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Aims and Scope

The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Turkey, Istanbul Istanbul Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (January, March, June, September and November).

The aim of the Medical Bulletin of Haseki is to publish original research papers of the highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

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The Medical Bulletin of Haseki

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The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

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The Medical Bulletin of Haseki

Contents

Original Articles

Case Reports

Original Article

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New Cut-off Value for Low-Dose Acth Stimulation Test in the Diagnosis of Adrenal Insufficiency

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Abstract

Aim: Although the peak cortisol response in the low-dose test does not reach the generally accepted value of 18 µg/dL, there are many patients whose adrenal insufficiency diagnosis was ruled out by getting an adequate response with the standard-dose test. Thus, the standard-dose adrenocorticotropic hormone (ACTH) stimulation test is unnecessarily applied to many patients. This study aims to compare low- and standard-dose ACTH stimulation tests in diagnosing adrenal insufficiency and to determine a new optimal threshold level for low-dose ACTH stimulation tests to avoid unnecessary standard-dose ACTH tests.

Methods: In this single-center cross-sectional study, patients with suspected adrenal insufficiency who underwent low-dose (1 mcg) and standard-dose (250 mcg) ACTH stimulation tests were evaluated. Cases were separated into two groups: (I) inadequate cortisol response (<18 mcg/dL) to low-dose test and adequate response (≥18 mcg/dL) to the standard dose, (II) adrenal insufficiency by inadequate responses to both tests. In addition, the cortisol responses to the stimulation tests of the group not diagnosed with adrenal insufficiency and those diagnosed with adrenal insufficiency were compared.

Results: Comparing 115 cases' peak cortisol levels, we found that the values of standard-dose tests were statistically significantly higher than those of low-dose tests ($p<0.001$). According to the receiver operating characteristic analysis we performed to determine a new cut-off level to eliminate adrenal insufficiency in the low-dose test, when the cut-off value was set as 16 µg/dL; 100% sensitivity, 35.64% specificities, 17.72% positive predictive value, and 100% negative predictive value were obtained. It has been shown that this new cut-off value would eliminate the diagnosis of adrenal insufficiency without performing the standard dose test in 36 cases.

Conclusion: The need for standard-dose testing can be reduced by lowering the cut-off point of the low-dose test from the accepted adequate cortisol level of 18 mcg/dL to 16 mcg/dL.

Keywords: Adrenal insufficiency, low-dose ACTH stimulation test, standard-dose ACTH stimulation test

Introduction

Adrenal insufficiency is a life-threatening condition that may cause different clinical presentations. If the early morning serum cortisol level is below 3 mcg/dL, adrenal insufficiency should be considered a definitive diagnosis (1). To evaluate hypothalamic-pituitary-adrenal (HPA) axis functions in cases with 3-18 mcg/dL basal cortisol levels and clinically suspected adrenal insufficiency, the insulin-induced hypoglycemia test (IHT) is recommended as the gold standard test (2). However, IHT is contraindicated in patients with arrhythmia, ischemic heart disease, or epilepsy because of the risks of hypoglycemia and should be applied with caution in elderly patients. It is also a seriously irritating test for patients, requiring hospitalization and close medical observation for testing. Thus, adrenocorticotropic hormone (ACTH) stimulation tests are the most commonly used method to evaluate the HPA axis in daily practice (3,4).

In ACTH stimulation tests, tetracosactide, a synthetic analog of ACTH (also known as cosyntropin- ACTH 1-24), is used. Performing the test with 250 mcg is called the standard dose, and performing the test with 1 mcg is called the low-dose ACTH stimulation test. Cortisol levels are measured at the 30th and 60th minutes after the administration of synthetic ACTH (cosyntropin), and the

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highest value is used to evaluate the response to the stimulation test (5). However, some authors consider the dose used in standard-dose ACTH stimulation to be above the physiological level. Therefore, a low-dose test using 1 mcg of cosyntropin has emerged to prevent supraphysiological stimulation of the adrenal cortex (6).

Although the low-dose test has been reported to be more correlated with IHT than the standard-dose test in patients after pituitary surgery (7), it was found that when specific threshold values are applied to low- and standard-dose ACTH stimulation tests, they are similar in sensitivity and accuracy (8).

