors had a lower sensitivity to NAC.

Ethics Committee Approval: The ethics committee approved the study by the Ethics Committee of the Gaziantep University Faculty of Medicine and the Gaziantep Provincial Directorate of Health (approval number: 2021/81, date: 01.09.2021).

Informed Consent: Retrospective study.

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The Effect of Probiotic Administration on the Level of Interleukin-6 and Interleukin-10 in Opioids Poisoned Patients Admitted to the Intensive Care Unit

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ABSTRACT

Introduction: Recent research has revealed that exposure to toxins and substances like cannabis, opium, heroin, and tramadol can inhibit the growth of lymphocytes. One of the key factors identified is the impact of probiotics on decreasing and managing inflammation in individuals affected by poisoning. This study examined the impact of probiotic treatment on interleukin-6 (IL-6) and IL-10 levels in opioid-poisoned patients.

Methods: This randomized clinical trial included 70 patients with opioid poisoning who were admitted to the poisoned intensive care unit for 6 months. Patients were randomly assigned to two intervention groups that received oral probiotics or a control group that received placebo. Data collected were analyzed using IBM SPSS version 22 software.

Results: The intervention group had methadone (28.6%) and tramadol as the most common causes of poisoning, whereas the control group had tramadol (45.7%) and methadone (28.6%). There was a noticeable decrease in Acute Physiology and Chronic Health Evaluation scores in the intervention group before and after the intervention, whereas no significant difference was observed in the control group. Significantly, the levels of IL-6 and IL-10 were lower in the probiotic group than in the control group.

Conclusion: Probiotic use improved the condition of patients and decreased IL-6 and IL-10. This shows the positive effect of probiotics as an adjunctive treatment in opioid-poisoned patients, improving the condition of the patients' immune system.

Keywords: Immune system, interleukins-6, interleukins-10, opioid, probiotics, poisoning

Introduction

Acute poisonings pose a major risk of death and create difficulties for emergency departments (ED) in many countries. The majority of cases treated in the ED are due to self-poisoning, with antidepressants, stimulants, street drugs, anti-histamines, and anti-convulsants being the substances that have led to severe outcomes in the past decade (1). Approximately 40% of individuals who come to the ED with intoxication are hospitalized, and on average, 1.5-3.7% of poisoned patients require admission to the intensive care unit (ICU) (2).

Research has shown that people who were poisoned and required admission to the ICU exhibited higher levels of high sensitivity-C-reactive protein (hs-CRP), leukocytes, neutrophils, and monocytes, along with increased RBC scatter within one day of exposure to a foreign substance (3). Interleukin-6 (IL-6) is a well-known cytokine that plays a role in preserving body equilibrium. When the body's balance is disturbed due to infections or tissue injury, IL-6 is rapidly produced, assisting in the body's protection against these sudden pressures by initiating acute phase and immune reactions (4). It has been confirmed that the levels of IL-6 change in cases of poisoning

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from substances like carbon monoxide, organophosphates, paraquat, and lead (5-8).

Probiotics are tiny organisms that offer health benefits to the host when provided in adequate amounts. Currently, they are utilized to address dysbiosis by aiming to rebalance the gut's microorganisms and modify the disturbed intestinal microbiota through specific, yet not fully comprehended, mechanisms of action (9). The immune system is influenced by the gastrointestinal microbiota through the creation of substances that stimulate immune cells and possess immunomodulatory and anti-inflammatory properties. The impact mentioned is caused by the interaction between probiotic bacteria and epithelial cells, dendritic cells, monocytes/macrophages, and lymphocytes (10). Probiotics primarily work by regulating the immune response of the host. The results of the meta-analysis and clinical trials suggest that probiotic supplementation may be linked to lower levels of inflammation markers, such as CRP, tumor necrosis factor-alpha, IL-6, IL-12, and malonedialdehyde. However, while different probiotic supplements have been shown to be beneficial, there are no consistent data on which bacterial strains are most effective, the optimal dosage, and the rate of effectiveness (11-13).

Lately, probiotics have been employed to complement the treatment of specific poisonings, including acetaminophen, lead, and alcohol poisoning, and have demonstrated positive outcomes (14-16). The goal of this study was to examine how probiotic treatment affects IL-6 and IL-10 levels in ICU-admitted critically ill patients poisoned with opioids.

Methods

The study was conducted as a double-blind randomized clinical trial involving the examination of 70 individuals admitted to the poisoned ICU of Loghman Hakim Hospital from November 2022 to April 2023 due to opioid poisoning. Convenience sampling was used to select patients without age or gender restrictions. The inclusion criteria were patients who were admitted to the ICU and received enteral nutrition for at least seven days. The exclusion criteria were patients who had been in the ICU for a duration of fewer than 7 days, intestinal obstruction, renal failure, pancreatitis, short bowel syndrome, or a history of chemotherapy. Patients were randomly assigned to their respective groups using a black and white beads pattern. Patients with black beads received probiotics.

The intervention group received two probiotic capsules (manufactured by Zisttakhmir company from Iran) containing probiotic elements (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophilus*) as one serving size, along with prebiotic elements such as *Fructo-oligosaccharides, Lactose, Mg stearate,* and *talc* via a nasogastric tube one hour after antibiotic administration, every 8 hours for 7 days. The control group received placebo using the same administration method and schedule as the probiotic capsules. The patients were followed up 6 weeks after the last probiotic or placebo intake.

Demographic information (age, gender and type of toxic substance) and the results of clinical tests, such as the IL-6 and IL-10, Acute Physiology and Chronic Health Evaluation-II (APACHE II) score, blood acidity, blood urea nitrogen level, creatinine level, lactate dehydrogenase, creatine phosphokinase, and blood sugar levels, were recorded before and after treatment in the two groups.

Compliance with Ethical Guidelines

Prior to participating in the trial, all patients or their legally eligible decision-makers were required to complete a consent form. Furthermore, permission was obtained from the legal guardians of patients aged below 16 years. The researchers followed the ethical guidelines outlined in the Declaration of Helsinki and ensured the confidentiality of patient information. Patient consent was obtained, and a consent form is available upon request.

The Research Ethics Committee of Shahid Beheshti University of Medical Sciences approved this study (approval number: IR.SBMU.RETECH.REC.1400.299, date: 15.08.2021). The trial was registered with the Iranian Registry of Clinical Trials (IRCT) (code: IRCT20210720051946N5).

Statistical Analysis

The data were analyzed using IBM SPSS software version 22 (IBM Corp, Armonk, New York, USA). The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. Then, central and descriptive indices were calculated and reported. Depending on the distribution of samples in the statistical population, parametric tests, such as independent t-tests and paired t-tests, or non-parametric tests like chi-square test, were utilized. A significance level of $p<0.05$ was applied to all variables.

Results

Table 1 shows the demographic information and results of the preintervention tests. Of the 70 patients who participated in the study, 59 were male. Among the male participants, 29 received probiotics as part of the intervention group and 30 were included in the control group. The average age of the intervention group was 37.42±14.1 years, and in the control group, it was 33.94±15.4 years. There were no significant differences in age and gender distribution between the two groups. The intervention and control groups had an average hospitalization duration of 7.3 and 7.9 days, respectively. The most common cause of poisoning in the intervention group was methadone (28.6%) and tramadol, whereas in the control group, it was tramadol (45.7%) and methadone (28.6%) (Figure 1).

Table 2 explain the results of the tests after the intervention. There was no significant difference in the levels of IL-6 and IL-10 before initiating treatment between the two groups. Following the intervention, the intervention group exhibited an average IL-6 level of 9.15±0.93 pg/mL, whereas the control group exhibited an IL-6 level of 10.9±1.5 pg/mL. A notable disparity was noted between the two groups ($p=0.0001$). Furthermore, there was a notable disparity in the levels of IL-10 between the intervention and control groups, with levels measuring 11.57±2.01 and 14.43±2.45 pg/mL, respectively.

Before the intervention, a notable contrast was noted in the APACHE II indices between the two groups. The probiotic group had a higher average score (22.29 vs. 19.26), indicating a more severe illness and higher

Table 1. Demographic information and test results are collected upon arrival at the two groups

Variable	Probiotic group (mean ± SD) or frequency, (%)	Control group (mean ± SD) or frequency, (%)	p-value
Gender (male)	29 (82.86%)	30 (85.71%)	0.5
Age (year)	37.42±14.1	33.94±15.4	0.349
IL-6 level (pg/mL)	13.05±2.1	12.71±1.3	0.416
IL-10 level (pg/mL)	16.35±2.25	16.38±2.37	0.963
APACHE score	22.29±6.8	19.26±5.6	0.046*
PH	5.2±3.3	6.2±2.6	0.15
BUN (mg/dl)	49.2±28.4	49.7±35.5	0.944
Cr (mg/dl)	1.5±0.8	1.5±0.8	0.214
LDH (U/L)	438.49±1228.6	383.51±884.7	0.831
CPK (U/L)	3756.03±10113.8	1817.14±6014.1	0.334
BS (mg/dl)	101.9±45.4	116.3±62.2	0.273
Length of hospital stay (day)	7.29±1.8	7.86±2.5	0.272

*P<0.05. SD: Standard deviation, IL-6: Interleukin-6, APACHE: Acute Physiology and Chronic Health Evaluation, BUN: Blood urea nitrogen, Cr: Creatinine, LDH: Lactate dehydrogenase, CPK: Creatine phosphokinase, BS: Blood sugar

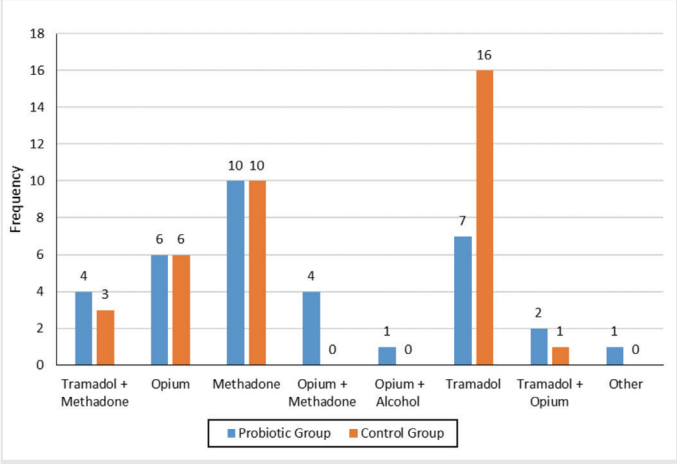

Figure 1. The types of opioids causing poisoning in the group of patients receiving probiotics and control patients

risk of mortality. After the intervention, no significant difference was observed between the two groups. However, the paired t-test revealed a significant contrast between before and after the intervention group, with a decrease in APACHE scores. In contrast, no significant difference was observed in the control group before and after the intervention (Table 3). There were no significant differences in other parameters between the two groups before and after treatment.

Discussion

The aim of this research was to examine the effects of probiotics on IL-6 and IL-10 levels in individuals who have experienced poisoning. The findings indicate that probiotics have a beneficial effect on lowering IL-6 and IL-10 concentrations in ICU patients with poisoning. The most common causes of poisoning in our study were methadone and tramadol.

Previous research has suggested that extended heroin abuse and higher substance doses can result in extensive inflammation and elevated levels of pro-inflammatory cytokines like IL-6 (17).

IL-6, a member of the pro-inflammatory cytokine group, stimulates the production of various proteins that contribute to immediate inflammation and also has a significant impact on the growth and specialization of human cells (18). A study on the utilization of probiotics in individuals with rheumatoid arthritis indicated that probiotics can have a beneficial impact by decreasing the levels of IL-6 (19). Research on professional athletes has indicated that probiotic supplementation can decrease the levels of IL-6 in their bodies (20). Similarly, in our study, the consumption of probiotics decreased the level of IL-6.

IL-10 is primarily known for its anti-inflammatory, inhibitory, and self-regulating properties. It acts as a potent regulator that helps control and resolve inflammation via autocrine and paracrine pathways (21). A comprehensive analysis of the impact of probiotics on inflammatory markers demonstrated a notable increase in IL-10 levels in the bloodstream, indicating an increase in anti-inflammatory cytokines following probiotic intake (22). However, our research found a notable reduction in IL-10 levels following probiotic treatment.

Study Limitations

Our study has some limitations. The small number of samples makes it difficult to generalize the results. We only examined opioid-poisoned patients, and the effect on other poisonings was not investigated. We investigated inflammatory and anti-inflammatory ILs. Examining more members of each group and adjusting factors can improve results.

Conclusion

Our study ultimately showed that in people who have been poisoned, the use of probiotics decreases the levels of inflammatory IL-6 and anti-inflammatory IL-10. This suggests that probiotics have a non-specific impact on the suppression of ILs. Additional research with a larger sample size and exploration of the upstream pathways may help to further elucidate the mechanism.

Table 2. Test results at the end of treatment in two groups of patients

Variable	Probiotic group, (mean ± SD)	Control group, (mean ± SD)	p-value
IL-6 level (pg/mL)	9.15±0.93	10.9±1.5	0.0001*
IL-10 level (pg/mL)	11.57±2.01	14.43±2.45	0.0001*
APACHE score	19.17±6.37	19.63±8.22	0.796
PH	5.2±3.4	6.2±2.6	0.179
BUN (mg/dL)	34.4±17.7	44.6±44.4	0.214
Cr (mg/dL)	1.1±1.2	1.3±1.5	0.564
LDH (U/L)	119.34±580.9	161.11±416.3	0.731
CPK (U/L)	1168.2±4238.9	1593.17±3481.3	0.648
BS (mg/dL)	123.6±65.6	110.7±56.1	0.377

*P<0.05. SD: Standard deviation, IL-6: Interleukin-6, APACHE: Acute Physiology and Chronic Health Evaluation, BUN: Blood urea nitrogen, Cr: Creatinine, LDH: Lactate dehydrogenase, CPK: Creatine phosphokinase, BS: Blood sugar

Table 3. Paired t-test results in APACHE score in two groups

Variable	APACHE score		p-value
	Pre-intervention measures	Post-intervention measures	
Probiotic group (mean ± SD)	22.29±6.8	19.17±6.37	0.0001*
Control group (mean ± SD)	19.26±5.6	19.63±8.22	0.705

*P<0.05. APACHE: Acute Physiology and Chronic Health Evaluation, SD: Standard deviation

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Prevalence, Risk Factors, and Statistical Analysis of Urinary Incontinence in a Tertiary Care Hospital in India

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ABSTRACT

Introduction: Urinary incontinence (UI) is a prevalent condition that significantly affects quality of life, particularly in women. This cross-sectional study aimed to investigate the prevalence, types, and associated factors of UI among female patients at a specialized healthcare facility in India.

Methods: The investigation was conducted from November 2022 to April 2023 in the obstetrics and gynecology department, where all female participants aged 18 years and above were queried regarding their UI history. The generalizability of this study may be limited due to the clinic's focus on women seeking specialized gynecological or obstetric care.

Results: The generalizability of this study may be limited due to the clinic's focus on women seeking specialized gynecological or obstetric care. This research may overrepresent health-conscious women or those with severe UI symptoms, potentially biasing results and underrepresenting women with mild to moderate UI or those from disadvantaged populations. Furthermore, tertiary care settings may disproportionately attract patients with complex conditions requiring specialized treatment, influencing the study's outcomes. Disparities in socioeconomic status, health literacy, and awareness regarding UI treatment across various demographic groups can also affect patient selection and consequently impact the study results.

Conclusion: Our research conducted at an Indian tertiary care hospital revealed a significant prevalence of UI among female patients, underscoring the necessity for further investigations into preventive measures and treatment modalities. The psychological implications and social stigma associated with UI highlight the critical need for comprehensive support systems and intervention programs for affected individuals. The findings demonstrated that obstetric risk factors were directly correlated with the incidence of UI, as evidenced by the study outcomes. Healthcare practitioners should advocate for lifestyle modification to mitigate UI.

Keywords: Urinary incontinence, stress incontinence, diabetes, and prevalence rates

Introduction

Urinary incontinence (UI) is a common disease that has a significant impact on patient lives. It can lead to feelings of awkwardness, embarrassment, and low self-esteem in social situations. The stigma associated with discussing incontinence with a medical professional means that many women with the issue do not receive appropriate treatment. It has been estimated that as much as 30% of the population suffers from UI (1). Hospital-based research indicates a high number of unreported cases in the general population. UI is a burden that can be alleviated with a better understanding of the variables that put people at risk of developing the disorder (2). UI has been linked to a number of different characteristics, including age, parity, mode of delivery, history of hysterectomy, smoking, obesity, diabetes, chronic cough, constipation, drug use, tea consumption, caffeine consumption, alcohol use, and lack of physical activity (3-5). Several forms of urine incontinence have been observed, including stress incontinence, urge incontinence, and mixed incontinence, in which both stress and urge incontinence coexist. Laughing, sobbing, coughing, climbing stairs, lifting heavy objects, bending over, and vigorous exercise are all examples of behaviors that could trigger stress incontinence. Symptoms of urge incontinence include a need to use the toilet more often and an inability to hold urine until you get there (6-9). UI is a

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common issue among adults, and women are more susceptible. The two most common types of UI in women are stress UI (involuntary leakage with physical activity) and urgency UI (involuntary leakage linked with a sudden, strong need to void). Mixed incontinence is common in women, with increased incidence during pregnancy and postpartum, with stress being more prevalent (10-12).

UI, defined as the involuntary loss of urine, is a prevalent and frequently underreported medical condition. It has been recognized as a significant global public health concern owing to its substantial impact on quality of life, particularly among elderly and female populations (11). In India, the prevalence of UI is high; however, it remains largely neglected in the public health discourse because of social stigma and limited awareness. Research conducted in India has revealed the prevalence and risk factors of UI. A comprehensive community-based study by Aggarwal et al. (13) found that approximately 26.8% of women aged 35 years and older in North India experienced UI. The study also revealed that the incidence of UI increased with age, with more than 40% of women aged 60 years and above experiencing moderate-to-severe forms of the condition. These findings are consistent with global statistics but underscore the necessity for region-specific investigations to elucidate the unique demographic and cultural factors contributing to UI in India. A separate investigation conducted by Kumar et al. (14) revealed that 24.6% of women in a South Indian sample experienced UI. The investigators identified obesity, childbirth trauma, and menopause as major contributing factors to UI onset (14). Notably, the study revealed that only a small proportion of affected women sought medical attention, indicating issues with healthcare access and patient awareness.

Additionally, researchers, conducted a population-based survey in urban regions of Northern India and found that 21.3% of adult females suffer from UI (15). This study categorized UI types, with stress urinary incontinence (SUI) being the most prevalent, affecting 12.5% of the surveyed individuals, followed by urge and mixed incontinence. Researchers, emphasized the significance of lifestyle factors in the development and progression of UI, including insufficient physical activity, tobacco use, and dietary practices, which are particularly relevant to India's urban population. The International Continence Society estimates that 10-20% of Indians experience some form of UI, with higher rates observed in women, especially postmenopausal women (16). These statistics are likely underestimated because of widespread social stigma and hesitancy to seek medical assistance. This issue is further exacerbated in rural regions, where limited healthcare infrastructure contributes to the condition that remains largely unaddressed. Given these findings, UI is evident as a significant yet often overlooked public health issue in India (14). The high prevalence of UI is compounded by social taboos, which prevent many individuals, particularly women, from seeking timely diagnosis and treatment. This reluctance leads to decreased quality of life, increased mental distress, and social isolation. Therefore, it is essential to examine not only the epidemiology of UI but also the cultural and socioeconomic factors influencing help-seeking behaviors in India (13). This study aimed to explain how often, where, and what causes UI in women who visit a tertiary care center for care.

Methods

The study was approved by the Ethics Committee of Santhiram College of Pharmacy (approval number: SCOP/PDV/2022/18, date: 25.10.2022).

From November 2022 to April 2023, a cross-sectional study was conducted at the department of obstetrics and gynecology at a tertiary care hospital. All women aged over 18 years who visited the obstetrics or gynecology outpatient department were interviewed about their history of urine incontinence.

Sample Size and Generalizability

The clinic primarily serves a demographics of women seeking specialized care for gynecological or obstetric issues. Therefore, the sample size may not represent the general population. It is important to consider this limitation when attempting to generalize findings from studies conducted at this clinic.

One significant limitation of this study is that it may include a higher number of women who are more health conscious or have more severe UI symptoms, as they are more inclined to seek specialized treatment in tertiary care facilities. This may introduce bias in the study, potentially leading to underrepresentation of women with mild-to-moderate UI or those from disadvantaged groups, such as low-income individuals or marginalized communities, which could skew the representation of specific groups in the study (17). This study may disproportionately represent patients with complex conditions because tertiary care centers tend to attract cases requiring specialized interventions and advanced medical care, potentially influencing the study outcomes. Furthermore, variations in income levels, disparities in health literacy, and diverse levels of understanding about UI treatment among different demographic groups can influence patient selection at these clinics and subsequently impact the study results (18). Furthermore, the exclusive focus on women attending gynecology and obstetrics clinics excludes individuals who may seek care at primary care or urology clinics, narrowing the study's scope and potentially limiting the diversity of patient perspectives. Additionally, not including male patients in the study overlooked important information about the experiences of men with UI, even though it is common in older men and those with conditions like benign prostatic hyperplasia (BPH), which increase the risk of UI. The inclusion of male patients in this study would offer a more comprehensive perspective on UI across genders, thereby enhancing the generalizability of the findings (19).

SEAPI Staging System Overview

The SEAPI staging system, used by healthcare professionals, is widely recognized in clinical practice as a methodology for assessing and classifying UI. Instability healthcare professionals can use this system to accurately document specific characteristics, such as the type, severity, triggers, and frequency of UI episodes. Moreover, it helps in developing an individualized treatment plan by identifying the root causes of UI and tailoring interventions to address the specific type of UI (20).

Stress (S): The "stress" element pertains to SUI, which is characterized by involuntary urine leakage during activities that increase intra-abdominal pressure (18). This condition manifest during activities

that increase intra-abdominal pressure, such as coughing, sneezing, laughing, heavy lifting, and exercise routines like running or jumping. In this study, individuals exhibiting SUI symptoms, notably prevalent among women with compromised pelvic floor muscles or those who have experienced parturition, were classified under this category. SUI has been extensively documented in the Indian population, particularly among postmenopausal women, due to hormonal alterations and trauma from childbirth affecting pelvic support structures, leading to a higher prevalence in this demographic (21).

Emptying (E): The "emptying" element assesses the bladder capacity for effective evacuation. In some individuals, incontinence may arise from voiding dysfunction, where the bladder fails to empty fully because of obstruction or an underactive detrusor muscle. These conditions contribute to difficulties in bladder emptying due to voiding dysfunction and are commonly observed in males with BPH and females with bladder outlet obstruction (17). This component of the SEAPI system aids in distinguishing between UI caused by filling problems, such as stress or urge incontinence, and issues related to bladder emptying dysfunction. A systematic evaluation was conducted using uroflowmetry and measurements of post-void residual urine (20).

Anatomical (A): Anatomical irregularities that contribute to incontinence are included in this classification. For instance, pelvic organ prolapse (POP), which is prevalent among elderly women, can lead to significant UI. The "anatomic" element in this framework facilitates the identification of structural alterations in pelvic organs that may directly affect continence (21). The study participants underwent a comprehensive evaluation to identify potential factors contributing to UI, focusing on pelvic floor disorders like prolapse or urethral hypermobility through detailed assessments and diagnostic tests. This component is crucial as it plays a vital role in distinguishing between UI caused by functional issues, such as muscle weakness, and those arising from anatomical abnormalities, like POP, guiding appropriate treatment strategies (19).

Protection (P): The "Protection" component encompasses the use of protective devices, such as pads, diapers, and catheters, to address UI. Individuals who required external assistance due to the severity of their symptoms were categorized under the protection category (21). This classification provides valuable insights into the severity of their condition and its significant impact on daily activities. During our investigation, we meticulously recorded the types and frequency of external protection used by the participants, offering valuable insights into how UI affects their quality of life and the social challenges they face due to their condition (17).

Instability (I): The "Instability" element refers to urge incontinence or detrusor overactivity, which is characterized by involuntary bladder contractions that cause an unexpected, strong urge to urinate that is challenging to suppress. Urge incontinence, which is commonly known as overactive bladder, is prevalent among elderly individuals (19). The bladder instability component assesses the presence of bladder instability, often through urodynamic testing.

In our study cohort, subjects who experienced frequent urination, urgency, and nocturia were classified under this category. Understanding detrusor instability is crucial for developing effective treatment strategies, especially pharmacological interventions like antimuscarinic medications. In our study, we applied the SEAPI staging system to comprehensively evaluate UI in our patient cohort, allowing for a detailed analysis of its various aspects. Our research employed the SEAPI staging system to comprehensively evaluate UI in our patient cohort. Applying this comprehensive five-domain classification to each participant provided a detailed understanding of the different facets of UI, leading to a more accurate characterization of the condition in our study group. Due to the diverse causes and symptoms of UI, including stress incontinence in postmenopausal women and voiding issues in men with prostatic diseases, the SEAPI system offers a thorough classification that extends beyond the typical two-part classification of UI (stress versus urge) (20). Furthermore, the implementation of this staging system ensured a standardized approach to diagnosing and categorizing UI, enabling comparisons among patients and across different studies. This systematic classification helped identify the primary type of incontinence in each patient and played a crucial role in determining appropriate treatment strategies tailored to individual needs (18).

Women answered a questionnaire about their demographics, including age, education, menopausal status, parity, number of home births, obstetric events like prolonged second stages of labor, birth weight, urinary frequency, diurnal as well as nocturnal voids, associated symptoms like burning micturition, and medical history (including hysterectomy, cesarean delivery, incontinence surgery, and activity limitations. Stress, urge, and mixed types of incontinence were identified. Women were diagnosed with stress incontinence if they experienced uncontrollable leakage of urine while laughing, sneezing, or carrying heavy objects. Those who experienced an urgent need to urinate that occurred suddenly were referred to as suffering from "urge symptoms." Epi Info was used for the data analysis (22). All participants signed an informed consent form before participating in the study. Participants were informed in their native language of the study's aims and procedures. It was made clear to those surveyed that their refusal to participate in the poll was not reflective of the standard of treatment they received.

Statistical Analysis

The study used IBM SPSS Statistics software to analyze relationships between pre- and post-counseling outcomes. The chi-square test was used to determine significant differences between pre- and post-counseling outcomes. The software provided tools for data analysis and calculating p-values for comparisons, where a p-value <0.05 is considered statistically significant (23).

Results

The majority of respondents were between the ages of 41 and 50. Figure 1 and the survey results indicate that 371 out of 500 women (74.2%) were continents and 129 (25.6%) are incontinent. Stress incontinence (57.3%), urge incontinence (5.4%), and mixed incontinence (3.1%) were the three most prevalent types among the 129 women who were incontinent. Women with incontinence had a mean age of 43 years and a mean

parity of 14.33 Table 1. We also looked into the various risk factors these women were dealing with, such as the fact that 38.7% of them were postmenopausal and that 8.5% of them had diabetes or asthma. The calculated percentage is displayed in Table 2. Incontinence affected 56.5% of women who drank tea regularly. Table 3 summarizes the types of births experienced by incontinent women, with normal vaginal births, abnormal vaginal births, and cesarean sections accounting for 37.9%, and cesarean sections accounting for 28.6%. Patients' symptoms are listed in Table 4. Over the course of the 14-month study, women who were incontinent and had trouble with daily tasks reported having UI with coughing and sneezing (57.3%), UI with urgency (33.3%), UI with coughing and sneezing (14.7%), and other symptoms. Seventy-four people had stress incontinence with urinary leakage during coughing and sneezing, although 37.8% only had minor leakage on occasion, scoring 1 (Table 5). There were 12 cases of mixed incontinence (9.3%) and 43 cases of urge incontinence (33.3%). The incontinence rate was significantly higher among consulters (115/420; 27.3%) than among non-consulters (14/80; 17.5%; p=3.88). Of the 129 women, 2.32% had undergone abdominal hysterectomy, 4 (3.1%) had undergone vaginal hysterectomy, 2 (1.55%) had undergone anterior colporrhaphy, and 4 (3.1%) had undergone posterior colporrhaphy (Table 6). Among those who performed the Valsalva procedure, the average Q-tip angle deviation was 63.40° out of 129 participants. UI is strongly correlated with consultative behavior and certain risk factors. The study found that stress incontinence was more common among women who had given birth vaginally, whereas urge symptoms were more prevalent among women who had undergone hysterectomy. The results suggest that different types of incontinence have different risk factors and require tailored treatment approaches.