A low-dose test is performed first in cases of suspected adrenal insufficiency. If the peak cortisol level is between 3 and 18 mcg/dL, a standard dose test is performed because adrenal insufficiency cannot be ruled out. If the cortisol level is above 18 µg/dL at the 30th or 60th minute, adrenal insufficiency can be ruled out (9). Values below 18 µg/dL should be considered adrenal insufficiency. However, although the peak cortisol response in the low-dose test does not reach the generally accepted value of 18 µg/dL, there are many patients whose adrenal insufficiency diagnosis was ruled out by getting an adequate response with the standard dose test. Thus, the standard-dose ACTH stimulation test is unnecessarily applied to many patients. Therefore, this study aimed to compare low- and standard-dose ACTH stimulation tests in diagnosing adrenal insufficiency and to determine a new optimal threshold level for low-dose ACTH stimulation tests to avoid unnecessary standard-dose ACTH tests.

Methods

Compliance with Ethical Standards

The University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital Local Ethics Committee reviewed and approved this study protocol on February 25, 2020 (approval number: 1458). Participants were informed that the data would be used for scientific purposes only.

Design and Study Population

This study was conducted as a retrospective, cross-sectional, single-center study. Patients who applied to the endocrinology department between January 2013 and December 2019 were screened for the study. Patients with clinical suspicion of adrenal insufficiency who underwent low- and standard-dose ACTH stimulation tests were included because the basal cortisol level was approximately 3-18 µg/dL in the examinations. The age range of the included patients was 18-80, and the study was conducted with 115 patients. Patients with congestive heart failure, uncontrolled diabetes mellitus, hypertension, chronic kidney injury, thyroid dysfunction, and drug use that would affect the metabolism of the synthetic ACTH analog cosyntropin used in the test were excluded from the study. Moreover, patients who had used topical or systemic steroids in the last 48 hours before the test were also excluded from the study.

Patients were separated into two groups according to the response to the low- and standard-dose ACTH stimulation tests: (1) inadequate response to the 1 mcg ACTH stimulation test (<18 mcg/dL at the 30th or 60th minutes) but adequate response to the 250 mcg ACTH stimulation test (≥18 mcg/dL at the 30th or 60th minutes), (2) inadequate response to both tests, thus diagnosed with adrenal insufficiency. Between Group 1 without adrenal insufficiency and Group 2 with primary or secondary adrenal insufficiency, the responses to the low- and standard-dose ACTH stimulation tests at the 30th and 60th minutes and the increase in basal serum cortisol values were compared. Receiver operating characteristic (ROC) analysis was applied to determine the optimal threshold value and diagnostic accuracy of the low-dose ACTH stimulation test in diagnosing adrenal insufficiency.

A 250 mcg preparation of cosyntropin (tetracosactrin 1-24, Synacten®), a synthetic analog widely used for ACTH stimulation tests, was used intravenously. A solution was prepared with 250 mcg of Synacthen® preparation diluted with 50 mL of normal saline for low-dose ACTH stimulation. This solution was used under the condition that it be stored for a maximum of three months at +4 degrees. When performing low-dose ACTH testing, 0.2 mL was taken from this solution, diluted to 10 mL with 0.9% NaCl, and then applied to the patient.

Blood samples were taken for basal cortisol at 8:00 a.m. After sampling, 1 mcg of the previously prepared solution was given as a bolus injection. Then, at the 30th and 60th minutes, blood samples were taken for plasma cortisol levels. At least three days later, the test was repeated in the same protocol, using 250 mcg of synthetic ACTH instead of 1 mcg.

Cortisol measurements were made with the COBAS 602 device between 2013 and 2017 and the Beckman DXI 800-3 device between 2017 and 2019. For measurement, the electroluminescence method was used. A plasma cortisol level of 18 mcg/dL or above during the test at the 30th and/or 60th minutes is considered a normal adrenal function indicator.

Statistical Analysis

Statistical analyses were performed using the SPSS version 17.0 program. The normality of the variables was examined using histograms and the Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used in descriptive analyses. The Mann-Whitney U test

was used to evaluate non-normally distributed (non-parametric) variables between two groups. A ROC analysis was performed to determine a new cut-off value for detecting adrenal insufficiency. Cases with a p-value below 0.05 were considered statistically significant.

Results

The study was executed with 115 patients, 40 males and 75 females. The mean age of the cases was 42.21±13.96 years, and 14 patients were diagnosed with adrenal insufficiency, seven of whom had primary adrenal insufficiency and seven had secondary adrenal insufficiency.

Responses to the low- and standard-dose ACTH stimulation of the patients are shown in Figures 1A and 1B.

When the cortisol results were compared to the minutes, the mean of the 30th and 60th-minute levels of the patients who underwent the standard dose test was statistically significantly higher than the low dose test (Table 1).

After the administration of cosyntropin, the percentage increase in cortisol with the 250 mcg test (151.86±148.90%) was significantly higher than the increasing percentage of the 1 mcg test (97.00±93.35%) (p<0.001) (Figure 2).

In the low-dose stimulation test, ROC analysis was performed over the 30th-minute values to determine a new cut-off value to rule out the suspicion of adrenal insufficiency. When the optimal cut-off value was taken at 16 mcg/dL at the 30th minute, 100% sensitivity, 35.64% specificity, 17.72% positive predictive value (PPV), and 100.00% negative predictive value (NPV) were obtained (Figure 3). When the 30th-minute cut-off value is taken at 16 mcg/dL in the low-dose test, 79 patients are referred to the second-line test, and adrenal insufficiency is detected in 14 of them. Therefore, this new cut-off value concluded that no standard dose test would be needed for 36 patients.

The ROC analysis found a cut-off value of 14.80 mcg/dL for primary adrenal insufficiency and 16 mcg/dL for secondary adrenal insufficiency. According to these values, 100% sensitivity, 67.33% specificity, 17.50% PPV, and 100% NPV were obtained when the threshold point was taken as 14.80 mcg/dL for primary adrenal insufficiency. On the other hand, when the threshold value of 16 mcg/dL was taken for secondary adrenal insufficiency, 100% sensitivity, 35.64% specificity,

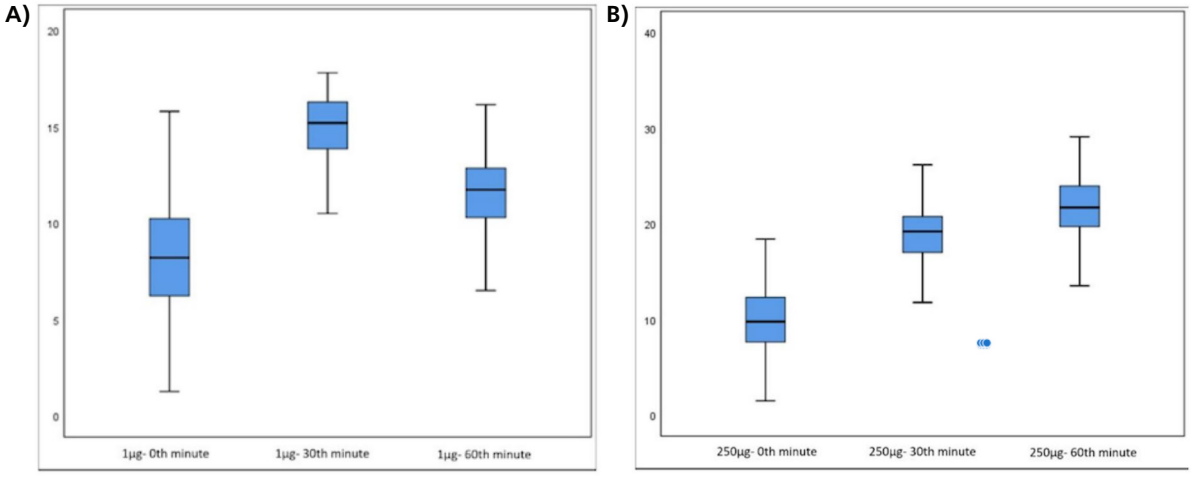

Figure 1. A) Responses to the low-dose ACTH stimulation test of the patients. **B)** Responses to the standard-dose ACTH stimulation test of the patients
ACTH: Adrenocorticotropic hormone

Table 1. Comparison of the results of low-dose and standard-dose ACTH stimulation tests by minutes

	Basal (0 min)		30 min		60 min	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
1 mcg ACTH	8.54±2.86	8.20	14.77±2.27	15.20	11.54±2.49	11.73
250 mcg ACTH	10.07±3.73	9.76	18.87±3.67	19.20	21.34±4.37	21.70
p-value*	0.14		0.01		<0.001	

*Mann-Whitney U test
Min: Minute, SD: Standard deviation, ACTH: Adrenocorticotropic hormone

9.72% PPV, and 100% NPV were obtained (Figures 4A and 4B).

For the detection of primary adrenal insufficiency, when the 30th-minute cut-off value is 14.80 mcg/dL in the low-dose test, 40 of 108 patients are referred to the second-line test, and primary adrenal insufficiency is detected in 7 of them. With this new cut-off value, 68 patients were not referred to the second step. For the diagnosis of secondary adrenal insufficiency, when the 30th-minute cut-off value is 16 mcg/dL in the low-dose test, 72 of 108 patients are referred to the second-line test. Secondary adrenal insufficiency was detected in seven of them. With this new cut-off value, 36 patients were not referred to second-line testing.