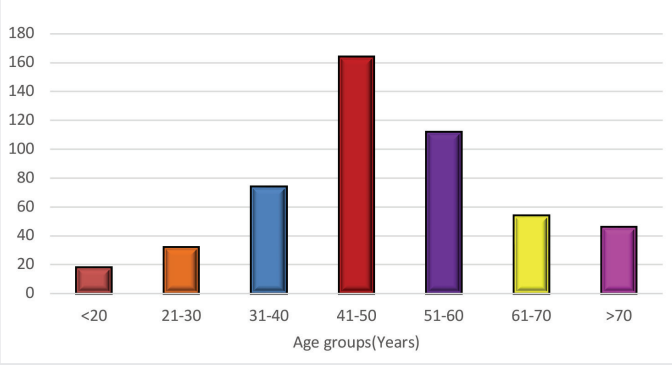

Figure 1. Age-related (years) distribution of urinary incontinence (%)

Table 1. Baseline characteristics of risk factors (n=129)

Risk factor	Range	Mean
Age	19-71	43
Parity	1-12	2.94
Height (cm)	132-176	152
Weight (kg)	43-76	43
BMI	15-29	25.8
Pad weight gain	1-32	4.9
Post-void residue	5-108	21.5

BMI: Body mass index

Table 2. Other risk factors

Risk factor	Consulters, (n=115)	Non-consulters, (n=14)	(n, %)
Diabetes	9	2	11 (8.5%)
Asthma	7	1	8 (6.2%)
Tea	67	6	73 (56.5%)
Tobacco	14	2	16 (12.4%)
Postmenopausal	42	8	50 (38.7%)

Discussion

Healthcare providers should consider a woman's reproductive history and surgical interventions when developing a treatment plan for UI. Differentiating between stress and urge symptoms is crucial because they may have distinct underlying causes (24). Further research could explore the effectiveness of targeted interventions for each type of incontinence, potentially leading to more successful management and improved quality of life for women experiencing these symptoms. Lifestyle factors, such as diet, exercise, and medication, can also play a

Table 3. Mode of delivery

Mode of delivery	Number	%
Normal vaginal delivery		
0	2	1.5
1	11	8.52
2	21	16.2
3	11	8.52
>4	4	3.1
Total	49	37.98
Cesarean section		
1	19	14.7
2	12	9.3
3	6	4.6
Total	37	28.6
Abnormal vaginal delivery		
Prolonged first stage	23	17.8
Prolonged second stage	11	8.52
Instrumental delivery	6	4.6
Birth weight >4 kg	3	2.3
Total	43	33.3

Table 4. Symptoms

Symptoms	Number	%
Urine leakage with cough and sneeze	74	57.3
Urine leakage with urgency	43	33.3
Urine leakage with cough and sneeze	19	14.7
Urgency alone	26	20.1
Urgency with frequency	18	13.9
Burning micturition	14	10.8
Nocturnal frequency	7	5.42

Table 5. Frequency of urinary incontinence

Type	Rarely score 1, (%)	Score 2 (%)	Often score 3 (%)	Most of the time, score 4 (%)	All the time, score of 5 (%)
Stress incontinence	37 (28.6)	28 (21.7)	6 (4.65)	4 (3.1)	0
Urge incontinence	7 (5.4)	12 (9.3)	17 (13.1)	7 (5.4)	0
Mixed incontinence	4 (3.1)	3 (2.3)	2 (1.5)	3 (2.3)	0

Table 6. Statistical test analysis

Test	Calculated t-value	p-value
Unpaired Student's t-test	3.88	<0.00014

crucial role in managing incontinence (25). Certain foods and beverages, like caffeine and alcohol, can exacerbate symptoms, whereas regular physical activity can strengthen pelvic floor muscles and improve bladder control. Psychological aspects of incontinence, such as embarrassment, isolation, and decreased self-esteem, should also be considered (26). Addressing these emotional issues alongside physical interventions can result in a holistic treatment approach. Education and lifestyle modification are essential components of a holistic approach to treating incontinence. Encouraging women to avoid bladder irritants, practice timed voiding, and avoid bladder irritants can also help reduce the frequency and severity of incontinence episodes (27). By addressing the multifaceted nature of incontinence, healthcare professionals can significantly improve women suffering from this condition.

Understanding the causes of stress, incontinence, and urge symptoms in relation to vaginal childbirth and hysterectomy is crucial for effective management and treatment (28). Factors such as weakened pelvic floor muscles and nerve damage can contribute to stress incontinence. The removal of the uterus can disrupt the normal communication between the bladder and brain, leading to sudden and uncontrollable urges to urinate (29). Healthcare professionals can tailor treatment plans that include pelvic floor exercises, medication, and behavioral interventions to manage and alleviate symptoms, ultimately improving the overall well-being of affected women (30). Hysterectomy can also result in a decrease in estrogen levels, which can further contribute to the development of urge symptoms. Hormone replacement therapy may help restore hormonal balance and reduce urge symptoms. Healthcare professionals can provide comprehensive care to women who have undergone hysterectomy, including hormone replacement therapy, pelvic floor exercises, lifestyle modifications, and counseling to address emotional or psychological factors that may be exacerbating urge symptoms (31). A holistic approach focusing on both physical interventions and mental and emotional well-being can help women manage and alleviate the symptoms associated with hysterectomy-induced urge symptoms. By combining pelvic floor exercises, lifestyle modification, and counseling, healthcare professionals can empower women to regain control over their bladder function and improve their overall quality of life (32). Research on lifestyle factors and dietary habits that contribute to urge symptoms could help educate women on how to modify their behaviors to lower their risk. Understanding genetic and hormonal factors can lead to targeted interventions or medications to prevent the onset of symptoms, particularly for women at a higher risk of developing incontinence after a hysterectomy. The risk of incontinence can be reduced by adopting a healthy lifestyle, including regular exercise and maintaining a healthy weight. Hormonal therapy or alternative surgical techniques can also help prevent the onset of symptoms in high-risk individuals (33). Comprehensive understanding and targeted interventions empower women to take control of their health and mitigate potential challenges associated with incontinence after a hysterectomy. Regular exercise and maintaining a healthy weight can also contribute to overall pelvic floor health, such as with kegel exercises (34). Education and awareness about pelvic floor health should be prioritized, as early intervention and preventive measures can significantly improve women's quality of life post-hysterectomy. Palacer floor physical therapists can also greatly contribute to pelvic floor health. They are trained to assess and treat pelvic floor dysfunction, offering personalized treatment plans and techniques to address specific issues (30). Incorporating these therapies into post-hysterectomy care can help women recover faster and improve their overall well-being. Pelvic floor therapy plays a crucial role in the holistic recovery process after a hysterectomy, promoting physical, emotional, and sexual well-being for women (16).

This study explored the pros and cons of various treatments for UI, enabling informed decisions by patients and healthcare providers (35). The study also explores the long-term outcomes and cost-effectiveness of these interventions, providing valuable insights into sustainable strategies. This comprehensive examination of treatment options can lead to improved patient quality of life and efficient healthcare resource allocation (18). By tailoring treatments to individual patients' needs and preferences, healthcare providers can increase patient satisfaction and adherence to treatment plans, ultimately improving treatment outcomes (36). Learning about the long-term effects and cost-effectiveness of these interventions can help shape healthcare policies and guidelines, making better use of resources and possibly easing the strain on the healthcare system (28). This holistic approach can lead to better patient care, enhanced health outcomes, and a more efficient and sustainable healthcare system. Incorporating patient feedback and involving patients in decision-making processes can also improve treatment outcomes (37). Empowering patients and fostering better communication between healthcare providers and patients can improve treatment outcomes and overall patient satisfaction. By combining these strategies, healthcare systems can achieve a more patient-centric, effective, and sustainable approach to care.

Study Limitations

One limitation of this study is the small sample size, which may limit the generalizability of the findings to other populations. Additionally, the study relied on self-reported data, which may introduce recall bias and underreporting of UI cases. Furthermore, this study only included

patients from one tertiary care hospital, which may not be representative of the overall population in India. Future research should include larger sample sizes and diverse populations to obtain more comprehensive and accurate results regarding the prevalence and risk factors of UI in India.

Conclusion

A cross-sectional analysis was conducted to examine the prevalence, types, and associated factors of UI among female patients at a specialized medical center in India between November 2022 and April 2023. The study's generalizability may be limited due to the clinic's focus on women seeking specialized care, potentially oversampling health-conscious individuals or those with severe UI symptoms. Disparities in socioeconomic status, health literacy, and awareness regarding UI treatment across different demographic groups could influence patient selection and affect the study outcomes. Despite these limitations, the present study contributes to our understanding of the prevalence, types, and risk factors of UI among women attending a tertiary care facility in India, highlighting the need for further research and interventions to address this significant public health issue.

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Hemoglobin Level as a Prognostic Factor of Neoadjuvant Chemoradiotherapy in Patients with Rectal Cancer

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ABSTRACT

Introduction: This retrospective study aimed to determine the effect of pre-treatment hemoglobin (Hgb) value on the prognosis of patients with advanced rectal carcinoma undergoing neoadjuvant chemoradiotherapy (nCRT) in terms of pathologic complete response (pCR).

Methods: A total of 192 individuals with rectal cancer who underwent nCRT were included in the study between 2011 and 2019. The patients were separated into anemic and non-anemic categories based on pretreatment Hgb values (Hgb <11 gr/dL).

Results: The Hgb threshold for defining anemia was assessed using receiver operating characteristic curve analysis. Of the 48 (25%) patients, 144 (75%) were in the non-anemic group. The median overall survival (OS) time was 27 months in the anemic group and 69 months in the non-anemic group patients (p=0.028). No statistically significant difference was observed in disease-free survival between the groups. When comparing the two groups "patients" pCR and partial response ratio was elevated in the non-anemic group (p<0.001). In anemic groups patients, female, median age, >60 years, and CA19-9 value was high (p=0.021, p=0.042, p=0.014 and p=0.030). In logistic regression analysis for pCR, tumor regression grade (0-1 vs. 2-3) and pathologic T-stage (0 vs. 1-2) was statistically significant (p<0.001 and p=0.03), anemia (Hgb <11 gr/dL vs. >11 gr/dL) was not statistically significant (p=0.219).

Conclusion: In the group with lower pretreatment Hgb values (<11 gr/dL), the pCR, partial response, and OS time were lower. However, Hgb levels with a cut-off of 11 gr/dL were not statistically proven to be prognostic factors for rectal carcinoma treated with nCRT.

Keywords: Rectal cancer, anemia, concurrent chemoradiotherapy, complete response

Introduction

Neoadjuvant chemoradiotherapy (nCRT) plays a significant role in locally advanced rectum cancer. It is currently the preferred treatment modality to resect tumors and preserve the rectal sphincter (1,2). While most patients receiving nCRT will experience tumor shrinkage, approximately 10-30% are expected to exhibit a pathological complete response (pCR), indicating the lack of living tumor cells in the excised specimen (3). Some patients achieve pCR, whereas others show significantly different results. It is unclear which patients will respond well to neoadjuvant therapy and whether responders will benefit from systemic adjuvant therapy. The reason for the difference in treatment responses is that their predispose to radiosensitivity is different. The ability to identify more radiosensitive patients using genetic, clinical, and histopathological biological markers may permit personalized intervention, better treatment, and lower local recurrence.

The prognostic factors currently known for rectal cancer receiving nCRT include age, carcinoembryonic antigen (CEA), tumor grade, total mesorectal resection, surgical margin, postoperative lymph node status, and pCR (4-6). Complete pCR after neoadjuvant therapy has been considered one of the most important prognostic response indicators. The ability to anticipate the pCR outcome among individuals receiving nCRT may allow for the provision of more individualized treatments. Individuals anticipated to exhibit good sensitivity to nCRT could be considered for the organ-preserving "watchful waiting" strategy, whereas those anticipated to exhibit poor sensitivity could be considered for the "total neoadjuvant therapy" strategy (7-9).

Tumor hypoxia is an indicator of resistance to radiotherapy (RT) and chemotherapy in various tumors, including colorectal cancer. As a result of hypoxia, neo-angiogenesis is caused in the tumor with the help of increased free radicals in the blood, which turns the tumor into an aggressive tumor resistant to apoptosis (10,11). Reduced hemoglobin (Hgb) concentration is considered an indirect sign of tumor hypoxia. Several studies have revealed that low pre-treatment Hgb values can be prognostic factors for chemoradiotherapy responses, tumor control, and survival outcomes in individuals diagnosed with rectal carcinoma (12,13). This investigation aimed to assess patients who reached pCR after

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nCRT in treatment and to illustrate the effect of low pre-treatment Hgb levels on pCR.

Methods

Patients' Characteristics

In this retrospective analysis, we assessed 192 individuals recently confirmed to have locally advanced rectal carcinoma following biopsy. The patients underwent nCRT between February 2011 and December 2019. The acceptability requirements included that the individuals must be over 18 years of age, Karnofsky performance ≥70 and diagnosed with histologically confirmed rectal cancer who had no prior rectal RT, who had not received palliative RT, had no distant metastasis and had not a blood disease that would cause anemia. Moreover, patients who underwent wait-and-see treatment were not included in the study.

Approval for the investigation was granted by the Institutional Review Board of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 17, date: 14.01.2022), aligning in accordance with the guidelines outlined in the Declaration of Helsinki. Informed consent was secured from all participants following a comprehensive description of the research. Relevant pathology and laboratory findings were extracted from the medical facility records, while information regarding post-treatment monitoring was sourced from the medical records.

Data on Chemoradiotherapy

Before undergoing nCRT, all individuals underwent diagnosis through biopsy. Each patient received external beam RT administered in daily fractions of 1.8-2.0 Gy, utilizing 6/18 megavolt photon radiation beams, five days per week, spanning a 6-week duration, facilitated by linear accelerators. RT was delivered through either the four-field box three-dimensional conformal technique or the field-in-field intensity modulated radiotherapy. The clinical target volume comprised both the tumor mass volume and the lymph nodes in the pelvic region, including their immediate extensions. The treatment planning volume was determined by adding a 1 cm clearance around the rectum and a 0.7 cm clearance around the pelvic lymph nodes to the clinical target volume. Each patient underwent a phase 2 tumor boost, with the rectum and pelvic lymph nodes receiving doses of 40-45 Gy, while the tumor(s) were irradiated with an administered dose of 50.4 Gy.

Concurrent chemotherapy was administered continuously during RT. The chemotherapy protocol included continuous infusion of 5-fluorouracil (5-FU) intravenously (180 mg/m^2/day) for a duration of 7 days or orally administered 5-FU-derived capecitabine (825 mg/m^2 twice a day) for a period of 5 days concurrent with RT. Postoperatively, individuals were directed to the medical oncology facility for adjuvant chemotherapy.

Evaluation of Therapeutic Outcome and Posttreatment Monitoring

Treatment toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 3.0. Throughout RT, patients underwent weekly evaluations, including clinical examinations, along with blood count and biochemistry parameter analysis. Pelvic magnetic resonance imaging (MRI) and colonoscopy were used to assess treatment response after 8-12 weeks of nCRT. After surgery, the treatment response was assessed by a gastrointestinal pathologist. The tumor regression grade (TRG) was measured using the modified Ryan classification. In the context of the modified Ryan classification, TRG0 corresponds to a pCR, TRG1 indicates the presence of several clusters of tumor cells, TRG2 indicates residual tumor, and TRG3 denotes no response (14).

Follow-up assessments included physical examinations and radiological scans every 3 months. The follow-up schedule comprised evaluations every 3 months for the initial 2 years and subsequently shifted to every six months for 3-5 years. Throughout the follow-up period, patients exhibiting suspected local or regional recurrence underwent MRI examinations for further evaluation.

Statistical Analysis

Patient and treatment characteristics were compared between the low Hgb and high (Hgb) Hgb groups using Pearson's chi-square test. The Mann-Whitney U test was used to evaluate non-parametric variables. Osteosarcoma (OS) and disease-free survival (DFS) were analyzed in both groups using Kaplan-Meier survival curves. The time between the onset of nCRT and either the last visit or the time of death was defined as OS. DFS was characterized by the time span between the inception of nCRT and disease progression. The factors associated with pCR were identified using binary logistic regression. The analysis was conducted with a significance level of 5% and a confidence interval of 95% using SPSS version 17.0 for windows (Chicago, IL, USA)

Results

The study included 192 individuals diagnosed with locally advanced rectal cancer. Patients were categorized into anemic (n=48 , 25%) and non-anemic (n=144, 75%) groups according to Hgb levels. During the analysis of the receiver operating characteristic (ROC) curve, the cut-off Hgb was identified at 11.1 g/dL [area under the curve (AUC): 602 sensitivity 83.8% and specificity 85.1%], which showed significant correlations with median OS (p=0.13). Table 1 presents the baseline parameters of patients and treatment characteristics. Comparative analyses showed that female patients (n=23, 35.9%) were found in the anemic group more than male patients (n=25, 19.5%), and this was statistically significant (p=0.021). The mean age was 65.5 (27-84) years in the anemic group and 59 (24-83) years in the non-anemic group, and there was a significant difference (p=0.042). The proportion of patients with mean age ≥60 (n=24, 35.8%) years and pre-treatment CA19.9 (33.5 ng/dL) level was elevated in the anemic group compared with the non-anemic group (p=0.014 and p=0.030). After nCRT, the pCR and partial response rates were higher in patients in the non-anemic group (n=25, 83.3% and n=95, 93.1%, respectively).

The Kaplan-Meier curves DFS and OS time are shown (Figure 1A, B). No statistical difference was found when the DFS value was evaluated in both groups. The median OS time was longer in the non-anemic group (69 versus 27 months). The 3-year OS was 71 in the non-anemic group and 58 in the anemic group patients (p=0.028). The 3-year DFS was 69 and 68% in the non-anemic group and 68% in anemic group (p=0.358).

Table 1. Comparison of anemic and non-anemic groups of patient's characteristics and treatment results

	Anemic, (n %)	Non-anemic, (n %)	Total, (n)	p-value
Gender				
Female	23 (35.9%)	41 (64.1%)	64	0.021
Male	25 (19.5%)	103 (80.5%)	128	
Median age	65.5 (27-86)	59 (24-83)	192	0.042
Age group				
≤60	24 (19.2%)	101 (80.8%)	125	0.014
>60	24 (35.8%)	43 (60.2%)	67	
CEA, ng/dL	30	17	20.5	0.222
CA19-9, ng/dL	33.5	13.5	47	0.030
cT-stage				
2-3	37 (24.3%)	115 (75.7%)	152	0.685
4	11 (27.5%)	29 (72.5%)	40	
cN-stage				
N0	1 (12.5%)	7 (87.5%)	8	0.682
N1-2	47 (25.5%)	137 (74.5%)	184	
pT-stage				
T0	6 (19.4%)	25 (80.6%)	31	0.602
T1-2	17 (28.8%)	42 (71.2%)	59	
T3-4	25 (24.5%)	77 (75.5%)	102	
pN-stage				
N0	29 (22.8%)	98 (77.2%)	127	0.380
N1-2	19 (29.2%)	46 (70.8%)	65	
Tumor regression grade				
0-1	15 (22.7%)	51 (77.3%)	66	0.726
2-3	33 (26.2%)	93 (73.8%)	126	
Chemoradiotherapy response				
Complete response	5 (16.7%)	25 (83.3%)	30	<0.001
Partial response	42 (8.9%)	95 (93.1%)	102	
Stabil response	36 (60.0%)	24 (40%)	60	

CEA: Carcinoembryonic antigen, CA19-9: Carbohydrate antigen 19-9

When all patients were included in the pCR analysis, the outcomes of the binary logistic regression analysis are presented in Table 2. Before nCRT, Hgb was found to be insignificant for pCR (anemic vs. non-anemic, p=0.219). TRG and after treatment pathologic T-stage were found to be significant (0-1 vs. 2-3, p<0.001 and 0 vs. 1-2, p=0.03).

Discussion

In this study, 192 patients with rectal carcinoma who received nCRT indicated that pretreatment Hgb levels were related to markedly poorer overall survival times. Furthermore, we demonstrated that high pretreatment Hgb levels were strongly associated with pCR in patients undergoing nCRT for rectal cancer.

Radiobiology has shown that hypoxia is responsible for the development of chemoresistance and radioresistance in numerous tumors (15,16). This has been studied under the name of re-oxygenation, which is called the 5-R of RT. In the presence of sufficient O_2 in the environment, therapeutic radiation has a greater effect. Enhancing the oxygen-carrying capacity of blood can improve tumor oxygenation and, consequently, tumor radiosensitivity. It is known that 40-60% of patients with malignancy experience anemia at the initiation of RT, and those with anemia generally exhibit a less favorable prognosis than individuals with normal Hgb values (17,18). Consequently, many studies have investigated the impact of anemia on outcomes in the treatment of rectal carcinoma (19,20).

The World Health Organization threshold for anemia is 12 g/dL for women and 13 g/dL for men (21). Many studies have used ROC analysis to determine the Hgb cut-off value (such as, 12 g/dL, 11 gr/dL) for the definition of anemia before treatment (22,23). We determined our cut-off value for the definition of anemia by ROC analysis. As a result of ROC analysis according to OS and DFS, we determined our cut-off value as 11 gr/dL (AUC: 602 sensitivity 83.8% and specificity 85.1%, p=0.013). We attributed the reason why the cut-off value was lower than the cut-off values in other studies, the bleeding before diagnosis in advanced rectal patients.

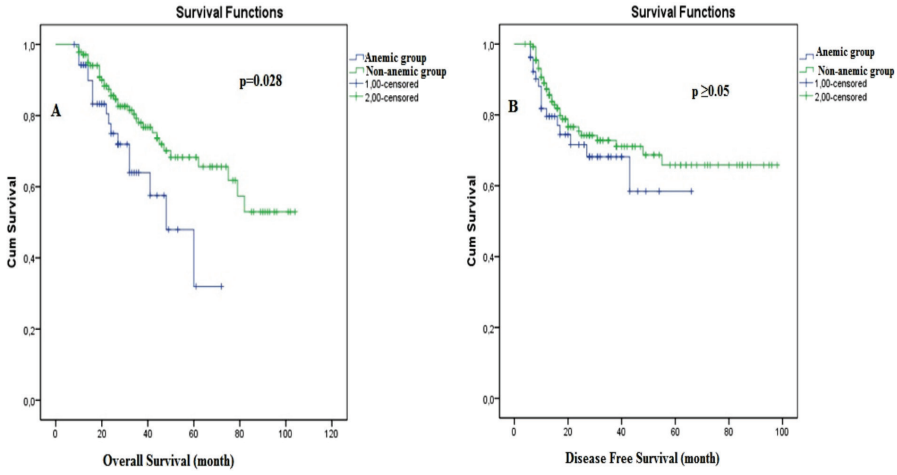

Figure 1. A) Kaplan-meier curve for OS, B) Kaplan-meier curve for DFS
OS: Osteosarcoma, DFS: Disease-free survival

Table 2. Binary logistic regression analysis of pCR

	HR	95%	p-value
Gender (female vs. male)	0.547	0.250-1,196	0.131
Age group (<60 vs. ≥60 years)	0.601	0.253-1,430	0.250
Clinic T-stage (2-3 vs. 4)	0.309	0.103-1,248	0.107
Clinic N-stage (0-1 vs. 2)	0.733	0.880-6,180	0.775
Pathologic T-stage (0 vs. 1-2)	0.107	0.025-0.465	0.003
(0 vs. 3-4)	0.522	0.325-1,311	0.145
Pathologic N-stage (0 vs. 1-2)	0.854	0.952-1,786	0.320
Tumor regression grade (0-1 vs. 2-3)	0.033	0.010-0.115	<0.001
Pretreatment hemoglobin (anemic vs. non-anemic)	0.528	0.191-1,462	0.219

HR: Heart rate, pCR: Pathologic complete response

In the investigation by Box et al. (19) 100 individuals diagnosed with rectal cancer and treated with nCRT were included. Among 25 individuals who were experiencing anemia (< mean Hgb value 12.4 g/dL), 75 patients were found to be non-anemic (>mean Hgb value 12.4 g/dL). Overall survival at 2 years was significantly higher in the non-anemic patients (p=0.021). In contrast, Khan et al. (20) study, who evaluated 463 patients with rectal cancer patient. They found that the Hgb cut-off value was 12 g/dL, and they could not show an association between Hgb level and overall survival or distant metastasis. In our study, we found that Hgb cut-off value 11 gr/dL and overall survival were higher in the non-anemic group (p=0.028).

Another vital finding of our study was Hgb <11.0 g/dL was effective for achieving a pCR. We found a statistically significant pCR in non-anemic and anemic individuals (p<0.01). While pCR was obtained in 5 (16.7%) patients in the anemic group, pCR was assessed in 25 patients (83.3%) in the non-anemic group. In addition, partial response was assessed in 42 patients (8.9%) in the anemic patient group, while it was assessed in 95 patients (93.1%) in the non-anemic group. Similarly, in the study of Box et al. (19), pCR was obtained in 7 (28%) of 25 anemic patients, whereas pCR was obtained in 41 (54%) of 75 non-anemic patients (p=0.028).

In a study by McGrane at al. (12), 273 individuals with rectal cancer who underwent nCRT were analyzed. Among these patients, 63 (23%) exhibited Hgb levels <120 g/L at diagnosis. Grades of Rectal Cancer Regression was worse (less regression, χ^2=10.14; p=0.006), and mortality rates were higher in anemic individuals than in non-anemic individuals. Our findings also showed that pCR, partial response, and survival were elevated in non-anemic individuals.

Wallin et al. (24) assessed the influence of various factors, including patient characteristics, tumor stage and size, circumferential extent, tumor location, and CEA pretreatment levels, on the occurrence of pCR following CRT. Their findings revealed a significant association between a smaller mean tumor size (4.7 vs. 4.2 cm; p=0.02) and a lower pretreatment CEA (9.6 vs. 3.4 ng/mL; p=0.008) and the occurrence of pCR. In our study, pretreatment CA19-9 levels were higher in anemic patients (33.5 gr/dL vs. 13.5 gr/dL, p=0.030). Logistic regression analysis showed that TRG (0-1 vs. 3-4) and pathologic T-stage (0 vs. 1-2) was statistically significant (p<0.001 and p=0.03). Low pretreatment Hgb level (<11 gr/dL) was not significantly associated with pCR, but low Hgb level was associated with OS.

Study Limitations

Some limitations inherent to our study comprise; First, it is not clear whether low Hgb values before treatment occur *de novo* (e.g., family history of anemia) or are due to bleeding. Moreover, this study did not examine whether blood transfusion or an erythropoiesis-stimulating agent is used due to anemia was not examined in this study. The second significant limitation is toxicity due to nCRT treatment, and discontinuation of treatment is one of the factors affecting the pCR response. The relationship between treatment side effects and anemia was not investigated in our study.

Conclusion

Based on the outcomes of the investigation, patients with pretreatment anemia had poorer survival than those with non-anemia who underwent nCRT for rectal cancer. Although pCR and partial response were higher in

patients without anemia, anemia could not be identified as a prognostic factor affecting pCR.

Ethics Committee Approval: The present study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 17, date: 14.01.2022).

Informed Consent: Informed consent was secured from all participants following a comprehensive description of the research.

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

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Risk of Hypocalcemia and Osteoporosis due to Vitamin D Deficiency in Patients Undergoing Sleeve Gastrectomy and Bypass Surgery for Obesity

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ABSTRACT

Introduction: Obesity is a chronic disease that is increasing worldwide. It is known that mineral and vitamin deficiencies develop in obese individuals. Surgical treatment options are becoming increasingly common for the permanent and effective treatment of obesity. It was observed that mineral and vitamin deficiencies increased after surgical interventions. The aim of this study was to investigate the efficacy of laparoscopic sleeve gastrectomy (LSG) and combined Roux-en-Y Gastric Bypass (RYGB) methods for weight loss in obese patients and their effects on vitamin D, calcium^{+2} (Ca^{+2}), parathyroid hormone (PTH), and P levels and the risk of osteoporosis in patients after surgery.

Methods: The study included 50 patients who underwent LSG and 47 patients who underwent RYGB. Routine preparations and standard surgical procedures were performed. Body mass index, blood vitamin D, Ca^{+2}, PTH, and P levels were measured preoperatively and postoperatively at 3-month intervals for 12 months. Data were analyzed using independent and dependent t-tests.