No statistically significant results were obtained in the ROC analysis to determine the threshold value using the percentage increase compared to the baseline to detect adrenal insufficiency. In addition, while there was a low and statistically significant correlation between the low and standard dose test 30th-minute values, no statistically significant correlation was observed between the 60th-minute values (Figure 5A, Figure 5B).

When the 30th and 60th-minute values were compared between low- and standard-dose tests, the 30th and 60th-

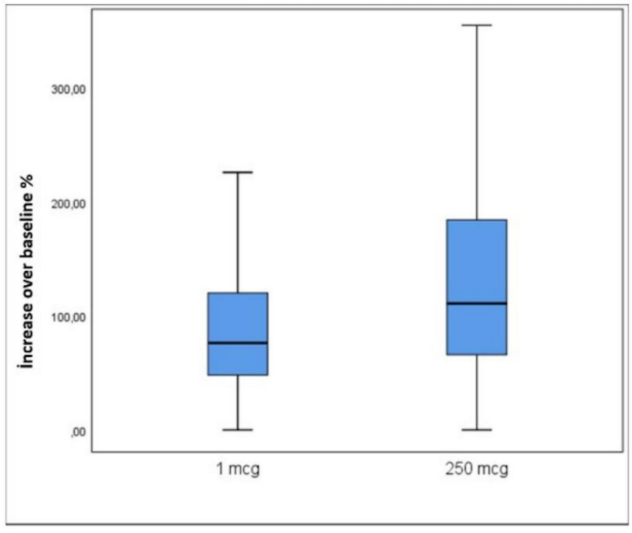

Figure 2. Percentages of increase in low-dose and standard-dose ACTH stimulation tests compared to basal
ACTH: Adrenocorticotropic hormone

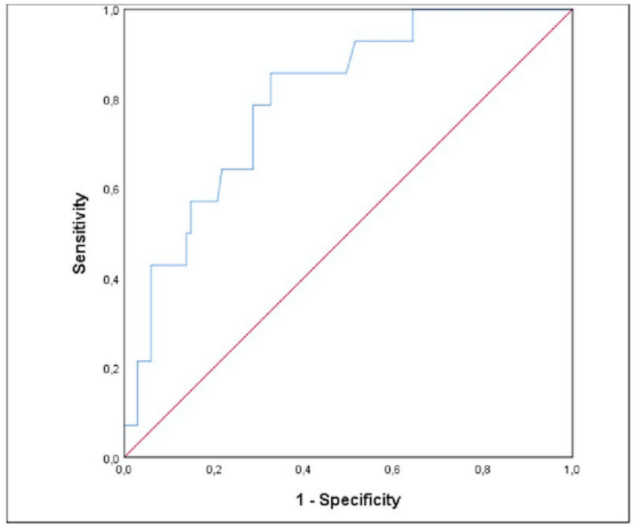

Figure 3. ROC analysis for the determination of low-dose ACTH test 30. minute value for adrenal insufficiency
ROC: Receiver operating characteristic, ACTH: Adrenocorticotropic hormone

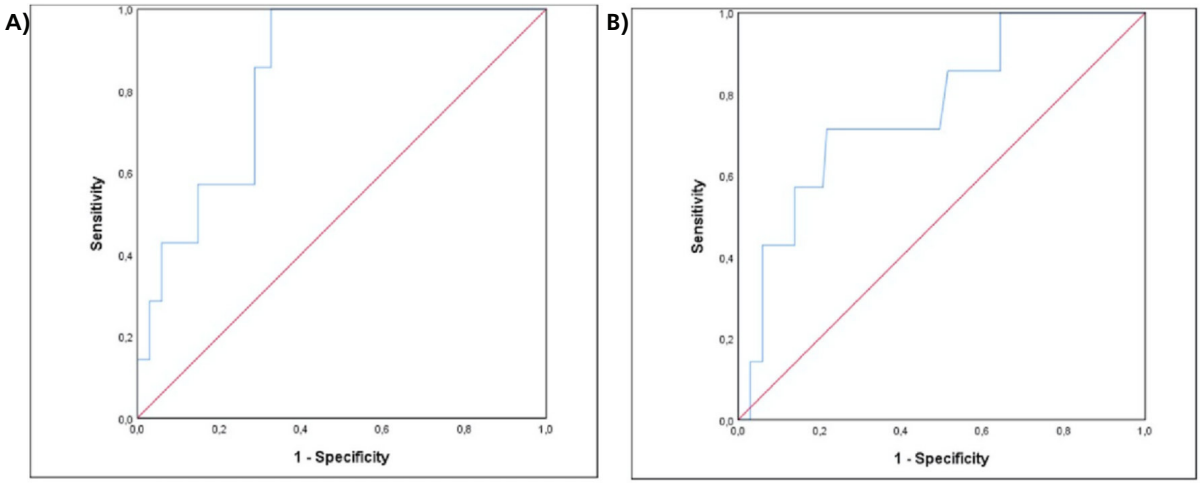

Figure 4. A) ROC analysis for the estimation of low-dose ACTH test 30th-minute value for primary adrenal insufficiency. **B)** ROC analysis for the estimation of low-dose ACTH test 30th-minute value for secondary adrenal insufficiency
ROC: Receiver operating characteristic, ACTH: Adrenocorticotropic hormone

minute values of the standard-dose test were significantly higher than those of the low-dose test (Table 2).

Discussion

This study provides information on the effectiveness of the low-dose ACTH stimulation test in screening and diagnosing adrenal insufficiency. In this study, it has been shown that when 16 mcg/dL is taken instead of the generally accepted 18 mcg/dL threshold value in the low-dose test, a high rate of 31.3% (36/115) of the patients exclude the diagnosis without the need for a standard dose test. Thus, it has been concluded that fewer patients will be exposed to supraphysiological doses of ACTH and that the test can be used more cost-effectively.

In evaluating the HPA axis, if the basal cortisol value is below 3 mcg/dL, intense HPA deficiency is considered. In comparison, if it is above 18 mcg/dL, the HPA axis is considered normal. No clear interpretation can be made between these values. In cases of clinical suspicion and necessity, the HPA axis is investigated with dynamic tests. The gold standard test accepted today in dynamic tests is IHT (3,7-11). The literature has different threshold values regarding interpreting cortisol values obtained by IHT. Also, this test cannot be applied in the presence of ischemic heart disease, epilepsy, and cerebrovascular disease. When applied, it requires close medical follow-up (12). Although IHT is the gold standard test for HPA axis evaluation, the ACTH stimulation test is preferred due to its low side effects (10).

Exogenously administered synthetic ACTH has been used to assess the HPA axis for many years. Wood et al. (13) measured plasma cortisol levels by administering intramuscular synthetic ACTH in the groups with normal adrenal functions, inadequate functions, and suspected insufficiency and showed that adrenal function could be evaluated at 30. min. Although some authors have stated that the standard dose test has more correlated results with IHT, it is well above the physiological dose of 250 mcg, and a study reported that it stimulates the adrenal gland 25 times more than the normal physiological response (5). Moreover, it has been shown that the 1 mcg test is more sensitive to secondary adrenal insufficiency (14). If the peak cortisol level is above 18 mcg/dL after a 1 mcg test, the patient is considered to have no adrenal insufficiency (15). Schultz et al. (16) showed that serum cortisol levels increase to 18 mcg/dL under stress in healthy individuals.

There is no clarity in the literature about the optimal threshold values for cortisol in response to dynamic testing. A study suggested values ≥19 mcg/dL as an