Results: Preoperative hypocalcemia was observed in both groups (LSG: 14%, RYGB: 19.1%). It was observed that both surgical methods were effective for weight loss. Postoperative hypocalcemia rates increased in both groups (LSG: 26%, RYGB: 33.3%). After vitamin and mineral supplementation, hypocalcemia rates improved but could not be brought to normal levels. In addition, decreased vitamin D and PTH levels were observed after the surgical intervention.

Conclusion: Low vitamin D and Ca^{+2} levels were increased in patients after bariatric surgery. Mineral and vitamin supplementation decreased these decreases but did not increase their normal levels. This treatment is thought to increase the risk of osteoporosis. It would be useful to investigate the effects of higher-dose supplements.

Keywords: Obesity, bariatric surgery, vitamin D, Ca^{+2}, hypocalcemia, PTH and P, osteoporosis

Introduction

Obesity is a chronic disease that is increasing worldwide (1). The first treatment methods to be tried are lifestyle changes, diet, exercise, medication, and hormonal therapies. However, surgical treatment may be required when these methods are inadequate (2). Laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y Gastric Bypass (RYGB) are the two most commonly used methods for the treatment of obesity (3). In these surgical methods, changes are made in the anatomy of the gastrointestinal system, which may affect vitamin and mineral absorption. Vitamin and mineral deficiencies, such as vitamin D, calcium^{+2} (Ca^{+2}), and potassium, are known to be present in obese patients. It can be predicted that deficiencies in these values may increase after surgical treatment. However, there is limited information on vitamin D, Ca^{+2}, parathyroid hormone (PTH), and P levels in patients undergoing bariatric surgery after surgical interventions. In this study, we aimed to compare the preoperative and postoperative vitamin D, Ca^{+2}, PTH, and P levels of patients undergoing LSG and RYGB.

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Methods

In our study, we retrospectively evaluated the data of 97 patients who underwent bariatric surgery for obesity between 01.01.2015-01.03.2016 at University of Health Sciences Turkey, İstanbul Training and Research Hospital. The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 164, date: 20.05.2022). Informed consent was obtained from the patients. The first group (group 1) included patients who underwent sleeve gastrectomy surgery, which is a volume restriction method, and the second group (group 2) included patients who underwent RYGB surgery, which is a volume restriction and malabsorption method. Twenty-four male and 73 female patients were included in the study. Birth dates, sex, height, weight, Ca, phosphorus, PTH, and vitamin D levels were recorded preoperatively and at 3, 6, 9, and 12 months. Patients with missing preoperative and postoperative laboratory data were excluded from the study.

Statistical Analysis

Prior to further analyses, Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of the variables. Non-parametric methods were used for non-normally distributed variables. Subsequently, the Mann-Whitney U test was used to compare the variables obtained from the measurements between groups. Chi-square and Fisher's exact tests were used to analyze the relationships or differences between groups regarding categorical variables. Repeated measures tests was used for comparison of repeated measurements. Periodic comparisons of values were performed using the paired sample t-test. Comparative results between groups based on other demographic characteristics are presented as the ratio of qualitative variables. Quantitative variables are expressed as mean and standard deviation. Statistical analysis was performed using the SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

Preoperative demographic characteristics, weight-height measurements, body mass index (BMI), mean age, Ca^{+2}, phosphorus (P), PTH, and vitamin D values of the patients included in the study are presented in Table 1.

Preoperative height, Ca^{+2}, PTH, and vitamin D values were similar between the patients were similar (p>0.05). The mean weight and BMI of the patients in group 1 were significantly lower in group 1 than in group 2 (p<0.001). The age of those in group 2 was higher than that of group 1 (p=0.006).

The postoperative body weight changes of the groups are shown in Table 2, Figure 1.

There was a significant difference between the body weights of both groups. Although this difference decreased over time, it remained statistically significant. In all follow-up periods, the weight of patients in group 2 was higher than that of patients in group 1 (p<0.001).

It was observed that both groups lost weight significantly in the measurements made in the 3-month periods, and this significance continued to decrease steadily from the date of surgery until the 12th month when the last controls were made (p<0.001) (Table 2, Figure 1).

The difference between the BMIs of both groups decreased over (p<0.001).

It was observed that both groups lost weight and their BMIs decreased significantly in the measurements performed at 3-month intervals (p<0.001) (Table 2, Figure 2).

The measured Ca^{+2} values of the groups are shown in Table 2, Figure 3.

Ca values were similar between the groups in almost every period. Only in the 9th month was the Ca value slightly higher in group 2 (p=0.037). In addition, no regular increase or decrease in Ca value was detected during the follow-up. In group 1, preoperative Ca values were significantly higher than those in the 3rd, 6th, and 9th months (p=0.009). In group 2, preoperative Ca values were significantly higher than those in the 3rd and 9th months (p=0.016).

The P levels of the groups are shown in Table 2, Figure 4. No significant difference in phosphorus values was observed between the groups in phosphorous values (p>0.05). In addition, when each group was

Table 1. Demographic and clinical data of the patients

	Sleeve gastrectomy (I)	Roux N-Y gastric bypass (II)	p
Age	47.9±10.3	55.2±14.3	**0.006**
Gender			
Male	14 (28%)	7 (14.9%)	0.14
Female	36 (72%)	40 (85.1%)	
Height (cm)	164.4±9	161.8±8.4	0.16
Preoperative weight (kg)	137.2±116.3	141.4±16	**<0.001**
Preoperative BMI (kg/m^2)	44.6±5.5	53.7±6.5	**<0.001**
Preoperative Ca (mg/dL)	9.3±0.7	9.3±0.5	0.66
Preoperative P (mg/dL)	3.7±0.4	3.9±0.8	0.58
Preoperative PTH (IU)	58.2±25.3	56.6±23.5	0.75
Preoperative vitamin D (IU)	14±6.6	19.5±13.1	**0.045**

BMI: Body mass index, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone

evaluated individually, no regular increase or decrease in phosphorous value was detected during follow-up. In group 1, preoperative phosphorus value was significantly lower than in the 3rd, 6th, 9th, and 12th months (p<0.001). In addition, the phosphorus value in the 3rd month was lower than in the 6th, 9th, and 12th months (p<0.001). In group 2, preoperative phosphorus value was significantly lower than in the 3rd, 6th, 9th, and 12th months (p<0.001).

The PTH values of the groups are presented in Table 2, Figure 5. PTH levels did not differ significantly between the groups (p>0.05). In addition, when each group was evaluated individually, no regular increase or decrease in PTH levels was detected during follow-up.

Vitamin D values are shown in Table 2, Figure 6. Vitamin D level was found to be higher in group 2 only in the preoperative period (p=0.045). No significant difference was observed between the two groups during the other periods. In addition, when each group was evaluated individually, no regular increase or decrease in vitamin D value was detected during follow-up.

Table 2. Clinical and laboratory data of the groups

		Sleeve gastrectomy (I)	Roux N-Y gastric bypass (II)	p
Weight (kg)	Preoperative	137.2±116.3	141.4±16	**<0.001**
	3rd month	105.5±17.2	122.7±15.1	**<0.001**
	6th month	93.7±15	107±14.3	**<0.001**
	9th month	85±13.4	94.3±12.3	**<0.001**
	12th month	78.3±11.7	83.8±10.6	**0.005**
	p	**<0.001**	**<0.001**	
BMI (kg/m^2)	Preoperative	44.6±5.5	53.7±6.5	**<0.001**
	3rd month	39±5.3	47±5.9	**<0.001**
	6th month	34.6±4.8	41.3±5.5	**<0.001**
	9th month	31.5±4.5	36.1±4.6	**<0.001**
	12th month	29±4	32.1±4.1	**<0.001**
	p	**<0.001**	**<0.001**	
Calcium (mg/dL)	Preoperative	9.3±0.7[a-c]	9.3±0.5[a,b]	0.66
	3rd month	9.1±0.8[d-f]	8.9±0.7[a]	0.24
	6th month	8.9±0.8[a,d]	9.1±0.8	0.16
	9th month	8.8±0.7[b,e]	9±0.6[b]	**0.037**
	12th month	8.9±0.7[c,f]	9.1±0.5	0.07
	p	**0.009**	**0.016**	
Phosphorus (mg/dL)	Preoperative	3.7±0.4[a-d]	3.9±0.8[a-d]	0.58
	3rd month	3.8±0.5[a,e-g]	4.2±0.8[a]	0.17
	6th month	4.1±0.6[b,e]	4.2±0.6[b]	0.61
	9th month	4.2±0.5[c,f]	4.3±0.7[c]	0.20
	12th month	4.1±0.5[d,g]	4.3±0.6[d]	0.13
	p	**<0.001**	**<0.001**	
Parathyroid hormone (IU)	Preoperative	58.2±25.3	56.6±23.5	0.75
	3rd month	60.5±27.1	63.2±31.9	0.65
	6th month	55±20.8	63.7±27.5	0.08
	9th month	53.3±19.1	58.9±20	0.16
	12th month	52.4±17.8	59.4±24.2	0.11
	p	0.06	0.06	
Vitamin D (IU)	Preoperative	14±6.6	19.5±13.1	**0.045**
	3rd month	14.5±7.3	19±11.1	0.08
	6th month	17.5±10.5	21.8±14.7	0.10
	9th month	18±12.7	20.6±13.5	0.23
	12th month	19.3±20.7	21±12.8	0.06
	p	0.13	0.55	

[a-g]: There was a statistically significant difference at the p<0.05 level between the subgroups marked with the same letters. BMI: Body mass index

Discussion

Today, obesity is a major public health problem, and it is widespread worldwide (1). Obesity was first recognized as a chronic disease by the World Health Organization in 1994 (4). In 1992, Colditz (5) identified obesity as a major risk factor for several chronic diseases (6).

Today, there are not many treatment options for obesity, which has become a major health problem and is gradually increasing. In the 90s, when attention was drawn to the health hazard of obesity, it was emphasized that medical and non-surgical treatment methods were not successful in weight loss and that patients who lost weight quickly returned to their old weight (7). In addition, in various consensus meetings, it has been stated that non-surgical treatments applied in morbidly obese patients have a low chance of success, and surgery is the most successful method to achieve permanent weight loss (8,9). Various surgical methods have long been recommended and applied for the permanent and effective treatment of obesity and its comorbidities (8,10,11).

In various studies, obese people were found to develop serious metabolic problems and various mineral and nutrient deficiencies occur (9,12-16). In addition, surgical methods applied for the treatment of obesity have been reported to cause the development of various vitamin and mineral deficiencies, although they are very successful in weight loss and correcting metabolic problems (15,17). Clinical studies have shown that problems such as anemia and bone demineralization occur after surgical interventions (18). Frame-Peterson et al. (9) a large literature review reported that surgical interventions provided

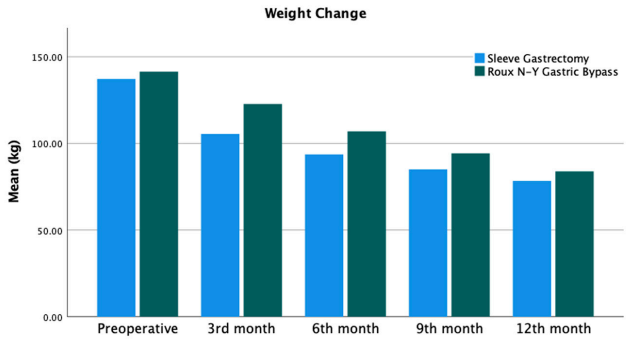

Figure 1. In-group changes in body weight values of both groups

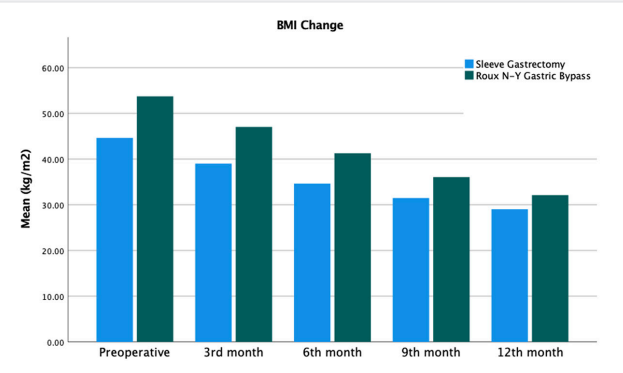

Figure 2. In-group changes in body mass index of both groups
BMI: Body mass index

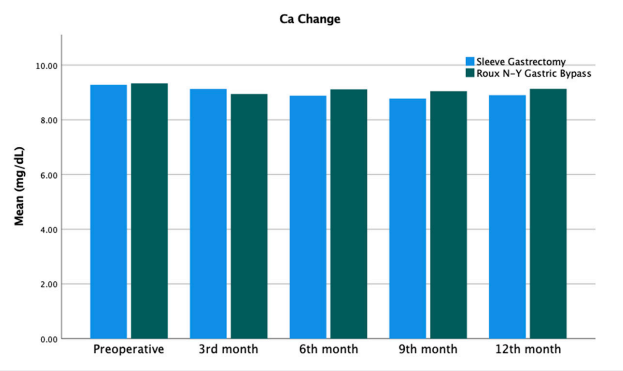

Figure 3. In-group changes in calcium values of both groups

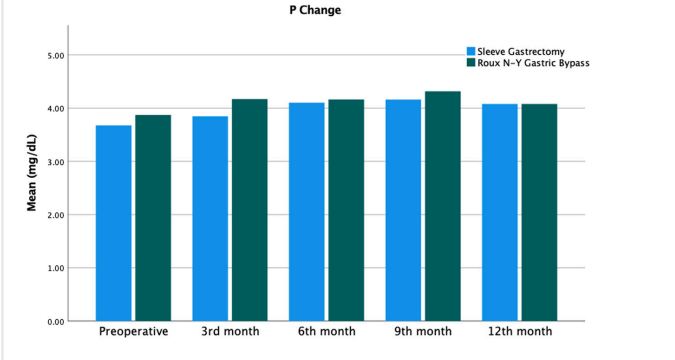

Figure 4. In-group changes in phosphorous values of both groups

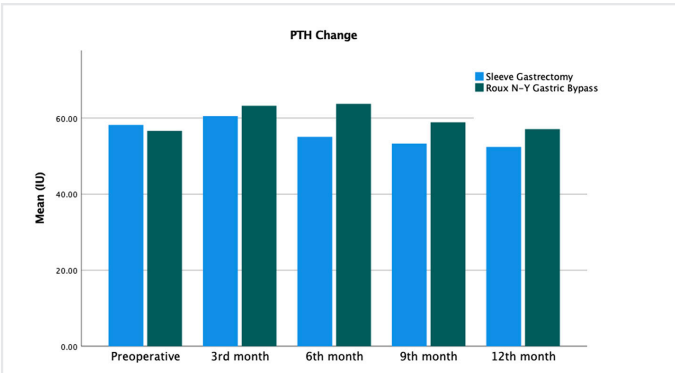

Figure 5. In-group changes in parathyroid hormone values of both groups
PTH: Parathyroid hormone

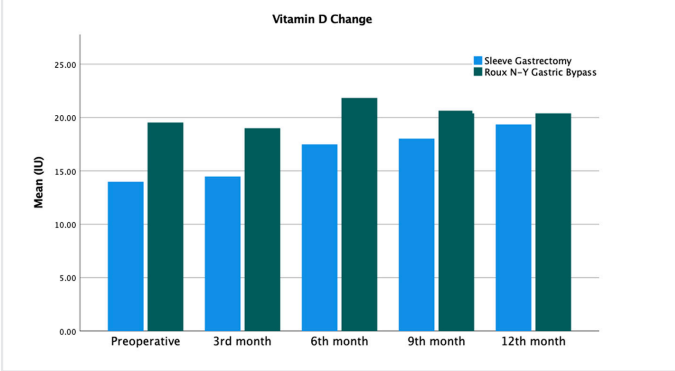

Figure 6. In-group changes in vitamin D values of both groups

effective and permanent weight loss, but severe nutritional deficiencies developed.

In our study, it was determined that 2 different surgical methods (LSG and RYGB) that we applied for the treatment of obesity effectively caused weight loss in patients (Table 2). The weight difference between the groups before and after the operation was gradually reduced. However, the difference continued to decrease at 12 months. The effects of the applied surgical methods on weight loss were in accordance with many clinical studies on this subject (8,10,12).

Ugale et al. (10) in their review emphasizing that obesity is a life-threatening pandemic disease, the authors stated that the success of bariatric surgery increased after the 1980s in parallel with technological developments. In the same study, it was reported that LSG and RYGB provided 50-75% of the excess weight in the body in a similar manner, and both methods were reported to be successful in weight loss. Lager et al. (19) In their study presenting their own clinical series, the authors stated that LSG and RYGB were similarly successful in weight loss.

In our study, we investigated vitamin D deficiency, hypocalcemia and related osteoporosis, which is a common public health problem, in obese people and the pathological conditions that occur after surgical interventions and the measures that can be taken to prevent the occurrence of these pathological conditions.

Costa et al. (12) In their clinical study, they reported that 29% of obese patients had hypocalcemia, and this rate increased to 63% after bariatric surgery. Many clinical studies on this subject have emphasized that vitamin D deficiency, hypocalcemia, and related hyperparathyroidism develop especially after bariatric surgical interventions with malabsorptive properties (9,12,13,18-21).

Costa et al. (12) they explained the reasons for the development of vitamin D insufficiency in obese people as inadequate exposure to sunlight, low mobility, overdressing, inadequate vitamin D intake, inadequate 25-hydroxylation process in the liver as a result of fatty liver developing due to obesity, and dilution of vitamin D by storage in adipose tissue, which is excessive in obese people.

Vitamin D insufficiency or deficiency in obese people causes a decrease in Ca^{+2} absorption from the intestines. The resulting hypocalcemia stimulates the release of PTH. Increased PTH attempts to balance hypocalcemia by causing the release of Ca^{+2} from the bone. However, demineralization, which is expressed as bone resorption, develops during this process, and pathological fractures may occur (12,18).

In this clinical study, patients were divided into 2 groups. A statistical significance was found between the groups in terms of BMI. It is clear that this difference was influenced by the inclusion of overweight patients in the 2nd group, as malabsorptive methods (RYGB) are more preferred in patients with higher body weights (Table 1).

The preoperative hypocalcemia rates were 14% in group 1 and 19.1% in group 2. These rates were not at the level reported in the literature (29%). This difference may be attributed to the advantageous utilization of sunlight in Turkey and the dietary habits of the Turkish people. In the 2nd group with higher BMI, the rate of hypocalcemia was significantly higher than in the 1st group (14% vs. 19.1%). This finding supports the claim that weight gain increases hypocalcemia. Asghari et al. (16) in their study of 2008 obese patients living in Tehran, they found that weight gain negatively affected blood Ca levels.

Postoperative hypocalcemia rates were higher in both groups. This finding is consistent with the literature (12,13,16,22). It has been reported that decreased Ca^{+2} intake due to restriction of food intake (LSG) and decreased Ca^{+2} absorption due to malabsorption methods (RYGB), increased adipose tissue loss due to weight loss, and increased vitamin D loss due to this loss are effective in the development of postoperative hypocalcemia (18,20). In this regard, Costa et al. (12) they made similar statements, stating that a 10% weight loss may cause a 1-2% loss in bone mass and that the reason for the loss in bone mass is both the loss in dry body weight and inadequate Ca absorption due to bariatric interventions.

In our study, no mineral supplementation was administered to patients in the first 3-6 months postoperatively. However, vitamin D and mineral supplementation (Ca^{+2}) was administered after 6 months. This supplementation prevented the increase in hypocalcemia and partially corrected it compared with the previous months, but could not bring it to normal levels (Table 2). This finding is consistent with the literature (12,20,23,24).

Moore and Sherman (23) They reported that vitamin D insufficiency developed in patients who underwent LSG and RYGB, and vitamin D insufficiency was reduced in patients who received 2,000 IU vitamin D3 and 1,500 mg Ca citrate daily, but none of the patients reached normal levels. These findings are consistent with our findings.

Muschitz et al. (18) they reported that both LSG and RYGB had a negative effect on bone metabolism and mineral density despite effective weight loss. They gave their patients 16,000 IU vitamin D daily and 1,000 mg Ca mono-citrate daily. They stated that although this application decreased vitamin D deficiency, it did not result in complete recovery.

In both groups, P (phosphorus) values were inversely proportional to the changes in Ca^{+2} levels and P levels increased inversely proportional to the decrease in postoperative Ca^{+2} levels (Table 2). Although these findings seemed to contradict physiological functioning, they were in accordance with the literature (12,20,23,24).

Normally, Ca^{+2} and phosphates interact together during bone mineralization. Vitamin D increases blood levels of both Ca^{+2} and phosphates. However, PTH increases blood Ca levels, whereas phosphates are excreted from the kidneys in the urine, leading to a decrease in phosphate levels in the blood (25). The reason for the Ca^{+2} and P discrepancy in our study may be explained by the fact that PTH, which increased in our patients due to hypocalcemia in the pre- and postoperative periods, caused a situation independent of the Ca^{+2} level in the increase or decrease of phosphates. It is possible that low vitamin D levels also contributed to this result.

In our study, PTH levels were found to increase or decrease inversely with Ca^{+2} levels and vitamin D levels (Table 2). These findings are consistent with the physiologic functioning of vitamin D and Ca^{+2} metabolism (25). PTH levels increase to compensate for hypocalcemia. Increased PTH causes an increase in blood Ca and decreases blood P levels by excreting phosphates in the urine (25,26).

Similar to the literature, vitamin D and Ca levels were found to be low in obese patients. These deficiencies are not as low as in western societies. We believe that the reason for this situation may be related to the fact that our country has the opportunity to benefit more from sunlight and the dietary habits of the Turkish people.

The LSG and RYGB methods for weight loss resulted in effective weight loss. Vitamin D and Ca deficiencies increased in parallel with weight loss after surgical interventions. This finding is consistent with the literature.

Vitamin D and Ca supplements were administered starting from the sixth month. Although these supplements partially corrected the patients' vitamin D and Ca deficiency, they could not bring them to normal levels. Similar findings have been reported in other studies.

Study Limitations

There are some limitations to this study. Our study was a two-center, retrospective study, and the results cannot be generalized to the general population. The sample size is small, so studies with more patients are needed.

Conclusion

In light of these data, vitamin D insufficiency and Ca deficiency, which are already present in obese patients, increase even more after bariatric interventions. These deficiencies are believed to increase the risk of osteoporosis. Supplements that correct the current picture are insufficient. We believe that higher doses would be beneficial for the complete resolution of vitamin D insufficiency and Ca deficiency.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 164, date: 20.05.2022).

Informed Consent: Informed consent was obtained from the patients.

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COVID-19 Seroprevalence in Cirrhotic Patients and Effect of COVID-19 Infection on Liver Cirrhosis by Clinical Form in the Postinfectious Period

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ABSTRACT

Introduction: There are very few studies demonstrating the seroprevalence of coronavirus disease-2019 (COVID-19) in patients with cirrhosis worldwide and in Turkey. This study aimed to investigate the seroprevalence of COVID-19 in patients with cirrhosis and its effect on liver cirrhosis by clinical form in the postinfectious period.

Methods: The study included 174 patients with cirrhosis. Patients with COVID-19 were identified using anti-severe acute respiratory syndrome-coronavirus-2-immunoglobulin G (SARS-CoV-2-IgG) and COVID-19 polymerase chain reaction assays and were divided into symptomatic and asymptomatic groups. The last polyclinic records of the patients before infection or testing were determined as 1st examination and the date of blood collection for anti-SARS-CoV-2-IgG was determined as the 2nd examination. Examination findings and liver tests of the patients in both periods were recorded; Child-Pugh Score (CPS) and Model for End Stage Liver Disease (MELD)-Na scores were calculated. Additionally, patients were evaluated for newly developed hepatic decompensation.

Results: The seropositivity of anti-SARS-CoV-2-IgG was detected in 35.6% of our patients, and the rate of those who had symptomatic COVID-19 infection was 23.6%, whereas the rate of those who had asymptomatic infection was 12%. There was no significant difference in liver tests, CPS, and MELD-Na scores before and after COVID-19 infection between symptomatic and asymptomatic patients, and new decompensation was found in 9.6% of patients with COVID-19 infection.

Conclusion: The incidence of COVID-19 among patients with liver cirrhosis is notably high. Although high decompensation rates were reported in the acute phase of the disease, such rates were not observed in the postinfectious period. Ultimately, our results indicated no significant difference in the course of existing liver disease according to clinical form.

Keywords: COVID-19, liver cirrhosis, seroprevalence

Introduction

Although coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is primarily a respiratory infection, it can also affect other organs and systems directly or indirectly through some biological processes. It has been reported that 14-53% of these patients have elevated liver enzymes (1,2).

Various liver and/or biliary tract diseases due to vascular or circulatory problems have been reported, as well as inflammatory, infectious, autoimmunity, or drug-related liver diseases that may occur in relation to COVID-19 infection (2). Studies have reported that among COVID-19 patients, 2-11% have pre-existing and diagnosed liver disease, of which 0.3-2.4% are cases of liver cirrhosis (1,3).

COVID-19 infection in patients with chronic liver disease may result in the development of serious clinical problems, such as acute insufficiency or decompensation of liver cirrhosis with a chronic background (2). Deficiencies in natural and acquired immunity in patients with cirrhosis increase the tendency to infections, and this is more evident in severe cases (4).

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Serological tests in COVID-19 infection are used as diagnostic tools to determine previous and active infection in both symptomatic and asymptomatic patients (5). Seroprevalence studies are used to estimate the extent of COVID-19, which can be useful in detecting asymptomatic patients (6). Few studies have shown the seroprevalence of COVID-19 in patients with liver cirrhosis worldwide or in Turkey. At this point, the finalization of the research initiated during the pandemic process is an important issue in the fight against this health problem that may recur in the future.

This study aimed to investigate the seroprevalence of COVID-19 in patients with liver cirrhosis, the seropositivity rate of symptomatic and asymptomatic COVID-19 patients, and whether there is a difference between the clinical forms of the disease and how it affects pre-existing liver disease in the postinfectious period. The study was conducted during the circulation of the Delta variant and before the vaccination period.

Methods

Study Population

The study included 174 patients with liver cirrhosis who were under follow-up at the İstanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department Gastroenterology, between December 2020 and June 2021. All patients included in the study were monitored in our clinic and diagnosed with cirrhosis based on the evaluation of previous clinical, radiological, histochemical, and laboratory parameters, and they were followed up with this diagnosis. Patients were included in the study irrespective of the cause of cirrhosis, treatment applied, or other accompanying diseases. Patients who received one or more doses of the COVID-19 vaccine were excluded from the study.

This retrospective study was conducted before the initiation of vaccination and the emergence of the omicron variant, during which the delta variant was predominant. The course and seroprevalence of COVID-19 in patients with liver cirrhosis may vary depending on vaccination and novel variants.

Blood samples were collected from all patients on the day of the examination for antibodies against SARS-CoV-2 infection [anti-SARS-CoV-2 NCP ELISA immunoglobulin G (IgG), Euroimmun AG, Lübeck, Germany], and then serum samples were separated from these blood samples and stored at -20 °C. Patients were asked whether they had COVID-19 and the symptoms associated with COVID-19.

In patients who reported having a symptomatic COVID-19 infection, this was confirmed by checking the polymerase chain reaction (PCR) test results through the central public health results system. The severity of symptoms and whether patients were hospitalized in the inpatient or intensive care unit were also assessed, and patients were classified into the symptomatic group (group 1).

Patients who neither reported a history of COVID-19-related symptoms nor received a previous diagnosis of COVID-19 based on PCR test results but tested positive for anti-SARS-CoV-2-IgG were considered to have had an asymptomatic COVID-19 infection, and they were categorized as the asymptomatic group (group 2).

Those who did not report any COVID-19-related symptoms, whose PCR test results were negative, and who tested seronegative for anti-SARS-CoV-2-IgG in the antibody test were classified as patients who did not have a COVID-19 infection (group 3).

The last clinical records of the patients included in the study before infection or testing were taken as pre-COVID-19 (1st examination), and the date of blood collection for anti-SARS-CoV-2-IgG was considered the post-COVID-19 examination date (2nd examination).

Current examination findings, complete blood counts, liver function tests [alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, prothrombin time, alkaline phosphatase and gamma-glutamyl transferase (GGT)], and radiological examinations of the patients in both examination periods were recorded, and Child-Pugh Score (CPS), Model for End Stage Liver Disease (MELD)-Na scores, and neutrophil/lymphocyte ratios were calculated from these data.

In patients with cirrhosis, the occurrence of one or more of the symptoms of ascites, variceal bleeding, icterus, and hepatic encephalopathy that were not previously present was defined as decompensation, and EASL-CLIF criteria were used for the definition of acute insufficiency on a chronic basis (7).

Ethics Approval

This study was approved by the Ethics Committee of İstanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: 83088843-604.01.01-73299, date: 16.07.2020). Informed consent was obtained from the patients.

Statistical Analysis

The demographic and clinical characteristics of the patients evaluated in the study were analyzed using descriptive statistics, such as numbers, percentages, means, standard deviations, and medians. Average data, such as age and MELD-Na score, which were normally distributed between cases with and without COVID-19, were evaluated using the Independent groups t-test. Mean blood values that were not normally distributed between patients with and without COVID-19 were evaluated using the Mann-Whitney U test. Proportional data according to disease severity groups were analyzed using chi-square analysis and Fisher's exact test between cases with and without COVID-19, as well as between symptomatic and asymptomatic COVID-19 infection. In this study, the change in normally distributed mean data, such as the MELD-Na score and hemoglobin, before and after COVID-19 was assessed using Paired Samples t-test. The conformity of the data to the normal distribution was checked using the kurtosis and skewness coefficients (±1.5). The significance level for all analyses was set up $p<0.05$ and IBM SPSS 22.0 (IBM SPSS Statistics for Windows, version 22.0. IBM Corp. (Armonk, NY, USA) software was used in the analysis.

Results

Of cirrhotic patients (n=174) included in the study, 79 were female and 95 were male, with ages ranging from 21 to 85 (median: 61.0, interquartile range: 50-68). Viral hepatitis is the leading cause of cirrhosis, and the other etiologic causes are presented in Table 1. One hundred thirteen

(64.9%) patients had class A cirrhosis, fifty (28.7%) had class B cirrhosis, and eleven (6.3%) had class C cirrhosis. In 61 of the patients (35%), there were diseases other than cirrhosis related to one or more organs or systems. The accompanying comorbid conditions are shown in Table 2.

In the grouping according to the outpatient clinic query, COVID-19 PCR result screening based on public health center test data, and anti-SARS-CoV-2-IgG results, 41 of the patients (23.6%) (66% of COVID-19 positive patients) had symptomatic COVID-19 infection (group 1). Additionally, 21 patients (12%) (34% of COVID-19 positive patients) had asymptomatic COVID-19 infection (group 2), whereas 112 patients (64.4%) have not had COVID-19 (group 3) (Figure 1).

No significant differences were observed between patients with or without COVID-19 in terms of demographic characteristics, cirrhosis etiology, and severity of liver disease (Table 3).

At this stage of the study, 62 patients who had COVID-19 infection were evaluated within themselves, and how the clinical status and liver tests of those with symptomatic or asymptomatic infections changed compared with pre-COVID-19 and whether asymptomatic COVID-19 infection had an aggravating effect on liver disease in cirrhotic patients (Table 4, 5).

No significant difference was observed between symptomatic and asymptomatic patients with COVID-19 in terms of demographic characteristics and severity of liver disease. In the etiological comparison of both groups, the rates of viral hepatitis in the symptomatic patient group and cryptogenic cirrhosis in the asymptomatic patient group were significantly higher (Table 4).

No significant difference was observed in liver test results, neutrophil-to-lymphocyte ratio, CPS, and MELD-Na scores before and after COVID-19 infection between symptomatic and asymptomatic patients with COVID-19 (Table 5).

Among patients with cirrhosis who had symptomatic COVID-19, 61.2% had respiratory symptoms, such as cough and shortness of breath, 32.2% had fever, 29% had myalgia, 19.3% had gastrointestinal

Table 1. The causes of cirrhosis in patients

Etiology	n (%)
Viral hepatitis	56 (32.2)
Alcoholic liver disease	10 (5.7)
Autoimmune hepatitis	6 (3.4)
Wilson's disease	6 (3.4)
PBC, PSK	7 (4)
Fatty Liver	33 (19)
Chronic liver disease with vascular disease	15 (8.6)
Others	9 (5.2)
Cryptogenic	32 (18.4)

PBC: Primary biliary cholangitis, PSK: Primary sclerosing cholangitis

Table 2. Other accompanying system diseases of the patients

	n (%)
Diabetes	15 (8.6)
Hypertension	13 (7.5)
Cardiovascular system diseases	12 (6.9)
Neurological diseases	1 (0.6)
Renal diseases	6 (3.4)
Rheumatological diseases	5 (2.9)
Gastrointestinal diseases	3 (1.7)
Pulmoner diseases	1 (0.6)
Oncological disease (except hepatocellular carcinoma)	2 (1.1)
Others	3 (1.7)
Total	61

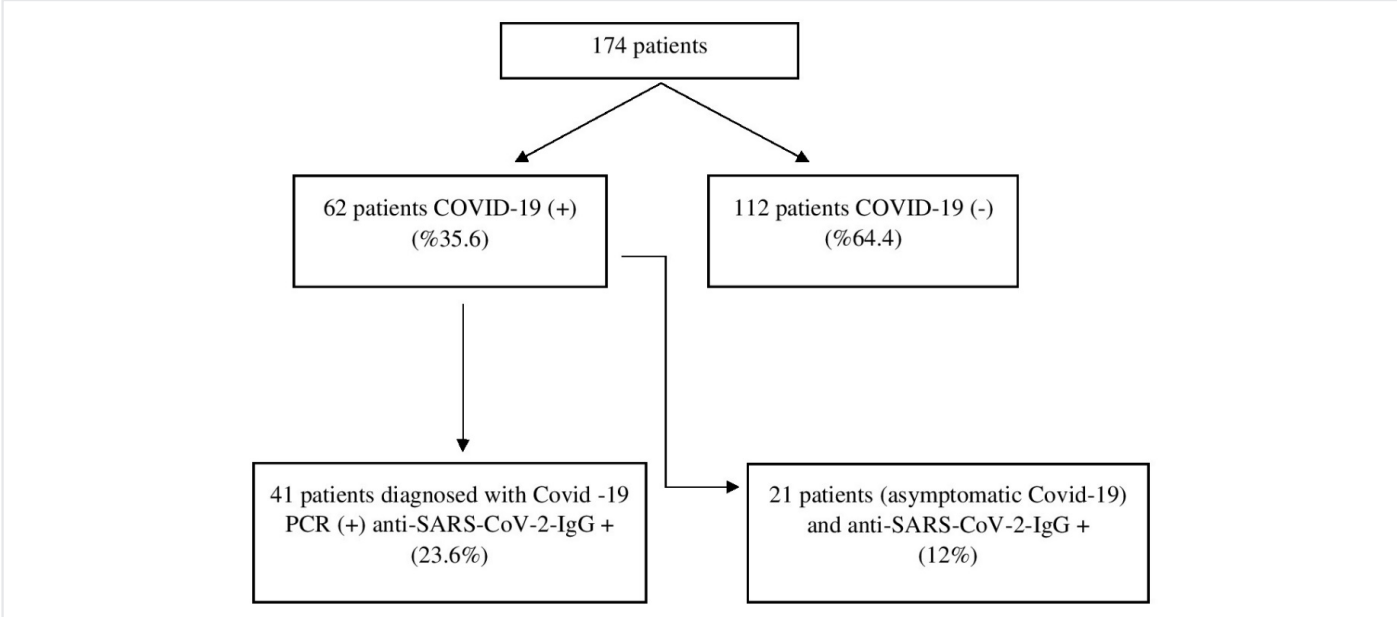

Figure 1. Flow chart of patient inclusion
COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, SARS-CoV-2-IgG: Severe acute respiratory syndrome-coronavirus-2-immunoglobulin G

Table 3. Demographic characteristics and liver disease status of patients with and without COVID-19

		COVID-19 (-) (n=112)	COVID-19 (+), (n=62)	p
Age (mean/SD)		59.05/14.18	57.16/10.19	0.356
Gender (n, %)	Male	62/55.4	33/53.2	0.787
	Female	50/44.6	29/46.8	
Etiological diagnosis (n, %)	Viral hepatitis	35/30.4	21/33.9	0.686
	Autoimmune hepatitis	4/3.6	2/3.2	
	Alcoholic cirrhosis	8/7.1	2/3.2	
	Cryptogenic cirrhosis	25/41.1	7/35.5	
	Fatty liver	20	13	
	Other reasons	30	17	
CPS (n, %)	A	67/59.8	46/74.2	0.163
	B	36/32.1	14/22.6	
	C	9/8.0	2/3.2	

CPS: Child-Pugh Score, SD: Standard deviation, COVID-19: Coronavirus disease-2019

Table 4. Characteristics of symptomatic and asymptomatic COVID-19 cases

		Symptomatic, (n=41)	Asymptomatic, (n=21)	p
Age (mean/SD)		56.3±9.3	58.8±11.8	0.14
Gender (n, %)	Male	23	10	0.5
	Female	18	11	
Etiological diagnosis (n, %)	Viral hepatitis	19	2	0.003
	Autoimmune hepatitis	2	0	0.54
	Alcoholic cirrhosis	1	1	0.61
	Cryptogenic cirrhosis	1	6	0.002
	Fatty liver	9	4	0.79
	Other reasons	9	8	0.17
CPS (n, %)	A	33	14	0.3
	B	7	6	
	C	1	1	

CPS: Child-Pugh Score, SD: Standard deviation, COVID-19: Coronavirus disease-2019

symptoms, such as abdominal pain and diarrhea, and 16.1% had other symptoms, such as headache and loss of smell. Of patients with cirrhosis and symptomatic COVID-19, 51.7% received outpatient treatment, 38.7% received inpatient treatment, and 9.6% required intensive care unit treatment.

Among the COVID-19 seropositive patients, new decompensation was seen in 6 patients (9.6%). The clinical features of patients who developed decompensation are presented in Table 6.

Discussion

In this study, we found anti-SARS-CoV-2 IgG seropositivity in 35.6% of patients with cirrhosis. The rate of COVID-19 infection with symptoms was 23.6%, and the rate of asymptomatic patients was 12%. When the literature is searched, different incidence and prevalence rates related to COVID-19 are encountered in studies conducted in various regions and at different times in patients with liver cirrhosis. In two studies conducted on hospitalized patients, the incidence of COVID-19 in patients with cirrhosis was 6.6% and 16.8%, respectively (8,9). In the seroprevalence study of Del Zompo et al. (5) in patients with cirrhosis, the rate of asymptomatic COVID-19 was found to be 1.9%. In our study, the rate of COVID-19 infection was quite high in patients with cirrhosis. The longer study period compared with other studies may have caused this rate to be higher. However, reasons such as the overpopulation of İstanbul, the lifting of curfews during the study period, and the lack of vaccination may have increased the risk and incidence of COVID-19 transmission.

In the meta-analysis conducted by Sah et al. (10), the estimated rate of asymptomatic COVID-19 infection among patients with COVID-19 infection was reported as 36.9%. In a study conducted by Brozat et al. (11), 62.5% of 70 patients with COVID-19-positive cirrhosis were found to have symptoms and 37.5% had asymptomatic infections. Respiratory symptoms and fever are observed most frequently in patients with symptomatic infection (11).

In our study, 66% of patients with COVID-19-positive cirrhosis had symptoms and 34% were asymptomatic, which is similar to the results of both the general COVID-19 population and Brozat et al. (11). Additionally,

Table 5. Laboratory parameters and liver disease status of symptomatic and asymptomatic patients before and after COVID-19

	Symptomatic (n=41)		Asymptomatic (n=21)		sPRE-asPRE	sPOS-asPOS
	Pre-COVID	Post-COVID	Pre-COVID	Post-COVID	p	p
Hgb (g/dL)	12.3±2.1	12.1±2.1	11.9±2.6	11.9±2.3	0.6	0.6
WBC (µL)	5.06±1.8	5.09±2.0	5.57±1.8	5.13±0.18	0.9	0.6
Neutrophils (µL)	2.9 (1.9)	2.7 (2)	3.2 (1.7)	2.9 (1.5)	0.2	1
Lymphocyte (µL)	1.2 (0.7)	1.1 (0.8)	1.3 (1)	1.3 (1)	0.9	0.7
Neutrophils/lymphocyte ratio	2.3 (1.8)	2.4 (1.8)	2.2 (1.9)	2.3 (2.1)	0.4	0.5
Platelet (µL)	97 (91)	106 (64)	118 (112)	108 (129)	0.1	1
ALT (IU/L)	27 (23)	28 (20)	24 (22)	22 (11)	0.4	0.1
n (%), normal ALT	76	78	81	85	0.6	0.4
AST (IU/L)	34 (26)	35 (17)	27 (24)	30 (21)	0.5	0.1
n (%), normal AST	63	66	66	76	0.8	0.4
Total bilirubin level (mg/dL)	0.9 (0.9)	0.9 (1.1)	1.2 (2)	1.2 (2.1)	0.1	0.4
Alkaline phosphatase (IU/L)	102 (62)	106 (74)	94 (69)	98 (69)	0.2	0.5
GGT (IU/L)	61 (69)	61 (77)	49 (93)	44 (109)	0.5	0.1
Albumin (g/dL)	3.9±0.6	3.7±0.7	3.9±0.5	3.7±0.6	0.5	0.4
INR	1.2 (0.2)	1.2 (0.2)	1.1 (0.2)	1.2 (0.4)	0.8	1
Creatinine (mg/dL)	0.7 (0.2)	0.7 (0.3)	0.8±0.4	0.7 (0.3)	1	0.7
CPS						
A	33	28	13	15		
B	7	9	7	4	0.2	0.9
C	1	4	1	2		
MELD-Na	11 (5)	10 (7)	10.5 (6)	10.5 (9)	0.8	0.8

Hgb: Hemoglobin, WBC: White blood cell, ALT: Alanine transaminase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, CPS: Child-Pugh Score, MELD: Model for End Stage Liver Disease, sPRE: Symptomatic patients before COVID-19, asPRE: Asymptomatic patients before COVID-19, sPOS: Symptomatic patients after COVID-19, asPOS: Asymptomatic patients after COVID-19, COVID-19: Coronavirus disease-2019

Table 6. COVID-19 seropositive patients developing hepatic decompensation

	Total (n=62)	Symptomatic, (n=41)	Asymptomatic, (n=21)
Decompensation	6 (9.6%)	4 (6.4%)	2 (3.2%)
Newly developed ascite	3 (4.8%)	3 (4.8%)	0
Hepatic encephalopathy	3 (4.8%)	1 (1.6%)	2 (3.2%)

COVID-19: Coronavirus disease-2019

respiratory symptoms and fever are in the first place in symptomatic patients. In our study, 51.7% of patients with cirrhosis and symptomatic COVID-19 received outpatient treatment, 38.7% received inpatient treatment, and 9.6% received intensive care unit treatment. These rates show that approximately half of the patients with COVID-19 with cirrhosis are hospitalized. According to data from the Turkish Ministry of Health, 21.1% of patients with COVID-19 were treated in hospital wards and 7.4% in intensive care units (12). Compared with these rates, the rate of hospitalized patients with cirrhosis due to COVID-19 seems to be higher than that of the general population.

Another result observed in our study was that the symptomatic infection rate was significantly higher in patients with liver cirrhosis due to chronic viral hepatitis, whereas the asymptomatic infection rate was significantly higher in patients with cryptogenic cirrhosis. Studies investigating the effect of viral hepatitis on COVID-19 have reported that COVID-19 infection progresses with more severe symptoms in this patient group. It has been stated that impaired intestinal flora in patients with viral hepatitis plays a role in the development of this condition (13,14). There are no studies or subgroup analyses on the relationship between cryptogenic cirrhosis and COVID-19 infection. It is not possible to determine from the current literature whether the reason for the high rate of asymptomatic infection in this patient group is a coincidence or if there is another reason.

Many studies and meta-analyses have evaluated the impact of COVID-19 infection on liver function. It has been reported that approximately half of patients with COVID-19 have elevated liver enzyme levels upon admission to the hospital, and similarly, aminotransferase levels are increased in patients with previous chronic liver disease (15,16). In the

follow-up of patients with COVID-19 with hepatic dysfunction until the second month after discharge, high aminotransferase and GGT levels decrease over time, and a longer follow-up period is recommended in some patients (17). In our study, the reason why there was no significant difference in liver function tests in both the asymptomatic and symptomatic groups before and after COVID-19 infection was thought to be that the tests returned to normal over time in the post-infection period.

There are many factors associated with liver injury during COVID-19. These include the direct cytopathogenic effects of the virus, abnormal immune responses associated with cytokine storms, vascular changes due to coagulopathy, hepatic ischemia/hypoxia-related injury, reactivation of existing liver disease, and drug-induced liver injury. Coronavirus directly causes liver damage through the use of the angiotensin-converting enzyme 2 receptor for cell entry, which is expressed mainly in cholangiocytes and less frequently in hepatocytes (3,14).

In the study of Moon et al. (18) in patients with cirrhosis who were followed up for COVID-19, hepatic decompensation was observed in 36.9% of the patients. New ascites formation or worsening of existing ascites developed in 27.2% of the patients, hepatic encephalopathy in 16.9%, spontaneous bacterial peritonitis in 2.9%, and variceal bleeding in 1%. In our study, no significant differences were observed in liver test results, CPS, and MELD-Na scores before and after COVID-19 infection between symptomatic and asymptomatic patients with COVID-19. On the other hand, 9.6% of the 62 patients with COVID-19 developed new decompensation. The lack of a significant difference in these results between the asymptomatic and symptomatic groups before and after COVID-19 infection may be explained by the fact that CPS A class patients constituted the majority in both groups, and the liver functions of these patients were largely preserved.

Study Limitations

The small patient population, especially in patients with decompensated liver cirrhosis, the single-center design, and the absence of a control group are considered important limitations of our study. Additionally, the retrospective nature of the study and the possibility that patients showed mild symptoms such as weakness, fatigue, and subfebrile fever and did not remember them may have affected the ratio of symptomatic to asymptomatic patients.

Conclusion

As a result of, the incidence of COVID-19 infection among patients with liver cirrhosis is notably high, with approximately half of these patients requiring hospitalization and some of them had to be treated in intensive care unit. There is no significant differences in the course of existing liver disease according to the clinical form of the disease. Although high decompensation rates were reported in the acute phase of the disease, such rates were not observed in the post-infection period. Nevertheless, hepatic decompensation can also develop in this patient group, and considering the magnitude of the impact of hepatic decompensation in terms of patient and healthcare costs, close follow-up of patients in this regard is of great importance.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University - Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (approval number: 83088843-604.01.01-73299, date: 16.07.2020).

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Evaluation of Variables Influencing Mortality in Periprosthetic Femur Fractures: Do Fracture Type and Surgical Method Affect Mortality?

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ABSTRACT

Introduction: We investigated the factors influencing mortality in patients with periprosthetic femur fractures (PFF). Our aim was to assess the effects of fracture types and treatment methods on mortality.

Methods: We identified 52 patients who met the inclusion criteria and underwent surgery for PFF between January 1996 and December 2020. Patient records were analyzed retrospectively to collect reports on patient demographics, hospitalization, and surgical details. The following parameters were assessed: age, sex, side, time to PFF, surgical procedure, fracture pattern, and American Society of Anesthesiologists Classification. The Vancouver classification was used to identify fracture patterns.

Results: The mean age was 73.6±13.5 years. Average of 5 years elapsed until PFF (range, one month to twenty years). Open reduction and internal fixation were performed in 61.5% of the patients, and revision arthroplasty was performed in 38.5%. Significant differences were found between patients' ages ($p=0.033$) and fracture types ($p<0.001$). The overall 30-day and 12-month mortality rates were 19.2%, and the 12-month mortality was 36.5%. The survival time of those who underwent surgical osteosynthesis was significantly longer than that of those who underwent revision arthroplasty ($p=0.048$). The risk of mortality for fracture classification B1 was higher than that for type A [odds ratio (OR): 6.93; confidence interval (CI): 95% (1.16-41.09) $p=0.033$], and the risk of mortality for fracture type B3 was higher than that for type A [OR: 16.75; CI: 95% (1.12-248.45) $p=0.041$].

Conclusion: The surgical method and type of fracture affected mortality. Mortality was higher among patients who underwent revision arthroplasty and had Vancouver type B3 fractures.

Keywords: Periprosthetic femur fractures, mortality, Vancouver classification, osteosynthesis, arthroplasty

Introduction

Major joint arthroplasty is one of the most popular and effective orthopedic surgeries, and its demand is increasing worldwide according to all relevant registries. The aging populations, which are projected to live longer, the broadening of indications for replacement surgery in younger populations, and the desire for a better quality of life and increased activity levels are all contributing factors to this trend (1-3).

The incidence of periprosthetic femur fractures (PFF) related to hip replacement has increased over time. This increase in prevalence may be due to several factors, including the increasing number of patients requiring arthroplasty, the growing number of elderly individuals with osteoporosis, the preference for cementless fixation techniques that emphasize the use of oversized press-fit implants, and recent advancements in surgical techniques that minimize surgical exposure. Furthermore, the prevalence of PFFs is expected to continue to increase by 4.6% every decade until 2045 (4,5). The incidence of PFF varies, with some reports stating that it occurs in 1% of primary hip arthroplasty cases and 4% of revision cases (6). After total hip arthroplasty (THA), PFFs are the third most common cause of revision (7).

Periprosthetic fractures are linked to high mortality rates. In a recent study, periprosthetic hip fractures were found to carry a similar mortality risk to that of femoral neck fractures in elderly patients. However, the risk appears to decrease after the first six months following surgery, with a reported 1-year mortality rate of 9.7% (8). Another study found that the overall complication rate for PFFs within 30 days after surgery was 45% (22% serious and 13% mild), with a 30-day mortality rate of 10% (9).

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Periprosthetic fractures are complex issues that require in-depth knowledge for prevention, recognition, and treatment. PFFs present a surgical challenge for orthopedic surgeons and require advanced trauma and arthroplasty skills. The Vancouver classification system, which serves as a management framework, is still frequently used and preferred. It classifies postoperative PFF according to the site of the fracture, implant stability, and quality of the surrounding bone (10).

We aimed to investigate the variables influencing mortality in patients with PFF. The objective of this study was to assess the impact of fracture types and treatment methods on patient mortality. A comparative analysis was performed to evaluate mortality rates between patients with PFF who underwent revision arthroplasty and those who received open reduction and internal fixation treatment. Additionally, the effects of various fracture types on mortality were thoroughly examined.

Methods

Study Design

We received approval to conduct this study from University of Health Sciences Turkey, İstanbul Training and Research Hospital Institutional Review Board (approval number: 39, date: 28.01.2022). All procedures were performed in accordance with the Helsinki Declaration and institutional and national ethical guidelines for human experimentation (11). Informed consent was obtained from each participant included in the study. The research was conducted in a single trauma unit.

By searching our trauma database and billing information, we identified individuals who had undergone surgical treatment for a PFF following uncemented THA and uncemented hemiarthroplasty. Surgical and anesthetic procedures were essentially the same in all patients. The rehabilitation program was tailored specifically for each patient, with the rehabilitation process being supervised by a physical therapy and rehabilitation specialist, as well as a specialist physiotherapist. The approach was based on fracture type and patient characteristics.

Patients with intraoperative fractures, prosthesis infections, high-velocity trauma, metastatic diseases, metabolic bone diseases other than osteoporosis, non-union at presentation, and those treated conservatively were excluded. All injuries were caused by low-energy trauma, typically resulting from falling from one's own height.

We identified 52 patients who met the inclusion criteria and underwent surgery for PFF between January 1996 and December 2020.

We retrospectively analyzed patient records to collect information on patient demographics, hospitalization, and surgical details. The collected parameters included age, sex, side, time to PFF, surgical procedure, fracture pattern, and American Society of Anesthesiologists Classification (ASA).

The Vancouver classification was used to identify fracture patterns. The appropriate treatment was determined by the operating surgeon, who considered the patient's condition during surgery and the Vancouver classification. Fractures with stable and well-fixed implants were treated with open reduction and internal fixation, whereas those with loose stems were revised (10).

Patients were invited to our outpatient clinic for follow-up. Those unable to visit our hospital completed the questionnaires via telephone. Information on deaths was obtained from hospital records, and relatives were contacted to determine the time of death for deceased patients.

Statistical Analysis

Statistical analyses were conducted using SPSS version 23.0. The normality of variables was assessed using histograms and the Kolmogorov-Smirnov/Shapiro-Wilk test. Descriptive analyses were performed using mean, standard deviation, and median values. The independent two samples test was used to evaluate normally distributed (parametric) variables between the two groups, while the Mann-Whitney U test was utilized to evaluate non-normally distributed (non-parametric) variables between the two groups.

For categorical variables, frequency and percentage values were used, and their analysis was performed with the chi-square (exact) test. Kaplan-Meier analysis was performed to determine differences in patients' life spans according to variable groups. Logistic regression analysis was used to investigate the impact of variables on survival. Odds ratios (OR) were calculated with 95% confidence intervals, and p-values 0.05 were considered statistically significant.

Results

Of the 52 patients included in the study, 40 (76.9%) were female and 12 (23.1%) were male. The mean age was 73.6±13.5 (48-102) years. Twenty-five patients had fractures on the right side, whereas 27 had fractures on the left. Regarding prosthesis type, 19 (36.5%) patients had un-cemented hemiarthroplasty (F40 stem, Zimmer-Biomet, Warsaw, Indiana), and 33 (63.5%) had non-cemented THA (F40 stem, Zimmer-Biomet, Warsaw, Indiana; CLS-Spotorno stems, Zimmer, Germany; Synergy stem, Smith & Nephew, Memphis, Tenn) with an average period of 5 years until PFF (range, one month to twenty years). All patients experienced PFF after a simple fall or low-energy trauma.

Open reduction and internal fixation with a single plate (locking plate, TST, İstanbul, Turkey; cable and/or trochanteric claw plate, Cable-ready, Zimmer Biomet, Warsaw, Indiana) was performed in 32 (61.5%) patients, while revision arthroplasty (Arcos stem, Zimmer Biomet, Warsaw, Indiana) was performed in 20 (38.5%).

The complications included two sacral pressure ulcers, four heel pressure ulcers, and five superficial surgical wound infections. Eight patients required intraoperative blood transfusions.

Of the patients, four (7.7%) were classified as ASA 2, 27 (51.9%) as ASA 3, and 21 (40.4%) as ASA 4. The majority of fractures were Vancouver B1 type (23 patients). Five (9.6%) patients had B2 fractures, eight (15.4%) had B3 fractures, and 16 (30.8%) had type Ag fractures. A total of 35 (67.3%) patients died and 17 (32.7%) survived, with a mean survival time of 20.9±23.9 months.

The comparison of variables according to surgical technique is summarized in Table 1. As a result of this evaluation, significant differences were identified between patients' ages ($p=0.033$) and fracture types ($p<0.001$). Patients who underwent revision arthroplasty were older than those who underwent internal fixation.

Surgical treatment was performed for type A fractures with significant displacement to avoid non-union and related complications. Osteosynthesis was performed in 11 (34.4%) patients with type A fractures, and revision arthroplasty was performed in 5 (25.0%) patients, which were found to have insufficient intraoperative prosthesis stability.

Osteosynthesis was performed in 21 (65.6%) patients with type B1 fractures, and revision arthroplasty was performed in 2 (10%) patients for whom osteosynthesis was not possible due to poor bone quality. Revision arthroplasty was performed in all patients with type B2 and B3 fractures. According to the statistical evaluation, osteosynthesis was performed more frequently than revision arthroplasty in B1-type fractures, and this difference was found to be statistically significant ($p<0.001$). Additionally, although there was no statistical difference between the groups, the survival time was 26.7 months in the osteosynthesis group and 13.3 months in the revision group ($p=0.093$). Although the difference was not significant, patients who underwent osteosynthesis had a longer survival time (Table 1).

The relationship between survival and variables is summarized in Table 2. Age, prosthesis type, and ASA levels differed significantly according to survival. The mean age of patients who died was significantly higher ($p=0.002$). The PFF rate after hemiarthroplasty was significantly higher among patients who died, whereas that after THA was significantly lower ($p=0.01$). No deaths were observed during follow-up among patients with ASA class 2. However, the mortality rate was significantly higher in patients with ASA class 4 ($p=0.003$). Of the 17 surviving patients, osteosynthesis was performed in 12 and prosthesis was applied in 5, with survival rates of 70.6% and 29.4%, respectively. Osteosynthesis was performed in 20 (57.1%) patients, and revision arthroplasty was performed in 15 (42.9%) of the 35 deceased patients. Although osteosynthesis was performed more frequently in surviving patients, no significant difference was found in the results ($p=0.350$) (Table 2).