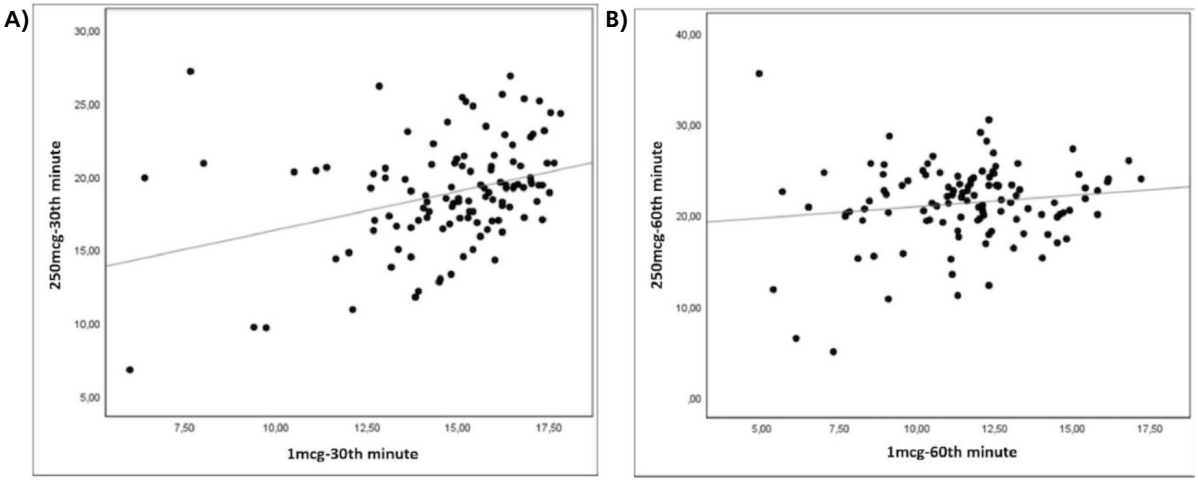

Figure 5. A) Correlation between low dose ACTH test 30th-minute and standard dose ACTH test 30th-minute values. **B)** Correlation between low dose ACTH test 60th-minute and standard dose ACTH test 60th-minute values
ACTH: Adrenocorticotropic hormone

Table 2. Comparison of peak cortisol values in low-dose and standard-dose ACTH stimulation test

	1 µg		250 µg		p-value*
	Mean±SD	Median	Mean±SD	Median	
30th min.	14.77±2.27	15.20	18.87±3.67	19.20	**<0.001**
60th min.	11.54±2.49	11.73	21.34±4.37	21.70	**<0.001**

*Mann-Whitney U test
Min: Minute, SD: Standard deviation, ACTH: Adrenocorticotropic hormone

adequate response to the low-dose test (17). In another study, 16 patients were evaluated with IHT and a 1 mcg test. When 18 mcg/dL was accepted as the threshold value for both tests, it was found that all patients responded adequately to the IHT and 1 mcg tests (18). A meta-analysis has commented that the lowest cortisol response in response to the 1 mcg test in healthy individuals may be lower than 12.5 mcg/dL. The same meta-analysis compared the 250 mcg and 1 mcg tests, and the optimal timing for measuring cortisol response was investigated. No significant difference was found in any study's diagnostic distinction between the 30th and 60th minutes and peak cortisol values. Again, the same meta-analysis compared the diagnostic performances of 1 mcg and 250 mcg ACTH stimulation tests. It was shown that the 1 mcg test performed better in diagnosis due to better sensitivity (19).

A study concluded that the cortisol threshold value sufficient for the low-dose test was 12.5 mcg/dL, based on a comparison of 1 mcg ACTH, 250 mcg ACTH, and glucagon stimulation test (GST) in 55 healthy volunteers aged 25-69 years. Peak cortisol level was reached at 30 min with the 1 mcg ACTH test, 90 min after the 250 mcg ACTH test, and 180 min after GST. The mean peak cortisol response to the 250 mcg ACTH test was significantly higher than that to 1 mcg ACTH and GST. While a positive correlation was found between mean peak cortisol responses in 1 mcg and 250 mcg ACTH stimulation tests, no significant correlation was found between GST and ACTH stimulation tests (20).

In our study, the lowest peak cortisol response of the cut-off value at the 30th minute in the low-dose ACTH stimulation test was 16 µg/dL. In the low-dose ACTH stimulation test for primary and secondary adrenal insufficiency, the lowest peak cortisol responses of the cut-off value at the 30th minute were 14.80 mcg/dL and 16 mcg/dL, respectively. In a meta-analysis, peak cortisol responses lower than 16 mcg/dL and higher than 30 mcg/dL in response to the standard dose test were high predictors of HPA axis insufficiency and adequacy, respectively. For the low-dose test, a peak cortisol response lower than 16 mcg/dL and higher than 22 mcg/dL, respectively, has been suggested as the best predictor for evaluating HPA axis insufficiency and adequacy (19). Abdu et al. (21) showed that the 21.75 mcg/dL cut-off value is safer than 18.12 mcg/dL for low- and standard-dose testing in clinical decision-making and treatment practice. If the response to the low-dose test is more excellent than 21.75 mcg/dL, it has 100% sensitivity, showing that the HPA axis is intact; it has been shown that less sensitivity and 3% false positive results are obtained at the standard dose compared to the low dose (21).

There are conflicting studies that show that the peak response to the 1 mcg test is altered in obese individuals. In a recent study, it was reported that the peak response to the 1 mcg test in obese individuals is lower than that of healthy controls (22). In our retrospective study, since not all individuals had body mass index (BMI) values, it was not possible to evaluate whether there was a change in the peak cortisol response in the 1 mcg test according to BMI.