Survival time was evaluated in the groups using the Kaplan-Meier (log-rank) test. The results are presented in Table 3. No significant difference was found between patient survival times in terms of gender ($p=0.618$). Similarly, survival times were similar for the fracture side ($p=0.971$). However, the survival time of patients who underwent surgical osteosynthesis was significantly longer than that of patients who underwent revision arthroplasty ($p=0.048$). The median survival time for those who underwent surgical intervention for osteosynthesis was 52 months, whereas that for revision arthroplasty was 5 months. The median survival time for those with PFF after THA was 52 months, which is a significantly higher life expectancy compared with hemiarthroplasty ($p=0.002$). Unfortunately, the median survival time was only 6 months for patients treated with PFF after hemiarthroplasty. According to the fracture classification, the mean survival time was 44.9 months. Life expectancy was higher among patients with type A fractures. The life expectancy of type A fractures was 67.3 months, which was higher than that of other types of fractures ($p=0.006$). No statistics could be calculated when the survival analysis was performed for the ASA group, as all cases were censored. However, there was a difference in survival between the ASA categories ($p=0.006$) (Table 3).

Upon examining the survival curves, the overall 30-day mortality rate was 19.2% (10/52), 36.5% at 6 months (19/52), and at 12 months, mortality was 36.5% (19/52).

Table 1. Comparison of variables according to surgical technique

Parameters		The type of surgery		p
		Open reduction and internal fixation, (n=32)	Revision arthroplasty, (n=20)	
Gender	Female	26 (81.3%)	14 (70%)	0.349
	Male	6 (18.8%)	6 (30%)	
Age (mean ± SD) (years)		70.5±14.4	78.7±10.3	**0.033**[a]
Side	R	16 (50.0%)	9 (45.0%)	0.726
	L	16 (50.0%)	11 (55.0%)	
The type of prosthesis	Hemiarthroplasty	11 (34.4%)	8 (40.0%)	0.682
	Total hip arthroplasty	21 (65.6%)	12 (60.0%)	
Time between the two surgeries (mean ± SD) (years)		5.38±5.5	4.5±5.0	0.513
ASA type	2	4 (12.5%)	0	0.255
	3	16 (50.0%)	11 (55.0%)	
	4	12 (37.5%)	9 (45.0%)	
Fracture type	A	11 (34.4%)[a]	5 (25.0%)[a]	**<0.001**
	B1	21 (65.6%)[a]	2 (10.0%)[b]	
	B2	0	5 (25.0%)[b]	
	B3	0	8 (40.0%)[b]	
Survival time (mean ± SD) (months)		26.7±26.0	13.3±18.9	0.093
Survival	Died	20 (62.5%)	15 (75.0%)	0.35
	Live	12 (37.5%)	5 (25.0%)	

Chi-square test. [a]: Independent sample test, [b]Mann Whitney U test, SD: Standard deviation, ASA: American Society of Anesthesiologists Classification

Logistic regression analysis was performed to identify the variables that had a significant effect on survival. The variables that significantly affected survival were age, prosthesis type, and fracture classification. As a result of the analysis, the effect of B1 fracture classification on survival was significant. However, multiple interrelationships were suspected between the variables, so different models were created. Accordingly, the risk of mortality was higher in those with B1 fracture classification than in those with fracture type A [OR: 6.39; CI: 95% (1.05-38.77) p=0.044].

When the variables found to be significant in the univariate model were included without the age variable in the model, the risk of mortality for fracture classification B1 was higher than that for those with A [OR: 6.93; CI: 95% (1.16-41.09) p=0.033], and the risk of mortality for fracture type B3 was higher than that for those with A [OR: 16.75; CI: 95% (1.12-248.45) p=0.041]. In addition, the risk of mortality was lower in total hip prosthesis patients than in hemiarthroplasty patients [OR: 0.11; CI: 95% (0.01-0.90) p=0.04]. When age was included in the model, its effect on

Table 2. Relationship between survival and the variables

Parameters		Died	Live	p
Gender	Female	28 (80.0%)	12 (70.6%)	0.45
	Male	7 (20.0%)	5 (29.4%)	
Age (mean ± SD) (years)		77.6±10.5	65.6±15.6	**0.002**[a]
Side	R	17 (48.6)	8 (47.1%)	0.918
	L	18 (51.4)	9 (52.9%)	
The type of surgery	Open reduction and internal fixation	20 (57.1)	12 (70.6%)	0.35
	Revision	15 (42.9)	5 (29.4%)	
The type of prosthesis	Hemiarthroplasy	17 (48.6)[a]	2 (11.8%)[b]	**0.01**
	Total hip arthroplasy	18 (51.4)[a]	15 (88.2%)[b]	
Time between the two surgeries (mean ± SD) (years)		4.2±4.7	6.8±6.2	0.13
ASA type	2	0	4 (23.5%)[b]	**0.003**
	3	17 (48.6%)[a]	10 (58.8%)[a]	
	4	18 (51.4%)[a]	3 (17.7%)[b]	
Fracture type	A	7 (20.0%)	9 (52.9%)	0.075
	B1	18 (51.4%)	5 (29.4%)	
	B2	3 (8.6%)	2 (11.8%)	
	B3	7 (20.0%)	1 (5.9%)	

Chi-square test, [a]: Independent sample test, [b]: Mann Whitney U test, SD: Standard deviation, ASA: American Society of Anesthesiologists Classification

Table 3. Evaluation of survival time in different groups

Parameters		Estimate	S.E.	95% CI		p
				Lower bound	Upper bound	
Sex	Female	48	19,719	9.35	86.65	0.618
	Male	48	25,632	0	98,239	
	Overall	48	18,971	10,817	85,183	
Side	R	48	23,257	2,416	93,584	0.971
	L	48	22,531	3,838	92,162	
	Overall	48	18,971	10,817	85,183	
Surgery	Open reduction and internal fixation	52	4.86	42,474	61,526	**0.048**
	Revision	5	1,118	2,809	7,191	
	Overall	48	18,971	10,817	85,183	
The type of prosthesis	Hemiarthroplasy	6	6,965	0	19,651	**0.002**
	Total hip arthroplasy	52	6,364	39,526	64,474	
	Overall	48	18,971	10,817	85,183	
Fracture type	A	67,333	11,769	44,267	90.4	**0.006**
	B1	34,939	6,809	21,594	48,285	
	B2	19.8	10,297	0	39,982	
	B3	25	8,796	7.76	42.24	
	Overall	44,877	6,079	32,962	56,792	

Kaplan-Meier Analysis (log-rank). S.E.: Standard error, CI: Confidence interval

survival was found to be significant. Accordingly, a 1-year increase in age increases the risk of mortality by 1.087 times.

Discussion

A rise in the frequency of fractures around the prosthesis has been observed globally as a result of the increasing number of arthroplasties performed (12). PFF following hip arthroplasty are complicated and clinically challenging problem (7). The type of fracture, stability of the prosthesis, and general health status of the patient must all be considered when choosing an appropriate treatment course (13). The Vancouver classification is useful for fracture classification and treatment management. In general, well-fixed stems require open reduction and internal fixation, whereas loose stems necessitate revision arthroplasty (10). The validity of the periprosthetic fracture classification system for the femur has been previously demonstrated (14).

According to our study, revision arthroplasty is more often preferred in elderly patients because the stability of the implant may be adversely affected by poor bone stock. We found that survival was longer in patients who underwent osteosynthesis, which can be explained by the fact that revision surgery is a major surgical intervention. At the same time, we believe that the deterioration of the general condition that affects survival is more common in elderly patients and the inability to perform osteosynthesis in patients with unsuitable bone quality are among the factors affecting the outcome. In addition, it may be that patients who underwent ORIF were younger than those who underwent revision THR. Moreover, patient comorbidities likely affected survival.

Our findings indicate that life span is better in patients undergoing osteosynthesis with a stable implant of good bone quality. However, some researchers have reported that the need for revision surgery is more frequent after the fixation of the periprosthetic fracture with osteosynthesis. They concluded that implant stability may have been misclassified by surgeons (3). According to Bhattacharyya et al. (15), revision arthroplasty may be associated with a lower mortality rate in patients with type B PFF than in those with osteosynthesis. At the same time, researchers have reported that revision arthroplasty may be the best option for patients for whom it is difficult to determine implant stability (15).

Patient age and ASA were found to be effective in reducing mortality. Drew et al. (16) reported that non-modifiable risk factors, such as advanced age and the number of comorbidities, were effective against mortality. It was a predictable conclusion. Similarly, it is not difficult to explain the increased mortality after PFF in patients undergoing hemiarthroplasty. Hemiarthroplasty is performed in elderly patients after trauma, and total hip replacement is performed in patients who already have high daily activity levels or elective surgical procedures. As a result, we conclude that, according to this study's outcome, the patient's age, general health status, and bone quality will affect mortality.

The data from the Swedish National Joint Registry underscore the severity of postoperative periprosthetic fractures of the femoral side, with >70% of patients having a loose femoral component, 30% requiring at least one revision, and 39% experiencing no pain relief following revision surgery (7). The high likelihood of additional surgeries and incomplete clinical recovery highlights the seriousness of this condition. Khan et al. (17) showed that revision hip arthroplasty for periprosthetic fractures carries a higher overall mortality risk than revisions for other reasons, and men aged 75 years or older have the highest mortality risk after revision hip arthroplasty for PFF. Although some researchers have identified female gender and age as independent risk factors, the evidence in the current literature is not entirely consistent (18). Our study found no gender effects on mortality.

Barrow et al. (19) reported that the development of a periprosthetic fracture after arthroplasty is as important as infection and aseptic loosening. Similarly, the severity of the situation was evidenced by the 13.3-month survival time in patients undergoing revision arthroplasty in our study. This further emphasizes the need for careful evaluation and management of periprosthetic fractures, considering factors such as patient age, general health status, and bone quality, to optimize treatment outcomes and reduce the risk of complications and mortality.

PFF significantly impact mortality rates and healthcare costs, emphasizing the importance of prevention strategies (20). The following arthroplasty, maintaining muscular strength, increasing functional capacity, and providing rehabilitation programs are essential to prevent fractures.

Open reduction and internal fixation have been shown to provide positive outcomes for types A and B1 fractures. In contrast, revision arthroplasty remains the gold standard for the treatment of types B2 and B3 PFF. Our study found that surgical treatment was performed on type A fractures (34.4%) with significant displacement to avoid non-union and related complications. Revision arthroplasty was performed in type A fractures (25.0%) with insufficient intraoperative prosthesis stability. Hsieh et al. (21) reported 23 periprosthetic fractures of the greater trochanter, 16 of which required revision because of excessive wear, loosening, or non-union. In our study, revision arthroplasty was performed for B2- and B3-type fractures, thereby facilitating early weight bearing and mobilization.

Canton et al. (22) found an association between delayed weight bearing and increased mortality risk, noting that elderly patients who underwent revision arthroplasty for types B2-B3 PFF often experienced superior long-term outcomes. Malige et al. (23) reported no difference in the complication rate between different types of B fractures, consistent with the literature showing that Vancouver B PFF following hip arthroplasty are associated with high complication rates and poor outcomes.

Considering these findings, it is crucial to understand the impact of fracture types and surgical techniques on patient outcomes and to adopt appropriate prevention and treatment strategies. Nonetheless, according to Legosz et al. (24), type B3 fractures have the worst prognosis. Consistent with this study result, when comparing B3-type fractures with A-type fractures, we discovered a 16.75-fold higher mortality rate. The benefits of arthroplasty are apparent in these types of fractures, particularly in elderly patients who need to be mobilized as soon as possible, as supported by the current literature.

Drew et al. (16) revealed that at one year, patients have a 24% probability of death or requiring additional surgery. Bhattacharyya et al. (15)

reported a mortality rate of 11% at the end of 1 year following PFF surgery. The mortality rate in our study was 19.2% at 30 days and 36.5% at the end of the first year after PFF. The mortality rate in our study was higher than that reported in the current literature. This situation is believed to be related to the socioeconomic status of the society in which we live. In accordance with the literature, the results of our study on aging as well as pre-existing general health conditions have a negative impact on mortality.

The findings of the present study show that PFFs are distressing for patients, have a high mortality rate, and pose challenges for surgeons. Each surgical procedure performed on these patients is associated with an increased risk of mortality, which may provide valuable prognostic information for both patients and their families. Greater mortality is associated with advanced age and poor general health.

Study Limitations

The retrospective methodology of the study and the relatively small number of patients are among the limitations of this study. Unfortunately, the number of patients in this special patient group at single centers is limited. We recommend that prospective multicenter studies be conducted in the future. We believe that there is another limitation in our study regarding the simultaneous evaluation of type A and B fractures.

Conclusion

We found that types of fractures and surgical methods affected mortality. Among the relevant characteristics of surgical techniques are age and type of fracture. We found that patients who underwent osteosynthesis had a longer lifespan. In addition, a high mortality rate was observed in B3-type fractures.

Ethics Committee Approval: We received approval to conduct this study from University of Health Sciences Turkey, İstanbul Training and Research Hospital Institutional Review Board (approval number: 39, date: 28.01.2022).

Informed Consent: Informed consent was obtained from each participant included in the study.

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

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Recent Vaccination Rates in Diabetic Patients

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ABSTRACT

Introduction: This study aimed to determine vaccination rates, attitudes toward vaccination, and factors influencing influenza, pneumococcal, hepatitis B, and coronavirus disease-2019 (COVID-19) vaccination among patients diagnosed with diabetes mellitus (DM) after the COVID-19 pandemic.

Methods: Vaccination rates for influenza, pneumococcus, hepatitis B, and COVID-19 among newly diagnosed patients with DM were analyzed using Stepwise Multivariate Logistic Regression models to identify influencing parameters.

Results: The study included 442 (88.4%) patients with type 2 DM and 58 (11.6%) patients with type 1 DM. The median diabetes duration was 10 (5-19) years. Diabetes follow-up was conducted for 275 (55%) patients in Internal Medicine, 156 (31.2%) in endocrinology, and 46 (9.2%) in family medicine, with 23 (4.6%) patients having no regular follow-up. Vaccination rates were influenza 28.2%, pneumococcus 23.6%, hepatitis B 9.6%, and COVID-19 91.2%. Patients who were informed about vaccines had significantly higher vaccination rates ($p<0.001$). The distribution of information sources for COVID-19 and other vaccines differed significantly ($p<0.001$). Patients received more COVID-19 vaccine information from TV, Ministry of Health messages, and social media, while information about other vaccines was obtained mainly from the family medicine and internal medicine departments. Influenza vaccination rates were higher among older age groups, those with higher education levels, longer diabetes duration, and regular diabetes follow-up ($p<0.05$). Pneumococcus vaccination rates were higher among older age groups, those with longer diabetes duration, and those with regular diabetes follow-up ($p<0.05$). Hepatitis B vaccination rates were higher among those with higher education levels ($p<0.05$). No significant differences in COVID-19 vaccination rates were observed across the factors examined.

Conclusion: Knowledge regarding vaccination necessity and actual vaccination rates among patients with diabetes is significantly low. Educating patients about vaccination is crucial. The COVID-19 pandemic has highlighted the importance of vaccination for patients with diabetes. Although COVID-19 vaccination rates are expected to be higher due to the pandemic, utilizing Ministry of Health messages, TV, and social media to inform diabetic patients about influenza, pneumococcal, and hepatitis B vaccinations could enhance vaccination rates. It is essential for all patients with diabetes to be fully vaccinated against these infections, regardless of age.

Keywords: Vaccination, diabetes, hepatitis B, influenza, pneumococcus, COVID-19

Introduction

Diabetes mellitus (DM), one of the major health issues of our time, increases susceptibility to infectious diseases and remains a significant cause of mortality and morbidity among patients (1). One of the most effective ways to protect diabetic patients from infectious agents is encouraging vaccination and ensuring complete vaccination (2). It is well known that vaccination against influenza, pneumococcus, and hepatitis B significantly reduces mortality and morbidity associated with these diseases in patients with diabetes (2-5). National and international authorities recommend influenza, pneumococcal, and hepatitis B vaccinations for patients with diabetes without age distinction (2,6,7). In addition, the recent coronavirus disease-2019 (COVID-19) pandemic has affected our country as well, highlighting diabetic patients as a high-risk group for COVID-19 infection and emphasizing the necessity for all diabetic patients to receive COVID-19 vaccination (8-10). This underscores once again that vaccination is one of the most important ways to protect patients with diabetes from infections, increasing awareness among both physicians and patients with diabetes regarding vaccination. Despite these efforts, studies conducted in Turkey in recent years have shown

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lower vaccination rates among patients with diabetes compared with developed countries (2,11-13). In our study, following the COVID-19 pandemic that affected our country, as in the rest of the world, we aimed to determine the vaccination rates against influenza, pneumococcus, hepatitis B, and COVID-19 among patients with diabetes who presented to our clinic for the first time, as well as their vaccination attitudes and the factors influencing these.

Methods

After obtaining consent from patients presenting to our clinic for the first time with type 1 and type 2 DM, vaccination rates against influenza, pneumococcus, hepatitis B, and COVID-19 were assessed, along with an examination of where patients received information about these vaccinations. Vaccination statuses of patients were documented individually through the e-Nabız system after obtaining consent from all patients. Hemoglobin A1c (HbA1C) levels, indicating diabetic regulation, were also documented. Patients with HbA1C levels ≤7% in the last 3 months were categorized as having controlled DM, whereas those with HbA1C levels >7% were categorized as having uncontrolled DM.

Factors influencing patients' vaccination rates (demographic characteristics, type of diabetes, duration of diabetes, control of diabetes, regularity of diabetes follow-up, location of follow-up visits, awareness of the necessity of vaccinations among patients, whether they knew about the vaccinations, sources of information if known, presence of comorbidities) were analyzed.

This study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee (approval number: 421, date: 13.09.2023).

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences software version 21.0 (IBM Corp, Armonk, NY). Descriptive statistics for continuous data are presented as medians with minimum-maximum values, whereas categorical data are expressed as numbers and percentages. Fisher's exact test or Pearson's chi-square test was used to assess differences in categorical data. A significance level of $p<0.05$ was considered statistically significant. Multivariable logistic regression analyses were performed to identify factors associated with self-reported pneumococcal, influenza, hepatitis B, and COVID-19 vaccination status.

Results

A total of 500 patients were included in the study, comprising 58 (11.6%) diagnosed with type 1 DM and 442 (88.4%) diagnosed with type 2 DM. The median duration of diabetes was 10 (5-19) years. The mean age of the patients was 52.6±17.5 years. The distribution of patients' sociodemographic and clinical characteristics is presented in Table 1.

Clinics for diabetes follow-up are presented in Table 1. Among patients diagnosed with type 1 DM, 77.6% were under follow-up care at the endocrinology department. Notably, patients followed by the endocrinology department had significantly higher rates of high school and university education compared with those followed by other clinics ($p<0.001$). There were no significant differences in other demographic characteristics among the clinics.

In our study, 70.8% (n=354) of the patients had comorbid conditions. The most common comorbidities were hypertension [52.2% (n=261)] and coronary artery disease [27% (n=137)].

The patients' average HbA1c levels was 9.1±2.4. Fifty-six percent of patients developed diabetes-related complications. Among the patients, 44% had diabetic nephropathy, 37% had diabetic retinopathy, 28% had diabetic neuropathy, and 34% had macrovascular complications. There was no statistically significant difference in vaccination rates between patients with and without diabetes-related complications (p=0.125).

The vaccination rates for the overall patient population were as follows: influenza, 28.2%; pneumococcal, 23.6%; hepatitis B, 9.6%; and COVID-19, 91.2% (at least two doses of BioNTech, Sinovac, or Turkovac). Among the patients who received the COVID-19 vaccine, 61.4% received Sinovac, with 55.9% having two doses; 81.1% received BioNTech, with 56.1% having two doses; and 3.9% received Turkovac, all with a single dose.

When examining vaccination rates according to the type of DM, the hepatitis B vaccination rate was significantly higher in patients diagnosed with type 1 DM than in those diagnosed with type 2 DM ($p<0.001$). However, there was no significant difference in the rates of other vaccinations.

The relationship between vaccination knowledge and vaccination rates is presented in Table 2.

Table 1. Distribution of the sociodemographic and clinical characteristics of the patients

	n (%)
Gender	
Female	274 (54.8)
Male	226 (45.2)
Marital status	
Married	433 (86.6)
Single	67 (13.4)
Educational status	
Illiterate	76 (15.2)
Primary school	258 (51.6)
Middle school	28 (5.6)
High school	79 (15.8)
University	59 (11.8)
Diabetes type	
Type 1	58 (11.6)
Type 2	442 (88.4)
Diabetes regulation	
Controlled	160 (32)
Uncontrolled	340 (68)
Clinic for diabetes follow-up	
Internal medicine	275 (55)
Endocrinology	156 (31.2)
Family medicine	46 (9.2)
Not followed	23 (4.6)

Upon examining where patients received their vaccination information, we found that the sources of information for the COVID-19 vaccine and other vaccines differed significantly (p<0.001). Patients reported obtaining information about COVID-19 vaccination more frequently from television, Ministry of Health messages, and social media, whereas information about other vaccines was generally obtained from physicians (Figure 1). Among healthcare providers, family medicine and internal medicine departments were the most common sources of vaccination information. It was noted that none of the patients followed in the endocrinology department received vaccination information from their endocrinology clinic.

Table 2. Relationship between vaccination knowledge and vaccination rate

	The vaccine	There is no vaccine	p
Influenza vaccine			
Informed	87 (61.7)	3 (0.8)	**<0.001**
Not Informed	54 (38.3)	356 (99.2)	
Pneumococcal vaccine			
Informed	50 (42.4)	3 (0.8)	**<0.001**
Not Informed	68 (57.6)	379 (99.2)	
Hepatitis B vaccine			
Informed	17 (35.4)	5 (1.1)	**<0.001**
Not Informed	31 (64.6)	447 (98.9)	
COVID-19 vaccine			
Informed	363 (79.6)	5 (11.4)	**<0.001**
Not Informed	93 (20.4)	39 (88.6)	

The p-value was obtained from the Pearson's chi-square test. COVID-19: Coronavirus disease-2019

When examining vaccination rates by age, we found that the rates of all vaccines differed significantly between individuals over and under the age of 65 (p<0.05). A comparison of vaccination rates by age in patients with diabetes is shown in Table 3.

The follow-up of patients at different clinics affected their vaccination status. The vaccination rates and clinics where patients were followed up for diabetes are shown in Table 4.

When factors that could influence vaccination were examined using multiple logistic regression analysis, influenza vaccination rates were found to be significantly higher among individuals of advanced age, with a high level of education, with diabetes duration over 10 years, and with regular diabetes follow-up (p<0.05). Pneumococcal vaccination rates were also significantly higher among patients of advanced age, those with diabetes duration >10 years, and those with regular diabetes follow-up (p<0.05). Hepatitis B vaccination rates were significantly higher among those with a high level of education (p<0.05). There were no significant differences in COVID-19 vaccination rates according to the factors examined (Table 5).

Table 3. Comparison of vaccination rates according to age among patients with diabetes

	Age <65, (n=339)	Age >65, (n=161)	p
	n (%)	n (%)	
Influenza vaccine	82 (24.2)	59 (36.6)	**0.004**
Pneumococus vaccine	58 (17.1)	60 (37.3)	**<0.001**
Hepatitis B vaccine	40 (11.8)	8 (5)	**0.015**
COVID-19 vaccine	302 (89.1)	154 (95.7)	**0.015**

The p-value was obtained using the Pearson's chi-squared test. COVID-19: Coronavirus disease-2019

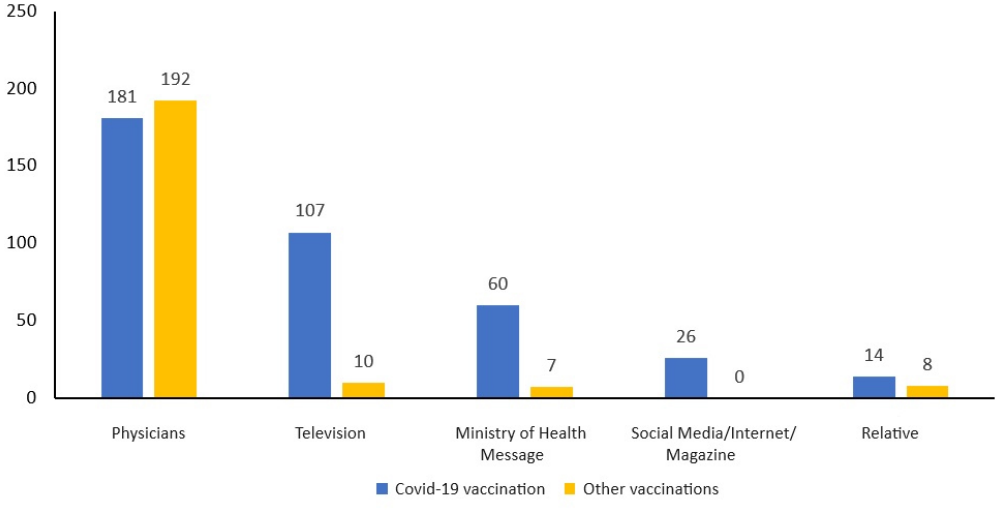

Figure 1. Bar graph showing the sources of information for COVID-19 and non-COVID-19 vaccinations
COVID-19: Coronavirus disease-2019

Table 4. Vaccination rates and clinics where patients are followed up for diabetes

	Clinic for diabetes follow-up			
	Family medicine, n (%)	Internal medicine, n (%)	Endocrinology, n (%)	p
Influenza vaccine				
Present	10 (21.7)	65 (23.6)	60 (38.5)	**0.003**
Not present	36 (78.3)	210 (76.4)	96 (61.5)	
Pneumococus vaccine				
Present	13 (28.3)	58 (21.1)	44 (28.2)	0.199
Not present	33 (71.7)	217 (78.9)	112 (71.8)	
Hepatit B vaccine				
Present	3 (6.5)	16 (5.8)	27 (17.3)	**<0.001**
Not present	43 (93.5)	259 (94.2)	129 (82.7)	
COVID-19 vaccine				
Present	46 (100)	251 (91.3)	139 (89.1)	0.068
Not present	0 (0)	24 (8.7)	17 (10.9)	

The p-value was obtained from the Pearson's chi-square test. COVID-19: Coronavirus disease-2019

Table 5. Examination of the variables affecting vaccination rates

	Influenza		Pneumococcal		Hepatitis B		COVID-19	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Gender (male)	0.723 (0.470-1,114)	0.142	0.83 (0.52-1.32)	0.429	1.74 (0.89-3.38)	0.105	0.49 (0.24-1)	0.051
Age (<65 years)	1,740 (1,094-2,768)	**0.019**	2.62 (1.61-4.25)	<0.001	0.58 (0.25-1.37)	0.213	2.31 (0.94-5.69)	0.069
Marital status (single)	1,196 (0.639-2,236)	0.576	1.67 (0.8-3.49)	0.174	2.58 (0.85-7.89)	0.096	1.88 (0.85-4.14)	0.118
Education (illiterate)								
Primary school	2,220 (1,090-4,522)	**0.028**	0.84 (0.44-1.63)	0.609	3.42 (0.76-15.28)	0.108	1.87 (0.77-4.56)	0.170
Secondary school	3,866 (1,363-10,962)	**0.011**	1.72 (0.6-4.89)	0.312	4.12 (0.61-27.66)	0.145	1.14 (0.27-4.9)	0.861
High school	3,207 (1,326-7,753)	**0.010**	1.53 (0.64-3.65)	0.339	5.66 (1.1-29.04)	**0.038**	1.14 (0.38-3.48)	0.814
University	2,880 (1,150-7,211)	**0.024**	1.86 (0.76-4.53)	0.172	8.43 (1.67-42.53)	**0.010**	1.45 (0.42-5)	0.552
Diabetes (uncontrolled)	0.919 (0.611-1,560)	0.919	1.08 (0.66-1.78)	0.754	1.07 (0.54-2.12)	0.853	1.42 (0.65-3.09)	0.377
The type of diabetes (type 1)	0.647 (0.309-1,351)	0.246	0.52 (0.22-1.22)	0.134	1.85 (0.78-4.39)	0.162	0.84 (0.32-2.22)	0.732
Duration of diabetes (<10 years)	2,290 (1,451-3,614)	**<0.001**	2.48 (1.5-4.1)	**<0.001**	1.2 (0.63-2.3)	0.583	1.41 (0.73-2.73)	0.304
Diabetes follow-up (none)	1,773 (1,111-2,830)	**0.016**	1.71 (1.04-2.81)	**0.035**	1.18 (0.57-2.45)	0.662	1.07 (0.52-2.18)	0.863

The reference categories for variables are indicated in parentheses. OR: Odds ratio, CI: Confidence Interval, COVID-19: Coronavirus disease-2019

Discussion

Vaccination against hepatitis B, influenza, pneumococcus, and COVID-19 in patients with diabetes is a critical factor in reducing hospitalization, mortality, morbidity, and healthcare costs in this patient group. The COVID-19 pandemic has once again highlighted the importance of effectively protecting patients with diabetes through vaccination. In our study, the influenza, pneumococcus, hepatitis B virus (HBV), and COVID-19 vaccination rates in patients diagnosed with DM during follow-up after the COVID-19 pandemic were 28.2%, 23.6%, 9.6%, and 91.2%, respectively. Vaccination rates for influenza, pneumococcus, and COVID-19 were significantly lower in individuals under 65 years of age than in those over 65 years of age, whereas the hepatitis B vaccination rate was higher among younger individuals. Vaccination rates were also higher in patients who were knowledgeable about vaccines. Patients reported receiving information about COVID-19 vaccination more frequently from TV, Ministry of Health messages, and social media, while information about other vaccines was often obtained from physicians (mainly from family physicians). Influenza vaccination rates were significantly higher in patients of advanced age, with a high education level, with a long duration of diabetes, and with regular diabetes follow-up. Pneumococcal vaccination rates were significantly higher in patients of advanced age, those with long-lived diabetes, and those with regular diabetes follow-up. Hepatitis B vaccination rates were significantly higher among patients with high education levels. There were no significant differences in COVID-19 vaccination rates according to the factors examined.

Vaccination rates for patients with diabetes in Turkey are significantly lower than those in developed countries (2,14). In a study conducted on patients with DM in Spain, the influenza, pneumococcal, and HBV vaccination rates were 55%, 18%, and 17%, respectively (15). In a prospective study by Tacken et al. (16), the influenza vaccination rates among patients with diabetes were reported to vary between 75% and

85%. In Turkey, a study by Apaydın et al. (12) on 504 patients with DM found influenza, pneumococcal, and HBV vaccination rates of 10%, 5%, and 6.9%, respectively. Another study by Arslan et al. (4) on patients with DM reported vaccination rates of 14.5%, 3.8%, and 15.5%, respectively, indicating relatively low levels.

In previous vaccination studies conducted in Turkey, data were generally obtained through surveys based on patient self-reports, and vaccination rates were determined accordingly (4,11-13). However, in our study, vaccination levels were accessed through individual entries for each patient in the E-health system. Although the influenza and pneumococcal vaccination rates in our study were lower than those of developed countries, they were higher than those reported in other studies conducted in Turkey. It is important to note that these studies in Turkey were conducted before the pandemic period (4,11-13,14,17). We believe that the higher rates of pneumococcal and influenza vaccination among patients with diabetes in our study are due to the pandemic. As is well known, during the pandemic period, all health authorities and the Ministry of Health recommended that patients with DM be fully vaccinated against influenza and pneumococcus, in addition to COVID-19, to reduce mortality rates. Patients were also informed about these recommendations during COVID-19 vaccination.

According to data from the Ministry of Health in Turkey, the COVID-19 vaccination rate in Istanbul is 77.8% (at least two doses) (18). The COVID-19 vaccination rate among patients with diabetes was 91.2%. We believe that the higher COVID-19 vaccination rate among patients with diabetes in our study compared with the general population in Istanbul is due to the Ministry of Health mandating vaccinations for patients with diabetes and conducting effective campaigns in this regard, as has been done worldwide. In a study conducted by Eren et al. (19) in Şanlıurfa on diabetic patients, the COVID-19 vaccination rate was 87.4%. The higher COVID-19 vaccination rate in our study may be attributed to the differences in socioeconomic status and education level, which influence vaccination rates, as highlighted in the TEMD vaccination study (20).

In our study, when examining vaccination rates according to the type of DM, there was no significant difference in vaccination rates, except for hepatitis B vaccination rates among patients with type 1 DM. This result is consistent with the TEMD vaccination study (20). Additionally, hepatitis B vaccination rates were significantly higher in individuals under 65 years of age than in those over 65. Since hepatitis B vaccination has been administered to the entire population during childhood in Turkey since 1998, we believe that the higher vaccination rates among the younger group of patients with type 1 DM can be explained by this. Given that the current adult population is not vaccinated during childhood and that hepatitis B is a significant infection risk for diabetics, many guidelines recommend hepatitis B vaccination for diabetics (2,7). However, similar to other studies conducted in Turkey and globally, our study also found that hepatitis B vaccination rates among patients with DM were quite low (4,11-13,15). This result highlights once again that adequate importance is not given to immunizing DM patients against HBV. Nevertheless, many guidelines recommend routine administration of the HBV vaccine three times for all diabetic patients aged 19-59 and for those aged 60 and above if there are additional risk factors for HBV (2,21).

Similar to the study by Arslan et al. (4), our study also found that influenza and pneumococcal vaccination rates were significantly higher in individuals over 65 years of age. While it is known that comorbidities and the potential for increased mortality and morbidity due to pneumonia are higher in patients over 65, both national and international authorities recommend immunization through vaccination for young patients with diabetes without age discrimination (2,7). In our study, contrary to the recommendations in the guidelines, we observed once again that immunization of young patients with diabetes through vaccination is being neglected. Therefore, we believe that additional support and information campaigns targeting the vaccination and immunization of young patients with diabetes in our country.

In a prospective study conducted by Satman et al. (14), factors that could affect vaccination status were examined, and it was found that the parameters increasing the rates of influenza and pneumonia vaccinations were advanced age and long duration of diabetes. We obtained results similar to those of Satman. However, unlike Satman's study, we observed that the presence of additional comorbidities and other illnesses did not affect the vaccination rates in our study. Similar to the results of the TEMD vaccination study, we found that these two vaccination rates were higher in patients with regular diabetes follow-up (20). We believe that this result is due to the close contact and information exchange between the patients, physicians, and healthcare institutions. In our study, similar to the results of Demirci's multicenter cross-sectional TEMD vaccination study, influenza vaccination rates were higher in those with higher education levels, whereas, unlike Demirci et al.'s (20) study, there was no such relationship for pneumococcal vaccination rates. As in Lu et al.'s (22) study in the United States evaluating hepatitis B vaccination rates in patients with diabetes, we also found that hepatitis B vaccination rates were significantly higher in those with higher education levels. In our study, COVID-19 vaccination rates were not affected by factors that could influence vaccination, as was the case in Eren et al.'s (19) study. Given the different dynamic nature of the COVID-19 pandemic, its higher mortality rates, and the inclusion of all patients with diabetes in the mandatory vaccination program, as recommended by health authorities, this is expected. The diagnosis of diabetes itself was the most significant reason for COVID-19 vaccination, independent of all other parameters.

In our study, we observed that the follow-up of patients with diabetes by different clinical units affected their vaccination rates. The influenza and hepatitis B vaccination rates of patients followed by the endocrinology department were statistically significantly higher compared with those followed by other clinical units, whereas there was no significant difference in other vaccination rates. However, we also found that the education level of patients followed by the endocrinology department was higher than that of patients followed by other clinical units. We believe that this difference in vaccination rates may be related to this disparity in education levels. Similar to previous studies, we observed that influenza and hepatitis B vaccination rates were associated with higher education levels in our study (4).

Consistent with previous studies, our study found that patients who received information about vaccines had higher vaccination rates (11,14,17). In our study, we observed that patients frequently obtained information about COVID-19 vaccination from TV, Ministry of Health messages, and social media, whereas they primarily received information about other vaccines from physicians. Although we consider the differences in COVID-19 vaccination rates and vaccination information compared to other vaccines and vaccination attitudes as a natural consequence of the pandemic, we believe that the effective use of social media, TV, and the Ministry of Health's vaccination information messages for informing diabetic patients about influenza, pneumococcal, and hepatitis B vaccines could significantly contribute to increasing their vaccination rates.

In our study, we observed that similar to the findings of the study by Kırık et al. (11), information about vaccinations other than COVID-19 was primarily provided by physicians. The diaVAX study, a multicenter prospective study conducted by Satman et al. (14), found that a 4-month physician training program resulted in an average increase of 2.5 and 4 times in influenza and pneumonia vaccination rates. Ensuring the education of physicians at all levels regarding the vaccination of patients with diabetes and maintaining the continuity of this education are crucial for bringing the vaccination rates among patients with diabetes in Turkey to the desired levels. In our study, we found that vaccination information was mostly provided by family physicians and internal medicine departments, similar to the findings of Arslan et al. (4). Contrary to Arslan et al.'s (4) study, it is striking that none of the patients followed by the endocrinology department in our study received vaccination information from the endocrinology clinic. We believe that the importance given to vaccination immunization in endocrinology clinics, where diabetic patients are referred as the last step, should be increased, and that information should be provided meticulously. It is concerning that, as shown in the studies by Arslan et al. (4) and Eren et al. (19), the vaccination rates in endocrinology clinics remain significantly below the expected levels for patients with diabetes even after the pandemic period (20).

Study Limitations

This study was limited by its retrospective design. Although the study included a significant number of patients, further research involving larger and more diverse populations would be beneficial to confirm and expand upon these findings.

Conclusion

Although there has been a slight increase in pneumococcal and influenza vaccination rates following the pandemic period, knowledge regarding the necessity of vaccination and the actual vaccination rates among patients with diabetes remain significantly below the desired levels. The COVID-19 pandemic has once again highlighted the importance of effectively protecting patients with diabetes through vaccination. Although it is expected that COVID-19 vaccination rates will be higher than other vaccinations due to the pandemic, we believe that the effective use of Ministry of Health vaccination information messages, TV, and social media to inform diabetic patients about influenza, pneumococcal, and hepatitis B vaccinations would be beneficial in increasing vaccination rates. Furthermore, regardless of age group, it should be remembered that all patients with DM, whether type 1 or type 2 DM, are at increased risk of infections, and it is essential to ensure that influenza, pneumococcal, and hepatitis B vaccinations are completed without fail.

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee (approval number: 421, date: 13.09.2023).

Informed Consent: It was obtained.

Authorship Contributions: Concept - Ö.P.K.; Design - Ö.P.K.; Data Collection or Processing - D.A., M.G.G., K.Ş., Ö.B.G., M.N.; Analysis or Interpretation - Ö.P.K., M.N., E.Ş.H.; Literature Search - Ö.P.K.; Writing - Ö.P.K.

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Retrospective Examination of Vessel Wall Imaging in Intracranial Arterial Structures in Cases with Acute or Chronic Cerebral Ischemia

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ABSTRACT

Introduction: We aimed to reveal the current status of high-resolution magnetic resonance imaging (HR-MRI) and its potential to identify different intracranial vessel wall pathologies. We also aimed to investigate the diagnostic performance of contrast-enhanced HR-MRI T1-SPACE sequence in determining vessel wall pathologies and to determine its contribution to conventional methods.

Methods: We retrospectively reviewed HR-MRI images of 33 consecutive patients with 30% or above stenosis based on clinical, digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) evaluations. All patients had a history of stroke, and 33 stenotic vessel segments in anterior-posterior circulation were reviewed. On HR-MR images, plaque eccentricity, presence or absence of intraplaque hemorrhage, contrast enhancement pattern, and plaque length were evaluated. As causes of atherosclerosis, the presence of diabetes mellitus, hemoglobin A1c, total cholesterol, trigylicerid, and high-density lipoprotein levels, history of smoking, history of taking statin drugs, and hemoglobin levels were acquired, and the correlation between these variables and plaques labeled as stable or unstable in these patients was investigated.

Results: Atherosclerosis was observed in 29 of the 33 cases included in our study, and stenosis in intracranial vascular structures due to moyamoya disease was observed in 4 cases. In patients with intracranial stenosis secondary to moyamoya disease, diffuse concentric homogeneous enhancement was observed within the vessel wall in the prestenotic artery segment. In patients with stenosis due to atherosclerosis, increased heterogeneous enhancement was observed within the atheroma plaque. A significant correlation was observed between eccentric-concentric plaque and atherosclerotic segment length.

Conclusion: The vessel lumen can be evaluated using CTA, MRA, and DSA, but the vessel wall cannot be evaluated using these traditional techniques. Vessel wall imaging is helpful for identifying atheromas in intracranial and cervical carotid arteries, and for determining the morphologies of vessel walls and the surrounding structures.

Keywords: Atheroma plaque, magnetic resonance imaging, digital subtraction angiography, vW-MRI

Introduction

Stroke is an important cause of disease-related deaths and leads to devastating outcomes. Atherosclerotic plaque formation in intracranial arteries is the most common cause of ischemic stroke (1,2). Vessel wall changes, such as vessel wall thickening or the presence of soft atherosclerotic plaques without luminal stenosis, are often overlooked; however, these morphological changes may be important for understanding the etiology of ischemic stroke (3). Conventional methods for assessing the vessel lumen often do not provide information about the underlying pathological processes involving the vessel wall (4).

Magnetic resonance angiography (MRA) is a good screening tool with minimal invasiveness and no ionizing radiation, and the vessel wall can also be evaluated with additional sequences. High-resolution magnetic resonance imaging (HR-MRI) has been introduced for direct assessment of the vessel wall beyond only luminal information, such as the severity of stenosis in the vessel walls (5). HR-MRI can reveal characteristic radiological features associated with vessel wall pathologies in diseases such as intracranial artery involvement, such as atherosclerosis, dissection, Moyamoya disease, and vasculitis (6,7). Black-blood HR-MRI is recently used in the evaluation of cerebrovascular diseases (2). Contrast-

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enhanced magnetic resonance high-resolution variable flip angle turbo-spin-echo (T1-SPACE) technique using different flip angle evolutions enables high-spatial-resolution images of the intracranial vessel wall and is helpful for more accurately detecting intracranial vascular lesions (2).

In this study, we aimed to reveal the current status of HR-MRI and its potential to identify different intracranial vessel wall pathologies. We also aimed to investigate the diagnostic performance of contrast-enhanced HR-MRI T1-SPACE sequence in determining vessel wall pathologies and to determine its contribution to conventional methods.

Methods

Study Population and Image Evaluation

Thirty-three patients [20 male, 13 female; mean age: 59.89 (ranged from 28 to 80)] with significant intracranial vascular stenosis in clinical examination, computed tomography angiography (CTA) or MRA evaluation, and no known cardiovascular disease were included in the study between 2018 and 2019. HR-MRI method was applied to all of the patients, and the images were analyzed through the local database system Sectra PACS. Images reported by 2 radiologists with more than 20 years of CTA and MRA reporting experience. HR-MRI was performed in patients who had stenosis >30% on CTA, MRA, or DSA. While 30-50% stenosis was considered as mild stenosis in our study; 50-70% was accepted as moderate; 70% and above were evaluated in the category of high-grade stenosis. The shape of the plaque, the segment involved, the length of the segment involved, the enhancement of the plaque, and the presence of intraplate hemorrhage were evaluated using retrospective HR-MRI images. If these cases have CTA examination, the presence of calcification in the plaque was evaluated. In patients with stenosis secondary to atherosclerosis, atheroma plaques are classified as eccentric or concentric.

When assessing intraplaque hemorrhage, abnormal intraplate T1 signal consistent with blood and blood products was defined as 150% of the T1 signal of the adjacent muscle. When evaluating significant plaque enhancement, the postcontrast T1 signal was defined as a 2-fold greater signal increase than the precontrast T1 signal. Cholesterol, triglyceride, high-density lipoprotein, mean platelet volume, hemoglobin A1c values of patients with atherosclerosis-related stenosis were examined. The use of aspirin in these cases was questioned.

Oral and written consent was obtained from all patients who participated in our study. The study was conducted in accordance with ethical standards as outlined in the Declaration of Helsinki of the World Medical Association. Ethical approval was obtained from a regional Ege University Ethics Committee (approval number: 19-12.1T/54, date: 25.12.2019). Cases with a history of cardioembolic cerebrovascular disease, allergy to MRI contrast agents, or acute renal failure were excluded from the study.

Imaging Technique and Protocol

MRI examinations were performed in the supine position using a 1.5 Tesla (Magnetom Amira, SIEMENS) and a 64-channel head coil. Patients admitted to the Tesla MR unit were seated, and a 20-gauge vascular access was established through the antecubital vein. In all patients, the examination was successfully terminated within 60 minutes. 0.1 mmol/kg Gadovist (gadobutrol, Bayer) or 0.2 mmol/kg Dotarem (gadoteric acid, Guerbet) was used as the IV contrast agent. Contrast material was administered at a rate of 3 mL/sec., and postcontrast imaging was performed 6 min after the contrast material was administered. T2-weighted and diffusion-weighted imaging (DWI) series were obtained after contrast agent administration. DWI series were obtained using non-ecoplanar imaging. After the contrast injection was finished, 30 mL of saline was infused. Localizer, 3D time-of-flight MRA, susceptibility weighted imaging, T1-SPACE three-dimensional (3D), pre-postcontrast 3D T1-SPACE, T2-weighted fat sat, DWI (b0 and b1000), and ADC mappings was performed.

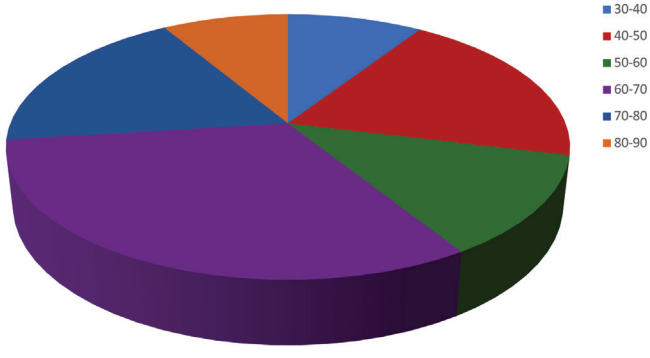
The imaging parameters for 3D T1-SPACE were as follows: TR, 900 ms; TE, 14 ms; matrix, 320 × 320; field of view, 17 × 17 cm^2; slice thickness, 0.5 mm; number of sections, 224; and scan time, 8:29 min. 3D thin-layer images were postprocessor, and the original images of 3D T1-SPACE sequence were imported into the Siemens workstation.

Statistical Analysis

IBM SPSS Statistics 25.0 software was used. The suitability of numerical variables to normal distribution was examined using the Shapiro-Wilk test (n<50). Numerical variables were presented as mean and standard deviation (SD) or median (minimum-maximum). Categorical variables are presented as numbers and percentages.

Results

The mean age of the patients was 59.89 years with a SD of 13.07. The youngest patient was 28 years old, and the oldest patient was 80 years old (Graphic 1). A total of 33 stenotic vessel segments were detected in 33 patients (25 male, 8 female). Atherosclerosis was observed in 29 of the 33 cases included in our study, and stenosis in intracranial vascular structures due to moyamoya disease was observed in 4 cases. Acute ischemia was observed in DWI-MRI in 5 of the cases with stenosis due to atherosclerosis. In our study, in patients with intracranial stenosis secondary to moyamoya disease, diffuse concentric homogeneous enhancement was observed within the vessel wall in the prestenotic artery segment. In patients with stenosis due to atherosclerosis, increased heterogeneous enhancement was observed within the atheroma

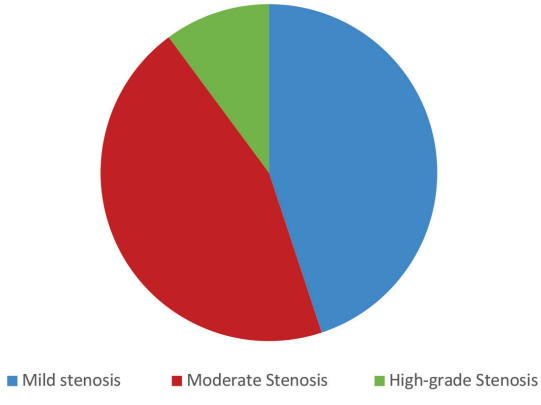


Graphic 1. Age distrubition in patients

plaque. In 13 of 29 cases of stenosis due to atherosclerosis; shows multi-segmental involvement. In 18 of 29 patients with atherosclerosis-related stenosis; a significant increase in contrast enhancement was observed in unstable plaques. In vascular structures with multisegmental involvement, the segment with the highest degree of stenosis was evaluated in each case, and the degree of stenosis was measured at the narrowest point. Intraplaque hemorrhage was observed in 9 of the patients with stenosis due to atherosclerosis. CTA examination was available in 13 patients, and 8 of these patients had calcification in the atheroma plaque. High-grade stenosis was observed in 18 cases (70% and above), moderate (50-70%) in 8 cases, and mild (30-50%) in 7 cases (Graphic 2). A significant correlation was found between eccentric-concentric plaque and atherosclerotic segment length (p-value=0.014) (Tables 1, 2). No significant correlation was found between the degree of stenosis and intraplaque hemorrhage (p>0.005) (Tables 3, 4; Figures 1, 2).

Discussion

HR-MRI effectively identified distinctive enhancement patterns associated with different pathologies, showing diffuse concentric enhancement in Moyamoya cases and increased heterogeneous enhancement in atherosclerotic plaques. Importantly, this study found a significant correlation between eccentric-concentric plaque morphologies and the length of atherosclerotic segments, highlighting the potential of HR-MRI for diagnosing and categorizing plaque stability.



Graphic 2. Severity of stenosis

Furthermore, although intraplaque hemorrhage was noted in 9 cases with atherosclerosis, the degree of stenosis did not significantly correlate with the presence of hemorrhage. This underscores the importance of

Table 1. Involved arteries and segments
Basilar artery
Vertebral
Vertebral and basilar
Left vertebral artery
Right internal carotid artery
Right vertebral artery
Right middle cerebral artery
Left internal carotid artery
Basilar artery
Basilar artery
Left vertebral artery
Left vertebral artery
Right middle cerebral artery
Right middle cerebral artery
Basilar artery
Bilateral internal carotid artery
Basilar artery
Middle cerebral artery
Right middle cerebral artery
Left vertebral artery
Basilar artery
Left vertebral artery
Left middle cerebral artery
Left middle cerebral artery
Left internal cerebral artery
Right vertebral artery
Left internal carotid artery
Basilar artery
Left internal carotid artery
Left internal carotid artery (Moyamoya)
Right internal carotid artery (Moyamoya)
Bilateral internal carotid artery (Moyamoya)
Bilateral internal carotid artery (Moyamoya)

Table 2. Involved segment lengths of eccentric plaques

Eccentric plaque, SD	**Mean value (mm)**		17.8667	2.56509
Segment length	95% CI for	Lower bound	12.3651	
	Mean	Upper bound	23.3682	

CI: Confidence interval

Table 3. The comparison of eccentric and concentric plaques length

	Sig. (2-tailed)		**Mean difference**	**S.E. difference**
Segment length	Equal variances are assumed	0.014*	8.61667	3.24406
	Equal variances are not assumed	0.010	8.61667	3.06590

*T-test was used for equality of means. A significant correlation was found between eccentric and concentric plaque and atherosclerotic segment length. The p-value was calculated as 0.014

Table 4. The comparation of intraplaque hemorrhage and degree of stenosis

Crosstab			Intraplaque hemorrhage		
			0	1	Total
Grade of stenosis	1	Count	4	1	5
		Degree of stenosis	80%	20%	100%
		Intraplaque hemorrhage	22.2%	11.1%	18.5%
	2	Count	5	1	6
		Degree of stenosis	83.3%	16.7%	100%
		Intraplaque hemorrhage	27.8%	11.1%	22.2%
	3	Count	9	7	16
		Degree of stenosis	56.3%	43.8%	100%
		Intraplaque hemorrhage	50%	77.8%	59.3%
Total Degree of stenosis Intraplaque hemorrhage		Count	18	9	27
			66.7%	33.3%	100%
			100%	100%	100%

*There was no significant relationship between the degree of stenosis and intraplaque hemorrhage

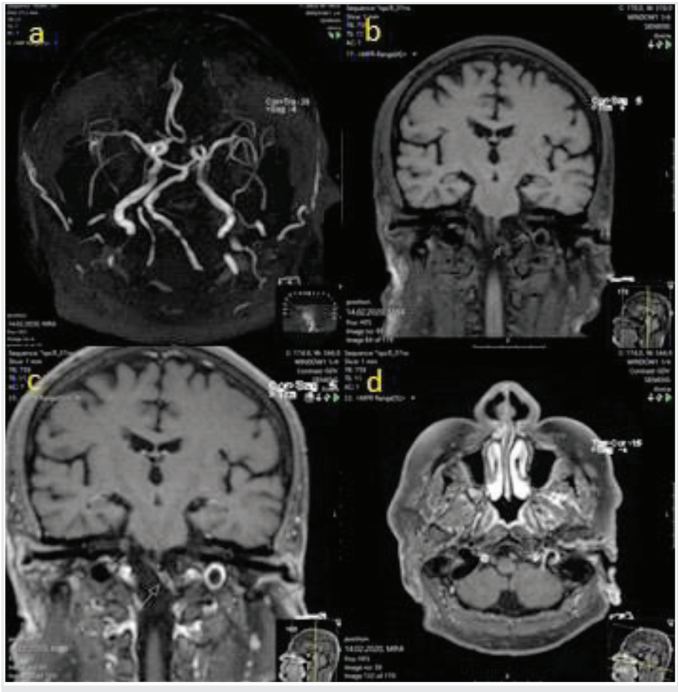


Figure 1. (a) 3D TOF MRA of the patient; high-grade stenosis was observed in the V4 segment of the left vertebral artery. (b) Atheroma plaque observed on precontrast T1W series (black arrow). (c) Contrast enhancement of the postcontrast T1W coronal atheroma plaque was observed. (d) Eccentric atheroma plaques are present in the axial T1W postcontrast series
TOF: Time-of-Flight, MRA: Magnetic resonance angiography

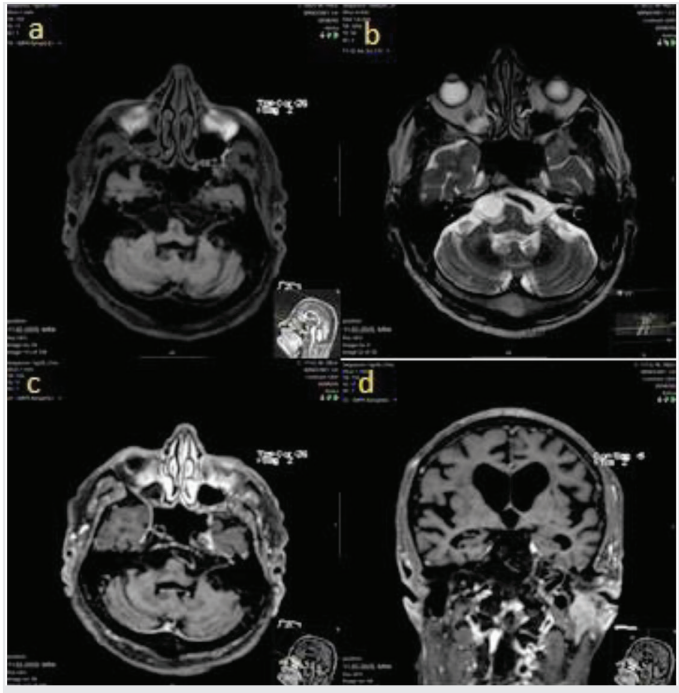


Figure 2. (a) Atheroma plaques observed in precontrast T1-weighted images. (b) Appearance of atheroma plaque in the V4 segment of the vertebral artery in the T2W series. (c, d) Axial and coronal images are enhanced in the postcontrast series

HR-MRI for providing detailed insights that are crucial for understanding the complexities of intracranial vascular diseases beyond what traditional methods offer. These techniques cannot provide detailed information about vascular diseases because luminal pathologies, such as stenosis, are caused by changes in the vessel walls (7). Angiography is a useful, important, and common imaging modality, with digital subtraction angiography (DSA) remaining the gold standard for luminal imaging. However, DSA is invasive and can contain ionizing radiation (8). The CTA, MRA, and DSA modalities focused on luminal imaging. Angiography often depicts intracranial artery disease as luminal stenosis, which is often insufficient for evaluating intracranial vascular pathology (8-10). In CTA examination, the vessel wall can be evaluated; however, the low contrast resolution and soft tissue resolution of CT do not provide sufficient information and can not clearly show changes in the vessel wall (11). HR-MRI can directly visualize the intracranial vessel wall, demonstrating its potential to characterize plaque properties (11,12). Atherosclerosis was observed in 29 of the 33 cases included in our study, and stenosis in intracranial vascular structures due to Moyamoya disease was observed in 4 cases. Acute ischemia was observed in 5 of

the cases with stenosis due to atherosclerosis on DWI-MRI. In the study of Turan et al. (12), in patients with extracranial carotid disease; it has shown that HR-MRI can reliably identify intraplaque bleeding, which can be a better predictor of clinical events compared to CTA and conventional radiographic methods. Inversion recovery was performed using T1-weighted scans to zero the signal from the blood with a high-resolution 3 Tesla MR (13,14). Abnormal intraplaque T1 signal consistent with bleeding or blood products was defined as 150% of the T1 signal of the adjacent muscle. The intraplaque signal was >150% of the muscle signal in the two central slices, consistent with the imaging features of intraplaque hemorrhage demonstrated in symptomatic middle cerebral arteries (15). There are similar findings in our study. Zhang et al. (16) reported that brain 3D HR-vW MRI is a reliable method for measuring intracranial vessel size and potentially useful for monitoring plaque progression and regression. Zhu et al. (17) reported that 3D T1-weighted SPACE can be used for intracranial vessel wall assessment on both 3T and 7T MRI.