A study analyzed 103 patients who underwent 1 mcg ACTH stimulation tests to determine the threshold value. Primary adrenal insufficiency was found in two of the four patients, and secondary adrenal insufficiency in two. When the standard threshold value was 18.12 mcg/dL, they reported 100% sensitivity, 67.3% specificity, and a high rate of false positive results. When 14.53 mcg/dL was taken as the threshold value, the sensitivity was 100% and the specificity was 93.9%. When 14.53 mcg/dL was taken as the threshold value in the low-dose test, it was observed that the rate of false positivity decreased significantly. Still, the sensitivity remained high (23). Our study obtained 100% sensitivity, 35.64% specificity, 17.72% PPV, and 100.00% NPV when the cut-off value for cortisol response to the low-dose test was more than 16 µg/dL. When the threshold value was 18 µg/dL, 100% sensitivity, 0% specificity, 12.17% PPV, and 0% NPV were obtained.

The study of Dekkers et al. (24) with 207 patients compared the cortisol response to the 1 mcg and 250 mcg ACTH stimulation tests in patients with suspected adrenal insufficiency. The mean difference between cortisol responses in both ACTH tests was 0.94 mcg/dL; a statistically significantly higher response was obtained in the 250 mcg ACTH test. In the study, the cut-off value of cortisol was taken as 19.93 mcg/dL; the diagnostic performances of both tests were found to be similar; however, it was observed that statistically significant average test results were obtained in the 250 mcg test. Individually, it has been observed that the difference in the cortisol response in both tests may be statistically significant. The response in the 250 mcg test may not always be higher than that in the 1 mcg test. Cortisol responses given at the 30th minute were correlated with each other in both tests (24).

The 1 mcg test is the lowest dose that gives the maximal cortisol response, but which dose should be applied in the initial evaluation is still controversial. The supraphysiological dose of 250 mcg is less sensitive in evaluating mild secondary adrenal insufficiency. Tordjman et al. (25) suggested that the 1 mcg test is more sensitive to secondary adrenal insufficiency and can replace the 250 mcg ACTH test. In our study, while there was a low

degree of similarity in the 30th-minute response to low- and standard-dose tests, there was no similarity between the 60th-minute values.

In another study, although the healthy volunteers underwent low- and standard-dose tests and had different baseline cortisol levels, the mean cortisol response at the 30th minute was similar. At the 60th and 90th minutes of the 1 mcg test, the mean cortisol response was significantly lower than the standard dose test. Again, the same study observed that the cortisol response to the ACTH test at the 30th minute did not change with basal cortisol values or at any time of the day. It was observed that the peak cortisol response reached the 30th minute in most of the 1 mcg ACTH stimulation tests (26). In our study, the average response to the low-dose test at the 30th minute was higher than that at the 60th minute; in the standard-dose test, the cortisol response at the 60th minute was higher than that at the 30th minute.

Studies have shown that an increase of 7 μg/dL or two times the value at the 0th minute, is expected with the ACTH stimulation test (27). In a study conducted with 21 healthy individuals, it was assumed that the increase in cortisol value was unsuitable for estimating adrenal insufficiency (28). In our study, the percentages of increases from baseline were compared between groups. Accordingly, the percentage of the increase of 250 mcg (151.86±148.90%) was significantly higher than the percentage of the increase of 1 mcg (97.00±93.35). However, it was concluded that the increase in cortisol levels is unsuitable for predicting adrenal insufficiency.

Study Limitations

The study was designed retrospectively. The BMI of individuals could not be evaluated because of a lack of data, although some studies show that obesity can alter the cortisol response to the 1 mcg ACTH stimulation test. Another limitation is that the stimulation tests were terminated after the 60th minute. In fact, in the generally accepted ACTH stimulation tests, it is considered sufficient to look at the 30th and 60th minutes to evaluate the cortisol response, which is routine practice. However, in the study of Karaca et al. (20), a peak cortisol response was reached at the 120th minute of standard dose test application in 55 healthy volunteers. In their study, if the standard-dose ACTH stimulation test were terminated after 60 minutes, 11% of the individuals would have been interpreted as having adrenal insufficiency. It was concluded that even if it was terminated after the 30th minute, the false positive rate would increase to 20% (20). For this reason, if 20 mcg/dL is not reached for 90 min in the standard dose test, an approach recommends extending the test time to 120 min if there are no clinical signs of adrenal insufficiency.

Conclusion

In this study, a 1 mcg ACTH stimulation test was found to be helpful in the diagnosis of adrenal insufficiency. In the 1 mcg ACTH stimulation test, when 16 μg/dL was taken instead of the generally accepted 18 μg/dL cut-off value at 30 min, it was shown that 31.3% of the patients did not need to apply the standard dose test. This will benefit both in terms of cost-effectiveness and by reducing exposure to supraphysiological ACTH doses. In this regard, future studies with more extensive series should determine the best cut-off values.