Intracranial intraplaque hemorrhage is an important component of plaque weakness (18). Although our study was performed with 1.5 Tesla, the black blood technique yielded good image quality with 0.7 mm isotropic and whole brain coverage in the basilar artery, vertebral artery, internal carotid artery intracranial segments, and MCA proximal and distal segments (19,20). The imaging features consistent with intraplaque hemorrhage on T1-weighted imaging and the characterization of contrast-enhanced T1-intracranial atherosclerosis were demonstrated in our study. Zhu et al. (17) recently successfully imaged intracranial vessel walls using 3D SPACE or equivalent arrays such as VISTA and CUBE with high scanning efficiency, high resolution, and black blood imaging. Swartz et al. (18) showed that T2 and pre- and postcontrast T1 inversion recovery images can distinguish vessel wall thickening (eccentric), inflammation (concentric), and other wall pathologies. In our study, an increase in eccentric wall thickness was observed in patients with concentric and atherosclerosis-related stenosis, similarly in patients with intracranial vascular stenosis due to Moyamoya disease.

Study Limitations

Our study had some limitations; most of the subjects included in the study had CVD, and a control group was not included. Interobserver variability was not evaluated. In our study, patients who were examined with MRA, CTA, or DSA and had significant stenosis were included in the study. Plaques considered unstable and shown to cause CVD in 60% of patients did not cause significant stenosis. The study was conducted using 1.5-T Tesla MRI. In the literature, most studies were conducted with 3 or 7 Tesla MRI.

Conclusion

Although HR-MRI is not frequently used in our country, it is routinely used worldwide, especially in the USA. Physically and mentally stable patients are preferred because the examination takes approximately 45-60 minutes. In our country, there are no provisions for health practice communication in social security institutions. The examination was coded as MRA and cranial MR with contrast. In cases with stenosis in intracranial vascular structures with DSA, MRA or CTA; HR-MRI is a problem-solving method in determining the etiology and distinguishing whether the plaque is stable or unstable. HR-MRI cannot be applied to every patient due to the long duration of the examination and the inability of the patient to remain still during the examination. HR-MRI is a suitable method in terms of direct imaging of the vessel wall, increased contrast in the wall, which is significant in terms of unstable plaque, and intra-plaque bleeding.

Ethics Committee Approval: This study was approved by the Ege University Ethical Committee (approval number: 19-12.1T/54, date: 25.12.2019).

Informed Consent: Oral and written consent was obtained from all patients who participated in our study.

Authorship Contributions: Concept - Ö.Ö.; Design - F.Z.A.; Data Collection or Processing - Ö.M.; Analysis or Interpretation - İ.T.R.; Literature Search - C.Ç.; Writing - F.Z.A.

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

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Rotational Analysis of Femur and Tibia with Bilateral Lower Extremity Computed Tomography Measurements: A Retrospective Study

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ABSTRACT

Introduction: This study aimed to emphasize the importance of assessing and correcting rotational alignment of the lower extremities after trauma. To examine the effects of differences in femoral and tibial rotation on optimal patient outcomes.

Methods: This single-center retrospective study was conducted at University of Health Sciences Turkey, İstanbul Training and Research Hospital in accordance with the guidelines of the Declaration of Helsinki. The study involved 130 patients who underwent lower extremity computed tomography (CT) angiography or venography between May 2015 and December 2022. Patients underwent CT scan in the supine position with their legs extended. Radiographic parameters were measured digitally, and femoral and tibial rotation angles were calculated.

Results: The mean femoral and tibial rotations were 12.2° and 31.3°, respectively. No significant difference was observed between femoral and tibial rotations in terms of sex. There was a moderate correlation in femoral rotation and a high correlation in tibial rotation between the right and left sides.

Conclusion: Gender was not a significant factor in the assessment of lower extremity rotational alignment. The importance of considering bilateral differences during surgical procedures is emphasized. These findings may help clinicians make more informed decisions when assessing and treating patients. However, further research is required before these findings are fully integrated into clinical practice.

Keywords: Femoral rotation, tibial rotation, rotational alignment, surgical planning

Introduction

Assessment and correction of rotational alignment in the lower extremities, especially after trauma, are crucial for optimal patient outcomes. There can be significant differences between femoral and tibial rotation in healthy individuals, and precise assessment methods may be required for patients with axial plane deformities. The healthy side often refers to the pre-traumatic rotation of the affected bones, particularly in comminuted fractures where anatomical landmarks are lost. Rotational dislocation is an important clinical problem after closed nailing of femoral and tibial shaft fractures, with rotational differences exceeding 15° in the femur and 10° in the tibia considered true deformities that may require corrective osteotomy (1).

Various methods have been proposed to accurately assess tibial rotation. For example, the intermalleolar method has demonstrated high accuracy by providing intraoperative tibial rotational measurements within 10 degrees of CT measurements, making it a reliable tool for intraoperative corrections (2). Furthermore, fibular alignment has been suggested as a surrogate marker for tibial rotation. Significant malrotation is probably absent when fibular contact disappears during medullary nailing (3).

The C-arm method using lateral axis views has also shown high accuracy in predicting CT measurements and preventing postoperative malrotation, with no reported incidence of malrotation greater than 10° (4). Furthermore, the thigh-foot angle and transmalleolar axis are common methods to assess tibial torsion, but their validity may be limited by foot alignment. Overall, CT-based torsion angle calculations remain a reliable indicator of malrotation, with studies showing a higher incidence of misalignment than previously reported, with studies underscoring the importance of accurate rotational assessment and correction in clinical practice (1).

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This study aimed to examine the importance of assessment and correction of lower extremity rotational alignment after trauma for optimal patient outcomes. It is known that differences between femoral and tibial rotations can play an important role in the correct diagnosis and treatment of patients with axial plane deformities. In this context, our research aimed to examine the accuracy and reliability of assessment methods used in both healthy individuals and patients with rotational deformities and to determine reference values that can be used in surgical planning and intraoperative correction.

Methods

This single-center retrospective study was conducted at University of Health Sciences Turkey, İstanbul Training and Research Hospital according to the guidelines of the Declaration of Helsinki. The University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee approved the study (approval number: 76, date: 09.08.2024). Informed consent was obtained through an "opt-out" form available on the hospital website. The sample size of the study is 130 patients included; 113 were male and 17 were female. All patients who underwent lower extremity CT angiography or venography at our hospital between May 2015 and December 2022 were identified using the hospital's Picture Archiving and Communication System (PACS). Patients with complete lower extremity CT angiography or venography images showing the entire femur, tibia, and talus on both sides were included. Patients under the age of 20 or over the age of 60 with leg asymmetry or flexion, osteoarthritis (OA) of the hip and knee joints with joint deformity (Kellgren and Lawrence grade 2/3/4) (5), endoprosthesis of the hip, knee, or ankle joint, postoperative variations in the lower extremity, or posttraumatic changes in the lower extremity were excluded.

Data Collection

The rotational alignment analysis was performed using lower extremity computed tomography (CT) angiography or venography. Patients were placed in the supine position stabilized with belts with their legs extended, while their ankles and knees were in contact with the table and each other. The ankles were 90° flexed with 45° between their toes during a standardized CT examination protocol. CT scans were performed using a 64-slice CT system (Toshiba, Aquilion, Tokyo, Japan) and a 128-slice CT system (Philips Brilliance 128, Amsterdam, Netherlands) with predetermined reconstruction parameters. 0.4 mm thick slices, 120 Kvp, and 80 mass were reconstructed from raw data.

Radiographic parameters were measured in the axial direction. Digital measurements were performed using the RİS-PACS image archiving system (Simple PACS V2, İzmir, Turkey). The measurements were performed independently by three orthopedic surgeons who were familiar with rotation analyses. The rotation angle values were calculated by averaging the two observers' measurements.

Femoral rotation was defined as the angle formed by the femoral neck and the line intersecting the distal femur's posterior condylar line (PCL). Reikerås et al. (6) defined the femoral neck axis as the line between the center of the femoral head and the middle of the neck in two CT sections with the widest femoral head and neck.

Positive and negative values indicated femoral retroversion and femoral neck anteversion, respectively, concerning the PCL. Tibial rotation was measured as the angle formed by the line connecting the posterior parts of the proximal tibial condyles to the bimalleolar axis. The line linking the posterior parts of the proximal tibial condyle was expanded to the top of the fibula (7).

In a cross-section just below the articular surface of the tibial pylon, the bimalleolar axis runs between the malleoli and the center of the talus dome (8). Positive values represent external rotation of the tibia. Negative values indicate internal rotation of the distal tibia with respect to the proximal posterior tibial plateau.

Furthermore, the knee and total leg rotation alignments were evaluated. Knee rotation was calculated as the angle created by the line linking the posterior proximal tibial condyles and distal femoral PCL. Positive values were used to represent the external rotation of the knee. These variables provide evidence of knee laxity in the extension position. Leg rotation with the knee was defined as the total axial lower-limb rotation based on the angle formed by the femoral neck and bimalleolar axes, which includes potential rotational elements caused by knee laxity. Leg rotation without the knee was defined as the total axial lower-limb rotation angle after subtracting the knee rotation, excluding potential rotational elements due to knee laxity.

Statistical Analysis

The SAS 9.4 package was used for the statistical analysis of the data obtained in this study. For the quantitative variables of the study determined by measurement, descriptive statistics were presented as mean and standard deviation; for the qualitative variables determined by counting, descriptive statistics were presented as numbers and percentages. The variables used in this study were first tested for conformity to a normal distribution using the Shapiro-Wilk test. For this purpose, Skewness values were also analyzed.

As a result of the tests, all variables were found to be normally distributed, and parametric tests were used in the statistical analysis. The paired two-sample t-test was used to compare the mean differences between right and left rotations. Student's two-sample t-test was used to compare rotation and individual bilateral differences (IBD) by gender. Pearson's correlation coefficient was calculated for the correlation of right-left rotations. The significance level was set at 0.05 throughout the study.

Results

In this study, a total of 130 consecutive bilateral lower extremity CT angiography and venography images of the femur and tibia were analyzed. The general descriptive statistics and gender comparison results obtained from the analysis are presented in Table 1. The study included 130 patients, with a mean age of 55.9±15.06 years, 55.8±15.15 years for males and 56.4±14.90 years for women.

Pearson's correlation coefficients between the right and left lower extremities for all patients are presented in Table 2. The Pearson correlation coefficient of femoral rotation between the right and left sides showed a positive, moderate, and statistically significant relationship for all patients ($r=0.59$, $p=0.0001$). In contrast, the Pearson

correlation coefficient of tibial rotation between the right and left sides was positive, high, and statistically significant (r=0.76, p=0.0001).

A comparison of the measurements of the right and left lower extremities among all patients is presented in Table 3. In the analysis of all extremities, the mean absolute bilateral difference (ABD) of femoral rotation was 5.11°, and the mean ABD of tibial rotation was 5.19°. Similarly, the mean relative bilateral difference (RBD) of femoral rotation was 0.57°, and the RBD of tibial rotation was 2.28° for all extremities. The RBD of femoral rotation showed no statistically significant difference between the right and left sides. The RBD of tibial rotation revealed a statistically significant difference between the right and left sides (p=0.0004), with the right side having a significantly higher external rotation.

Table 4 compares the results of measuring the right and left lower extremities according to gender. There was a significant difference between the right and left lower extremity averages of femoral rotation in males. A statistically significant difference was found between the right and left lower extremity averages of femoral rotation in females (p=0.0001) and a significantly higher internal rotation was observed on the left side. Moreover, when the comparisons of the measurements of the right and left lower extremities of the tibial rotations of different genders are examined, it is seen that there were no significant differences.

The basic descriptive statistics and analysis results for male and female patients are presented in Table 5. The results show no statistically significant differences between all paired independent samples' t-test results according to gender.

The distribution of the ABD between the femur and tibia is presented in Figure 1. From this figure, it can be seen that 93.84% of the femur rotation was ≤15° and 96.99% of the tibia rotation was ≤15°.

Discussion

One of the most important clinical implications of this study is the absence of significant gender-based differences in femoral and tibial rotation. This demonstrates that clinicians can use the same reference values when assessing patients, regardless of gender. With this in mind, this approach could potentially provide a more standardized approach, simplifying diagnosis and treatment planning.

Table 1. General descriptive statistics and comparisons by gender

	Gender					
	Male (n=113) Mean (SD)	Female (n=17) Mean (SD)	All (n=130) Mean (SD)	p-value	95% CI	
Age	55.8 (15.15)	56.4 (14.90)	55.9 (15.06)	0.9780	-8.33	7.23
Femoral rotation	12.2 (7.12)	13.3 (7.38)	12.3 (7.13)	0.5052	-4.77	2.59
Tibial rotation	31.3 (9.76)	34.9 (10.52)	31.8 (9.90)	0.0887	-8.71	1.45

CI: Confidence interval, SD: Standard deviation

Table 2. Pearson's correlation coefficient between right and left lower extremities

	r	p-value	95% CI	
Femoral rotation	0.59	<0.0001	0.46	0.69
Tibial rotation	0.76	<0.0001	0.68	0.82

CI: Confidence interval

Table 3. Comparison of right and left lower extremity measurements

	Right (n=130) mean (SD)	Left (n=130) mean (SD)	RBD mean (SD)	ABD mean (SD)	p-value RBD	95% CI RBD	
Femoral rotation	12.62 (8.26)	12.05 (7.73)	0.57 (7.24)	5.11 (5.14)	0.3721	-0.68	1.82
Tibial rotation	32.93 (10.43)	30.65 (10.63)	2.28 (7.18)	5.19 (5.45)	0.0004	1.03	3.53

CI: Confidence interval, ABD: Absolute bilateral difference, RBD: Relative bilateral difference, SD: Standard deviation

Table 4. Comparison of right and left lower extremity measurements according to gender

	Gender	Right (n=130) mean (SD)	Left (n=130) mean (SD)	RBD mean (SD)	ABD mean (SD)	p-value RBD	95% CI RBD	
Femoral rotation	Male	12.54 (8.21)	11.84 (7.79)	0.70 (7.32)	5.13 (5.25)	0.3086	-0.66	2.06
	Female	13.12 (8.78)	13.45 (7.41)	-0.34 (6.77)	4.97 (4.44)	<0.0001	-3.28	-1.65
Tibial rotation	Male	32.56 (10.46)	35.35 (10.16)	2.50 (7.27)	5.17 (5.68)	0.7899	-1.36	1.76
	Female	30.06 (10.37)	34.52 (11.81)	0.83 (6.58)	5.31 (3.74)	0.6101	-2.55	4.21

CI: Confidence interval, ABD: Absolute bilateral difference, RBD: Relative bilateral difference, SD: Standard deviation. External rotation is shown as positive values; concurrently internal rotation is shown as negative values

Table 5. Basic descriptive statistics and analysis results for male and female patients

	Gender				
	Male (n=113) mean (SD)	Female (n=17) mean (SD)	p-value	95% CI	
Femoral rotation (right)	12.5 (8.21)	13.1 (8.78)	0.6837	-4.84	3.69
Femoral rotation (left)	11.8 (7.79)	13.5 (7.41)	0.3459	-5.60	2.37
RBD of the femoral rotation	0.7 (7.32)	-0.3 (6.77)	0.8305	-2.69	4.77
ABD of femoral rotation	5.1 (5.25)	5.0 (4.44)	0.8063	-2.50	2.81
Tibial rotation (right)	32.6 (10.46)	35.4 (10.16)	0.1555	-8.16	2.57
Tibial rotation (left)	30.1 (10.37)	34.5 (11.81)	0.0671	-9.90	0.97
RBD of the tibial rotation	2.5 (7.27)	0.8 (6.58)	0.6736	-2.03	5.37
ABD of tibial rotation	5.2 (5.68)	5.3 (3.74)	0.3436	-2.96	2.68

CI: Confidence interval, ABD: Absolute bilateral difference, RBD: Relative bilateral difference, SD: Standard deviation. External rotation is shown as positive values; concurrently internal rotation is shown as negative values

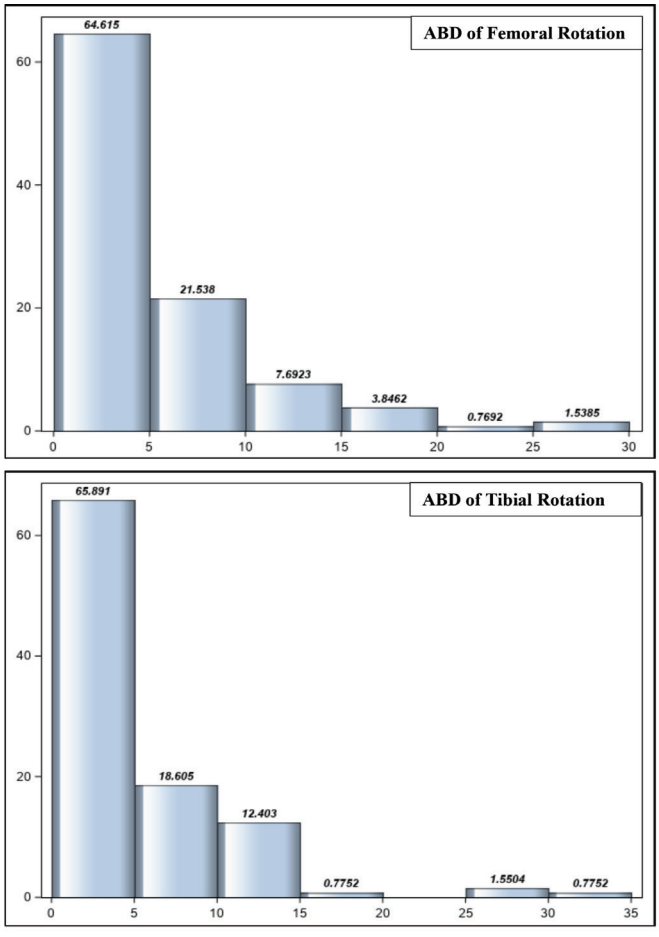

Figure 1. Distribution of absolute bilateral rotation difference between the femur and tibia
ABD: Absolute bilateral difference

Another important finding of our study was the rotational symmetry between the right and left extremities, which correlated moderately with femoral rotation and highly with tibial rotation. This symmetry provides a valuable reference point for orthopedic surgeons, allowing them to more precisely identify rotational abnormalities and make more informed decisions regarding surgical interventions or conservative treatments.

The fact that right tibial rotation is significantly more outwardly rotated than left tibial rotation is an important clinical implication to consider, especially in the treatment of conditions such as tibial torsion. This asymmetry can lead to functional and biomechanical consequences that may have implications for surgical planning and postoperative rehabilitation. Therefore, clinicians can tailor treatment plans to the specific needs of each patient while considering rotational differences.

In a study by Kinami et al. (9) in healthy Japanese subjects, remarkable bilateral symmetry in rotation of the femur and tibia was observed, with mean ABD of 6.5° and 5.1°, respectively. Furthermore, 95% of femoral rotation was within ≤15° US, while 89% of tibia rotation was within ≤10° US (9). The current study, together with our previous one, provides a basis for understanding the nuances of lower extremity rotational alignment. In our study, we examined the rotation of the femur and tibia in a different cohort and found mean values of 12.2° and 31.3°, respectively. In contrast to the Japanese study, our data revealed no significant rotational differences between genders. Both studies emphasize the importance of considering IBDs during surgical interventions to avoid potential functional impairments. While the Japanese study highlighted the tendency for higher external rotation on the right side, especially during tibial surgery, our study emphasizes the importance of accurate intraoperative assessments to avoid significant malrotation.

Another study by Ries et al. (10) aimed to establish reference values for lower extremity rotation in a healthy population and revealed significant side-to-side asymmetry in femorotibial torsion. The left femur showed greater anteversion and the right tibia showed more external rotation (10). This finding is important for clinical applications, particularly in the diagnosis and treatment of rotational deformities. Similarly, Zheng et al. (11) found significant individual differences in femoral and tibial torsion between patients with bilateral varus-type knee OA and controls, emphasizing the need for caution when assessing rotational alignment in such patients. Gallo et al. (12) also emphasized the variability in tibial torsion, reporting that 12.3% of patients had IBDs of ≥10 degrees and that race/ethnicity affected the magnitude of torsion but not the IBDs.

Ivanov et al. (13) compared three fluoroscopic methods for identifying femoral rotation and found that the true lateral and neck-horizontal angle techniques were more reliable than the smaller trochanter profile method, resulting in more significant malrotation.

Finally, Roberts et al. (14) validated the intermalleolar method for intraoperative assessment of tibial rotation during intramedullary nail fixation and demonstrated its accuracy to be 10° within CT measurements. These studies emphasize the importance of recognizing IBDs in femorotibial rotation and the need for precise measurement techniques to ensure correct rotational alignment during orthopedic procedures.

The strengths of this study include the fact that it was performed in a large patient population and the use of CT angiography and venography methods for the evaluation of femur and tibia rotations. The high accuracy of the data increases the reliability of the findings. In addition, the diversity of experience levels of the orthopedic surgeons involved in the study ensured that the measurements were performed in an independent and unbiased manner.

Study Limitations

The study has some limitations. The retrospective design and single-center nature of the study may limit the generalizability of the results. The relatively homogeneous study population was relatively homogeneous and did not include individuals with different ethnicities or underlying pathologies suggests that the results may not apply to all patient groups. An increased study size and an equally balanced gender ratio could have been determined if the study were not planned as a retrospective study. Furthermore, the lack of long-term follow-up data limits the assessment of the long-term effects of rotational variations on lower limb function. In future studies, large-scale investigations with more diverse populations and long-term follow-up data are recommended.

Conclusion

In conclusion, this study provides valuable insights into the variations in femur and tibial rotation in the lower extremities. The findings have important clinical implications that may help clinicians make more informed decisions when evaluating and treating patients. However, further research is required before these findings are fully integrated into clinical practice. In particular, understanding the long-term effects of rotational variations on lower limb function and the underlying mechanisms of these variations are important areas for future research.

Ethics Committee Approval: The University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee approved the study (approval number: 76, date: 09.08.2024).

Informed Consent: Informed consent was obtained through an "opt-out" form available on the hospital website.

Authorship Contributions: Concept - A.Ç.; Design - A.Ç., B.A., İ.T.A.; Data Collection or Processing - A.Ç., Ö.D.G., E.K., İ.T.A.; Analysis or Interpretation - A.Ç., İ.T.A.; Literature Search - A.Ç., B.A., Ö.D.G., E.K.; Writing - A.Ç., İ.T.A.

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Assessment of Oral Capecitabine in Elderly Patients with Stage 2 Colon Cancer: Toxicity, Tolerability, and Survival Outcomes

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ABSTRACT

Introduction: Adjuvant chemotherapy, particularly oral capecitabine, is often considered for stage 2 colon cancer despite its controversial use in elderly patients with comorbidities. This study aimed to assess the toxicity, tolerability, and survival outcomes of oral capecitabine in elderly patients diagnosed with T4N0, stage 2 colon cancer.

Methods: This retrospective study included 52 patients aged >70 years who were diagnosed with T4N0M0 colon cancer and received adjuvant capecitabine. Treatment toxicities were graded according to the National Cancer Institute of Canada Common Toxicity Criteria v4. Overall survival (OS) was analyzed.

Results: The study revealed that 86% of patients experienced treatment-related adverse events, with 29% exhibiting grade 3 and 23% grade 4 toxicities. Common severe adverse events include diarrhea and nausea. Despite starting treatment at lower doses, a significant proportion of patients required further dose reductions due to side effects, with only seven patients completing the full eight cycles of capecitabine. The median follow-up was 48 months, with disease-free survival and relapse-free survival rates of 61.6% and 67%, respectively. The 5-year OS rate was 71%.

Conclusion: In stage 2 colon cancer, administering adjuvant capecitabine to elderly patients aged >70 years poses challenges due to significant toxicity and tolerability issues. However, our study found that even with dose reductions, adjuvant therapy remains crucial for elderly patients, with a 71% 5-year OS rate similar to that of younger populations.

Keywords: Colon neoplasms, chemotherapy, adjuvant, aged, capecitabine

Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy globally, affecting both sexes. According to GLOBOSCAN data, an estimated 1.9 million new cases and 1 million deaths were recorded in 2020. The majority of diagnoses are manifest in individuals aged 65 years (1,2). Notably, the critical determinant influencing patient survival in colon cancer postoperatively revolves around the disease stage at diagnosis. For stage 2 tumors, the 5-year disease-specific survival rate ranges from 60% to 86% (3,4).

According to TNM staging, T4N0 tumors fall within stages 2B and 2C, with the distinction hinging on the tumor's invasion pattern. T4a signifies penetration of the visceral peritoneum surface, while T4b denotes direct invasion or histological adherence to structures or other organs (5,6). Although negated, lymph node involvement does not guarantee a favorable prognosis. Interaction of T4 tumors with other organs increases the risk of recurrence and metastasis.

The potency of adjuvant chemotherapy is most pronounced in stage 3 (node-positive disease). Nevertheless, several trials have indicated the benefit of adjuvant chemotherapy for high-risk patients with stage 2 disease, such as T4 (7,8). Given the roadblocks posed by comorbidities and suboptimal performance scores in elderly patients, the administration of adjuvant chemotherapy becomes constrained. Moreover, the customization of chemotherapy for older patients, particularly oxaliplatin-containing regimens, remains a subject of debate. The recommended postoperative chemotherapy regimen for elderly patients is oral capecitabine or a fluoropyrimidine regimen (9,10).

This study aimed to assess the toxicity, tolerability, and survival impact of oral capecitabine in patients aged >70 years diagnosed with T4N0

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colon cancer following complete mesocolic excision with lymph node dissection.

Methods

The ethics approval of the study was obtained from the Local Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-04-16, date: 24.06.2024).

Patients

The research design was a retrospective cross-sectional study. The study involved the analysis of patient files from 180 individuals diagnosed with early-stage colon cancer who underwent surgery between 2014 and 2019. Specifically, 52 patients meeting the criteria of T4N0M0 according to TNM staging and aged over 70 years were included in the study after excluding those unable to receive adjuvant capecitabine. The eligible patients received at least one course of adjuvant capecitabine (1000 mg/m^2 twice daily for 14 days, followed by a 7-day rest period). Data on the patients' demographic and pathological characteristics were retrieved from patient files and the hospital database. Retrospective treatment toxicities and tolerances were evaluated based on patient records.

Furthermore, treatment-related adverse events were retrospectively compiled from patient data files. Adverse effects, such as hand-foot syndrome, fatigue, alopecia, diarrhea, laboratory abnormalities, nausea, vomiting, and stomatitis, were graded by the National Cancer Institute of Canada Common Toxicity Criteria v4. Progression-free survival was defined as the duration from the commencement of the first chemotherapy treatment to disease progression. In contrast, overall survival (OS) was defined as the duration from the initiation of the first chemotherapy treatment until death (Figure 1).

Statistical Analysis

Statistical analyses were conducted using the SPSS version 22.0 for Windows. Categorical and continuous data were analyzed using the chi-squared test, while continuous data were analyzed using the Student's t-test. Survival analysis was performed using the Kaplan-Meier test. Results were assessed using a 95% confidence interval with a significance level set at $p<0.05$.

Results

A total of 52 elderly patients were included in our study database between 2014 and 2019. The median age at the time of colon cancer diagnosis was 77.9 years (range, 70-87 years). The gender distribution was almost equal, with a male-to-female ratio of 1.17:1. Table 1 shows the detailed demographic characteristics, data, and pathological features of all patients.

In treated patients, 86.0% experienced adverse events related to capecitabine, with 29% and 23% of the patients encountering grade 3 or 4 treatment-related adverse events, respectively (Table 2). The most common grade 3 or 4 capecitabine-related adverse events were diarrhea and nausea. As a result of capecitabine-related adverse events, 86% of the patients (n=45) had to discontinue treatment, some due to low-grade side effects.

Eight patients developed capecitabine-related hand-foot syndrome, with three cases classified as grade 3-4 severity. For grade 1-2 adverse effects, local treatments and maintenance of capecitabine dosage were employed, whereas treatment was discontinued in patients experiencing persistent toxicity from grade 3-4 side effects.

Table 1. Baseline demographics, clinical, and pathologic characteristics of patients

Characteristic	n (%)
Age, median (range)	77.9 (range, 70-87)
Gender	
Male	28 (54%)
Female	24 (46%)
Comorbidities	
None	4 (8%)
1-2	31 (60%)
>2	17 (32%)
Smoking status	
Current smoker	12 (23%)
Former smoked	27 (52%)
Never smoked	13 (25%)
ECOG performance-status-score	
0	9 (17%)
1	32 (61%)
2	11 (22%)
Primary tumor locations	
Left site	33 (64%)
Right site	16 (30%)
Other site	3 (6%)
Lymphovascular invasion	
Present	42 (80%)
Absent	10 (20%)
Perineural invasion	
Present	40 (77%)
Absent	12 (23%)
Grade	
Well-differentiated	37 (71%)
Moderately differentiated	10 (20%)
Poorly differentiated	5 (9%)

Table 2. Capecitabine-related adverse events

Treatment-related adverse events	Grade 1-2 (n)	Grade 3-4 (n)
Nausea	20	3
Vomiting	28	4
Diarrhea	12	1
Fatigue	3	1
Stomatitis	7	1
Neutropenia	6	13
Hand-foot syndrome	5	3
Increased creatinine	6	2
Hyperbilirubinemia	2	1

Neutropenia was the most common laboratory abnormality caused by capecitabine, with 8 and 5 patients experiencing grade 3-4 neutropenia, respectively. Capecitabine-induced creatinine elevation led to acute renal failure in 8 patients, with two cases attributed to fluid loss from diarrhea. Intravenous fluid replacement was administered, and the dose was reduced in these patients. Ultimately, capecitabine was discontinued in 6 of these patients.

All patients initially received a daily dose of 2000 mg of capecitabine, which was adjusted in the second cycle according to tolerance. Despite starting with a lower dose during the first cycle, eight patients exhibited poor tolerance, preventing any dose increase. Ultimately, 28 patients required dose reductions because of side effects, whereas only seven completed eight cycles of capecitabine. Gastrointestinal intolerance, particularly nausea and vomiting, was the most common reason for the early discontinuation of capecitabine (Table 3).

Table 3. Treatment modifications in patients

Average number of cycles	5 (10%)
Patients who completed full cycles of capecitabine	7 (13%)
Patients with treatment delay	34 (65%)
Patients with reduced dose	28 (53%)
Patients who stopped treatment	45 (86%)

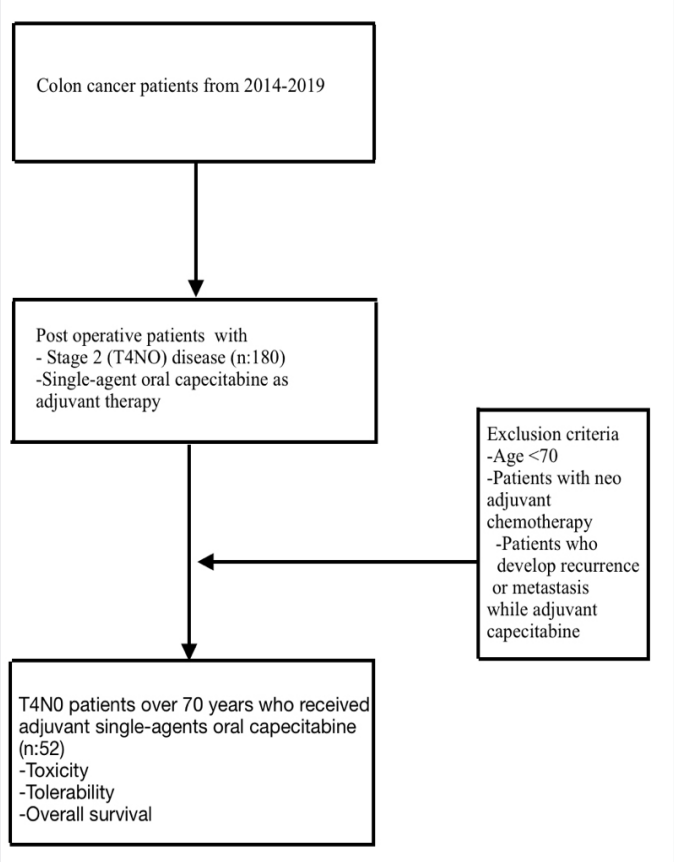

Figure 1. Flow of patient

Survival Outcomes

The median follow-up duration was 48 months. Four patients died because of unrelated health conditions, and there were no recurrences of CRC. The disease-free survival (DFS) rate was 61.6% (n=32), and the relapse-free survival (RFS) rate was 67% (n=35) for all patients. The 5-year OS rate was 71% (n=37) (Figure 2).

Discussion

Based on the available data, the prognosis of stage 2 colon cancer is variable due to various factors, with pathological changes being a significant determinant. Notably, stage 2b and 2c colon cancers, which are characterized by T4 tumors, exhibit a higher incidence of postoperative residual tumors compared with stage 3 tumors, resulting in poorer prognoses and lower 5-year survival rates (11). Effective adjuvant treatment for T4 tumors is therefore crucial. Nevertheless, administering practical nursing oncological treatments at appropriate doses can be a complex challenge, particularly for elderly patients.

Clinical studies have shown that the addition of oxaliplatin to capecitabine in adjuvant therapy does not provide survival benefit for patients over 65 (12). However, it is important to note that oral capecitabine alone can cause numerous side effects in elderly patients. The variability in response to and toxicity of capecitabine is influenced by several factors, including ethnicity. For instance, studies have reported variations in the tolerability and toxicity of capecitabine among different ethnic groups (13,14). Notably, there are no clinical studies that directly demonstrate the toxicity of capecitabine in Turkish patients, but existing studies suggest that the Turkish group may exhibit lower tolerability (15,16).

In our study involving patients aged >70 years, a maximum dose of 1000 mg/m^2 of capecitabine twice daily was administered, with cautious initial dose escalation to assess tolerability. Despite these precautions, the occurrence of drug-related toxicity was high, with a notable proportion of patients experiencing grade 3 and 4 toxicity. This is consistent with the established role of genetic variations

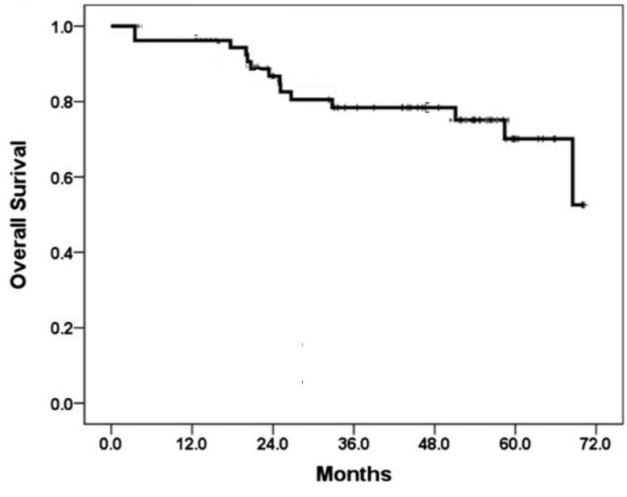

Figure 2. Overall survival of all patients

in capecitabine-related toxicity, specifically the well-documented association between dihydropyrimidine dehydrogenase (DPD) genetic variations and predisposition to fluoropyrimidine-induced toxic effects (17,18). Deficiencies in DPD activity cause severe, life-threatening drug-related toxicities in capecitabine-treated patients.

In routine oncology practice, DPD enzyme activity should not be assessed before initiating capecitabine treatment. However, it is advisable to assess it in patients experiencing severe toxicity (19). Unfortunately, since DPD enzyme activity tests cannot be performed in our oncology center, we lack information on our patients' genetic polymorphisms. We suspect that *DPD* gene polymorphisms and similar genetic variations may be present in a significant proportion of patients who experience grade 3 or 4 side effects.

Our study observed a high treatment discontinuation rate due to side effects, with a small percentage of patients completing the recommended eight cycles of adjuvant capecitabine at the total dose. In addition, more than half of the patients required dose reduction. Similar observations have been reported in other studies, suggesting the challenges associated with tolerability and the necessity of dose adjustments in elderly patients receiving capecitabine-based therapy (20,21). Notwithstanding the challenges, our study demonstrated a 3-year DFS rate of 61.6%, an RFS rate of 67%, and a 5-year OS rate of 71%, which are comparable to the existing literature. These findings indicate that adjuvant capecitabine may improve survival rates, regardless of age, for patients with stage 2 colon cancer. Additionally, the occurrence of side effects and dose reductions during treatment implies that these challenges may also be relevant in younger patient populations. Notably, our study revealed no significant difference in survival rates between the two age groups in the context of colon cancer.

Study Limitations

The study presented herein is subject to several limitations that warrant consideration. Primarily, the restricted number of patients included in the study limits the ability to draw definitive conclusions. Furthermore, the retrospective nature of the analysis may have introduced biases, potentially leading to deficiencies in the evaluation of retrospective side effects. Additionally, although the comorbidities of the patients were known, the medical treatments administered for these coexisting conditions were not comprehensively documented. Consequently, the evaluation of toxicity may not fully capture the potential interactions of these treatments with capecitabine.

Conclusion

Our study is the first to demonstrate elevated toxicity and challenging tolerability of adjuvant single-agent capecitabine in Turkish patients aged >70 years. Despite these challenges, the survival outcomes were comparable to those of the younger population. This finding highlights the significance of adjuvant treatment in the geriatric population, even with dose reduction.

Ethics Committee Approval: The ethics approval of the study was obtained from the Local Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-04-16, date: 24.06.2024).

Informed Consent: Retrospective study.

Authorship Contributions: Concept - E.D., İ.G.; Design - E.D., R.Ç.; Data Collection or Processing - C.K., M.S.D.; Analysis or Interpretation - A.G.S.D., M.Y.; Literature Search - E.T.C.; Writing - E.D.

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An Analysis of Vitamin B12 Levels in Patients Admitted to the Internal Medicine Ward Over the Past Five Years and Their Relationship with Admission Diagnoses

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ABSTRACT

Introduction: Vitamin B12 is an essential micronutrient involved in various metabolic processes, including DNA synthesis and neurological function. B12 deficiency can lead to significant hematological and neurological disorders. This study aimed to evaluate changes in serum vitamin B12 levels in patients admitted to the internal medicine department over the past 5 years and examine their relationship with admission diagnosis.

Methods: This retrospective study included 500 patients hospitalized in the Internal Medicine Department at University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2020 and 2024. Patient data were obtained from the hospital information system and categorized according to demographic variables, reason for hospitalization, chronic diseases, vitamin B12 supplementation, metformin use, and serum vitamin B12 levels.

Results: The study cohort comprised 500 patients with a mean age of 63.1 years. No significant differences in B12 levels were found between different age groups or genders, nor across the years studied. However, patients hospitalized for pancreatitis and those using metformin had significantly lower B12 levels ($p<0.05$), whereas patients in palliative care or those with malignancies had significantly higher levels ($p<0.05$). The use of vitamin B12 supplements was correlated with significantly higher serum B12 levels ($p<0.05$).

Conclusion: The serum vitamin B12 levels of patients admitted to the internal medicine department remained stable over the past 5 years. However, certain subgroups, such as patients with pancreatitis, malignancies, and metformin use, exhibited significant variations in B12 levels. Regular monitoring of B12 levels in high-risk groups, such as patients with diabetes receiving metformin, is recommended to prevent deficiency-related complications. Elevated B12 levels in patients with cancer should prompt further investigation into the underlying malignancies.

Keywords: Vitamin B12, vitamin B12 deficiency, hematopeosis, pancytopenia, myelin, malignancy

Introduction

Vitamin B12, also known as cobalamin, is an essential micronutrient that must be obtained from animal-derived proteins because it cannot be synthesized or stored in the human body (1). Dietary sources of vitamin B12 include meat, fish, eggs, and dairy products (2).

Vitamin B12 involves many complex physiological pathways. It is essential for hematopoiesis and plays a key role in the production of leukocytes, erythrocytes, and platelets in bone marrow. Vitamin B12 deficiency impairs purine and thymidylate synthesis, disrupts DNA synthesis, and induces erythroblast apoptosis, leading to ineffective erythropoiesis and anemia (3). Therefore, vitamin B12 deficiency should be considered in the differential diagnosis of pancytopenia.

Vitamin B12 is vital for the health of the nervous system, particularly in maintaining myelin synthesis by oligodendrocytes and supporting both central and peripheral nervous system function (4). Vitamin B12 deficiency is associated with a range of neuropsychiatric disorders, from confusion to coma (5). Furthermore, studies indicate that vitamin B12 deficiency can impair the parasympathetic and sympathetic nervous systems (6). Although autonomic dysfunction associated with B12 deficiency is often clinically mild, it is associated with a significant risk of severe cardiac arrhythmia, contributing to increased morbidity and

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mortality. Additionally, sympathetic dysfunction can result in orthostatic hypotension, increasing the risk of falls and subsequent fractures in elderly patients (7). Reduced mobility and social isolation after such events can also lead to depression in this patient group (8).

Vitamin B12 deficiency is common across different populations, with those at greatest risk included the elderly, pregnant women, and individuals with renal or gastrointestinal diseases. Furthermore, vegetarian and plant-based diets have gained popularity across all age groups. As a result, long-term B12 deficiency has been increasingly observed, particularly among individuals adhering to vegetarian diets, leading to various hematological and neurological disorders (9). Neurological manifestations of vitamin B12 deficiency are often non-specific and may become irreversible if not promptly diagnosed. Therefore, an early identification using sensitive and specific markers is crucial (10).

In this study, we aimed to investigate the changes in serum vitamin B12 levels in patients admitted to the internal medicine department over the past 5 years and examine the relationship with admission diagnosis.

Methods

Ethics committee approval was received from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 14, date: 05.07.2024). All procedures performed in the study were in accordance with the 1964 Helsinki Declaration.

This retrospective study included patients hospitalized in the Internal Medicine Department of University of Health Sciences Turkey, İstanbul Training and Research Hospital during the month of January over the past 5 years. The inclusion criterion for this study was admission to the internal medicine ward within a specified timeframe. No exclusion criteria were applied. For each year, 100 patients were randomly selected for inclusion, resulting in a total of 500 patients. Patient data were retrieved from the hospital information system and categorized according to age, gender, reason for hospitalization, presence of chronic diseases, serum vitamin B12 levels, use of metformin, and administration of vitamin B12 supplementation. The variables were systematically recorded for analysis.

Statistical Analysis

Descriptive statistics were presented as mean, standard deviation, median, minimum, maximum, frequency, and percentage. The distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For the analysis of quantitative independent data with a non-normal distribution, the Kruskal-Wallis test and Mann-Whitney U test were employed. Statistical analyses were performed using SPSS version 27.0.

Results

A total of 500 patients were included in the study, with 100 patients admitted to the internal medicine ward from January 2020 to 2024. The mean age of the patients was 63.1±17.7 years, with 53.4% being male and 46.6% female (Table 1).

The reasons for hospitalization, chronic conditions, and the percentage of patients receiving metformin are presented in Table 1.

The mean serum vitamin B12 level across the cohort was 440.5±383.4 pg/mL. A total of 24.8% of the patients (124 patients) were using vitamin B12 supplements, whereas 75.2% (376 patients) were not (Table 1).

No significant differences in B12 levels were observed between the 18-44, 45-54, 55-64, 65-74, and 75-101 ($p>0.05$), nor between male and female patients ($p>0.05$). B12 levels remained consistent across the years 2020, 2021, 2022, 2023, and 2024 ($p>0.05$) (Table 2).

B12 levels were lower in patients hospitalized for pancreatitis than in those not hospitalized for pancreatitis ($p<0.05$). Additionally, B12 levels were higher in the group hospitalized for palliative care than in those not receiving palliative care ($p<0.05$) (Table 2).

Among patients with diabetes, B12 levels were lower than in non-diabetic patients ($p<0.05$), whereas B12 levels were higher in patients with malignancy than in those without malignancy ($p<0.05$) (Table 3). Patients using metformin had lower B12 levels than those not using metformin ($p<0.05$), and patients taking vitamin B12 supplements had significantly higher B12 levels than those not using supplements ($p<0.05$) (Table 3).

No significant differences in B12 levels were found between patients with and without gastrointestinal bleeding, infection, acute renal failure, decompensated heart failure, diabetic ketoacidosis, hypertension, ischemic heart disease, chronic kidney disease, cerebrovascular disease-dementia, liver disease, or other diseases (all, $p>0.05$) (Tables 2, 3).

Discussion

Vitamin B12 deficiency has been extensively linked to a wide range of systemic diseases, particularly neurological and hematological disorders. In the field of neurology, deficiencies in B12 are primarily associated with conditions such as Alzheimer's disease, ischemic stroke, and peripheral neuropathies (11-13). Hematologically, it is strongly associated with isolated thrombocytopenia, megaloblastic anemia, pancytopenia, and pernicious anemia (14-17). Beyond these well-known associations, B12 deficiency has been implicated in disorders affecting various systems. For instance, studies have suggested a relationship between B12 deficiency and sarcopenia in older adults (18), excessive daytime sleepiness (19), and olfactory disorders (20). Furthermore, patients with autoimmune thyroid diseases have been found to have lower serum B12 levels than the general population (21). Additionally, Tamura et al. (22) highlighted the role of vitamin B12 in cellular immunity, suggesting that it acts as an immunomodulator.

In our study, we observed significantly lower serum B12 levels in patients hospitalized for pancreatitis compared with those hospitalized for other reasons. Pancreatitis, particularly non-biliary pancreatitis, is a common cause of emergency admissions to internal medicine departments. Diagnosing pancreatitis requires meeting two of the following three criteria: elevated pancreatic enzyme levels, characteristic abdominal pain, and supportive imaging findings (23). Although our study identified an association between lower B12 levels and pancreatitis, Glasbrenner et al. (24) reported no such link in their study of 137 patients with

chronic pancreatitis, suggesting that B12 deficiency is a rare finding in this patient population. However, Girish et al. (25) found that serum B12 levels were significantly lower in patients with chronic pancreatitis, supporting our findings. Although further research is needed to establish whether pancreatitis, particularly the chronic form, is a risk factor for B12 malabsorption, it is clear that healthy gastrointestinal tract and functional pancreatic enzymes are essential for B12 absorption.

Another significant finding of our study was the higher B12 levels observed in patients receiving palliative care. These patients, many of whom have malignancies, are typically hospitalized for short periods for symptom management, including pain management, correction of serum electrolyte imbalances, and blood sugar regulation. Elevated B12 levels in patients with cancer have been well documented, particularly in relation to lung, pancreatic, and liver cancers and hematological malignancies, such as myeloproliferative disorders (26). For instance, Fanidi et al. (27) supported the hypothesis that high serum B12 levels are associated with lung cancer. Similarly, Cinemre et al. (28) found that patients with myeloproliferative disease exhibited falsely elevated serum B12 levels. These findings indicate that high serum B12 levels in patients not receiving B12 supplementation should prompt consideration of an

Table 1. Demographic characteristics of the patients, distribution by years, comorbidities, serum B12 levels, metformin and B12 supplementation status

		Min-.max.	Median	Mean ± SD, (n %)
Age (years)		18.0-101.0	65.0	63.1±17.7
Age distrubition	18-44			84 (16.8%)
	45-54			67 (13.4%)
	55-64			90 (18.0%)
	65-74			111 (22.2%)
	75-101			148 (29.6%)
Gender	Male			267 (53.4%)
	Female			233 (46.6%)
Years	2020			100 (20.0%)
	2021			100 (20.0%)
	2022			100 (20.0%)
	2023			100 (20.0%)
	2024			100 (20.0%)
Reason for hospitalization				
Pancreatitis				22 (4.4%)
GIS bleeding				68 (13.6%)
Infection				176 (35.2%)
AKI				138 (27.6%)
Palliative				41 (8.2%)
DHF				29 (5.8%)
DKA				26 (5.2%)
Chronic diseases				
DM				93 (18.6%)
HT				51 (10.2%)
IHD				61 (12.2%)
CKD				68 (13.6%)
Malignancy				128 (25.6%)
CVE-dementia				27 (5.4%)
Hepatic diseases				21 (4.2%)
Others				1 (0.2%)
Metformin	(-)			426 (85.2%)
	(+)			74 (14.8%)
B12 level (pg/mL)		30.0-2000.0	310.0	440.5±383.4
B12 supplimentation	(-)			376 (75.2%)
	(+)			124 (24.8%)

GIS: Gastrointestinal system, AKI: Acute kidney injury, IHD: Ischemic heart disease, DHF: Decompensated heart failure, DKA: Diabetic ketoacidosis, DM: Diabetes mellitus, HT: Hypertension, CKD: Chronic kidney disease, CVE: Cerebrovascular event, Min.: Minimum, max.: Maximum, SD: Standard deviation

Table 2. Serum B12 levels according to patient demographics and reason for hospitalization

		B12 levels			p
		Min.-max.	Median	Mean ± SD	
Age disrubition	18-44	68.0-1760.0	304.0	388.6±276.0	0.731[K]
	45-54	64.0-2000.0	277.0	397.9±370.0	
	55-64	102.0-2000.0	306.5	416.0±348.2	
	65-74	30.0-2000.0	272.0	430.8±404.6	
	75-101	55.0-2000.0	358.5	511.4±436.7	
Gender	Male	30.0-2000.0	307.0	424.1±365.0	0.731[m]
	Female	55.0-2000.0	315.0	459.2±403.4	
Years	2020	30.0-1856.0	260.5	390.1±353.8	0.098[K]
	2021	68.0-2000.0	326.5	485.0±416.6	
	2022	96.0-2000.0	316.5	480.3±443.2	
	2023	102.0-1984.0	331.5	403.7±282.5	
	2024	55.0-2000.0	313.0	443.5±397.8	
Pancreatitis	(-)	30.0-2000.0	311.5	447.7±388.6	**0.010[m]**
	(+)	86.0-842.0	209.0	283.0±186.4	
GIS bleeding	(-)	30.0-2000.0	316.5	455.4±400.2	0.072[m]
	(+)	68.0-1315.0	267.5	345.9±231.7	
Infection	(-)	55.0-2000.0	319.0	419.7±338.9	0.798[m]
	(+)	30.0-2000.0	302.5	478.8±452.6	
AKI	(-)	30.0-2000.0	306.5	441.0±375.7	0.699[m]
	(+)	64.0-2000.0	319.0	439.0±404.2	
Palliative	(-)	30.0-2000.0	304.0	437.8±391.9	**0.033[m]**
	(+)	117.0-1525.0	444.0	470.7±271.0	
DHF	(-)	30.0-2000.0	304.0	435.7±383.1	0.051[m]
	(+)	55.0-1614.0	370.0	518.5±385.9	
DKA	(-)	30.0-2000.0	310.0	440.8±388.2	0.486[m]
	(+)	102.0-1247.0	316.0	434.9±286.5	

[K]Kruskal-Wallis (Mann-Whitney U test), GIS: Gastrointestinal system, AKI: Acute kidney injury, DHF: Decompensated heart failure, DKA: Diabetic ketoacidosis, Min.: Minimum, max.: Maximum, SD: Standard deviation

underlying malignancy. Additionally, patients with cancer often take vitamin supplements, which could further contribute to elevated B12 levels. Our study is consistent with the existing literature on this topic.

Consistent with the literature, our study found significantly lower serum B12 levels in patients with diabetes and those using metformin (29-31). This finding reinforces the need for regular monitoring of B12 levels in patients with diabetes, particularly those on metformin therapy, due to the well-established association between metformin use and B12 deficiency.

Conversely, we did not observe lower B12 levels in patients with chronic renal failure compared with those with other conditions. In contrast, Mushtaq et al. (32) found that patients undergoing chronic hemodialysis had significantly lower B12 levels, with the deficiency becoming more pronounced over time. We attribute the difference in our findings to the fact that many of the patients with CKD in our study did not undergo hemodialysis.

Moreover, in the aftermath of the COVID-19 pandemic, there has been a noticeable increase in the use of multivitamin supplements, as individuals seek to boost their immune systems and prevent deficiencies, sometimes without medical supervision. We hypothesized that the unsupervised use of vitamin B12 supplements during the COVID-19 pandemic may have resulted in increased supplementation post-pandemic because vitamin supplementation might be viewed as essential for supporting human health and the immune system. However, our findings did not support our hypothesis. The B12 levels of patients hospitalized in the internal medicine ward did not significantly differ over time.

Lastly, the growing influence of social media and the promotion of over-the-counter products by influencers may have long-term implications for public health. These promotions, which are often driven by economic interests, could influence vitamin intake and potentially alter population health outcomes. The full impact of these practices on vitamin levels in the general population is yet to be determined.

Study Limitations

The number of patients in this study is limited. A longer duration of vitamin B12 level evaluation with a higher number of participants could have provided more comprehensive results.

Table 3. Serum B12 levels according to comorbidities, serum B12 levels with metformin use and B12 supplementation

		B12 levels			p
		Min.-max.	Median	Mean ± SD	
DM	(-)	30.0-2000.0	333.0	463.9±391.6	**0.000[m]**
	(+)	62.0-2000.0	216.0	338.1±327.7	
HT	(-)	30.0-2000.0	304.0	444.0±397.9	0.157[m]
	(+)	134.0-1234.0	355.0	409.6±217.7	
IHD	(-)	30.0-2000.0	310.0	437.6±383.3	0.313[m]
	(+)	55.0-2000.0	321.0	461.5±386.0	
CKD	(-)	30.0-2000.0	307.0	435.1±366.4	0.889[m]
	(+)	108.0-2000.0	319.0	474.7±479.1	
Malignancy	(-)	55.0-2000.0	301.0	424.6±376.4	**0.024[m]**
	(+)	30.0-2000.0	347.5	486.7±400.8	
CVE-dementia	(-)	30.0-2000.0	306.0	435.1±380.6	0.066[m]
	(+)	62.0-2000.0	432.0	535.4±426.0	
Hepatic diseases	(-)	30.0-2000.0	310.0	434.9±373.0	0.837[m]
	(+)	108.0-1988.0	302.0	567.0±569.0	
Others	(-)	30.0-2000.0	310.0	440.9±383.7	0.690[m]
	(+)	257.0-257.0	257.0	257.0±	
Metformin	(-)	30.0-2000.0	334.0	467.7±392.6	**0.000[m]**
	(+)	62.0-1615.0	202.0	284.1±279.4	
B12 supplimentation	(-)	30.0-2000.0	256.0	304.3±236.3	**0.000[m]**
	(+)	209.0-2000.0	687.5	853.5±444.1	

[m]Mann-Whitney U test, DM: Diabetes mellitus, HT: Hypertension, IHD: Ischemic heart disease, CKD: Chronic kidney disease, CVE: Cerebrovascular event, Min.: Minimum, max.: Maximum, SD: Standard deviation

Conclusion

Vitamin B12 deficiency is a prevalent clinical condition affecting patients of all ages. Despite its relatively simple diagnosis, B12 deficiency is often overlooked in clinical practice. B12 deficiency can lead to complex, multisystemic disorders, particularly affecting neurological and hematological systems. With improved access to healthcare, diagnosing B12 deficiency may become more straightforward.

Our study found that serum vitamin B12 levels in patients hospitalized in the internal medicine department remained consistent over time. However, patients hospitalized for pancreatitis, malignancies, or palliative care exhibited significantly different B12 levels compared with the other patient groups.

It is important to remember that elevated serum vitamin B12 levels may warrant screening for underlying diseases, whereas low levels can contribute to various multisystemic conditions. Early detection and management of B12 deficiency are essential to prevent its associated complications.

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