Ethics

Ethics Committee Approval: The University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital Local Ethics Committee reviewed and approved this study protocol on February 25, 2020 (approval number: 1458).

Informed Consent: Participants were informed that the data would be used for scientific purposes only.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K.T., M.M.C., Concept: M.M.C., Y.A., Design: M.M.C., Y.A., Data Collection or Processing: B.K.T., Analysis or Interpretation: B.K.T., M.M.C., Y.A., Literature Search: B.K.T., M.M.C., Writing: B.K.T., M.M.C., Y.A.

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Original Article

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Effect of Biological Therapy on Systemic Inflammatory Markers Among Patients with Chronic Plaque Psoriasis

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Abstract

Aim: Psoriasis is a chronic systemic inflammatory disease. A generally accepted laboratory marker for monitoring the treatment response of psoriasis is not yet available. The aim of this study was to evaluate the effects of biologic therapy on the novel inflammatory biomarkers neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), and plateletcrit (PCT) in psoriasis.

Methods: Fifty-five patients with psoriasis who received biologic therapy including tumor necrosis factor-alpha, interleukin (IL)-17, IL-12/23, and IL-23 inhibitors for at least three months were retrospectively evaluated. Psoriasis area severity index scores, hemogram data, and C-reactive protein (CRP) levels were analyzed before and after three months of therapy.

Results: The CRP, neutrophil count, platelet count, NLR, PLR, and PCT values revealed a significant decrease after three months of therapy, irrespective of the type of biologics used (p=0.008, 0.012, 0.017, 0.001, 0.011, and 0.009, respectively). After treatment, NLR and PLR decreased promptly in parallel with a decrease in CRP, in which NLR has a low-moderate (p=0.025, r=0.303), and PLR has a moderate correlation (p=0.000, r=0.525).

Conclusion: Neutrophil-lymphocyte ratio, PCT and particularly PLR parameters derived from hemogram data can be used to assess the effect of biological therapy on systemic inflammation among psoriasis patients.

Keywords: Psoriasis, biologic therapy, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

Introduction

Psoriasis is a chronic inflammatory disease with a frequency of 0.1-3% in various populations. The rates of diabetes mellitus (DM), atrial fibrillation, hypertension, atherosclerosis, stroke, myocardial infarction (MI), cardiovascular mortality, and metabolic syndrome are significantly higher among psoriasis patients. Psoriasis is no longer considered a disease limited only to the skin and joints; yet, it has been a systemic inflammatory disease potentially accompanied by various comorbidities (1). Various markers can be used to access systemic inflammation. Recent studies revealed that neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), and plateletcrit (PCT) values are potential markers of systemic inflammation, and they are associated with prognosis in several cardiovascular diseases, malignancies, and chronic inflammatory diseases, correlating with C-reactive protein (CRP) values (2-6). Numerous studies in the literature have reported that patients with psoriasis have higher NLR, PLR, MPV, PCT, and CRP values than the control groups (7-13).

Therefore, this study aimed to analyze the changes in the levels of NLR, PLR, MPV, PCT, and CRP, the risk markers for systemic inflammation and cardiovascular diseases, before and after treatment among patients with chronic plaque psoriasis receiving biological therapy.

Methods

Compliance with Ethical Standards

The study was conducted according to the Declaration of Helsinki. Ethics approval for the study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Training and Research Hospital with decision number 2022/62. Written informed consent was waived because of the retrospective nature of this study.

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Study Design

In this single-center cross-sectional study 55 patients with chronic plaque psoriasis who had received biological agents for the first time, at least three months of duration between January 2019 and August 2022 were evaluated.

The exclusion criteria were as follows: a history of malignancy; systemic diseases such as DM, cardiac, renal, or hepatic disease; active infection; inflammatory diseases; dermatological disease other than psoriasis; and previously receiving biological therapy.

Age, gender, duration of disease, family history, scalp and nail involvements, having concomitant psoriatic arthritis, receiving a biological agent, pre- and post-treatment psoriasis area severity index (PASI) values, neutrophil, lymphocyte, and platelet counts, and NLR, PLR, MPV, PCT, and CRP values, were recorded from the patient files. Neutrophil-lymphocyte ratio refers to the counts of neutrophils divided by the number of lymphocytes, and PLR denotes the platelet count divided by the lymphocyte count.

The application of the biological agents was as follows: The first two doses of ustekinumab with four weeks interval, then a dose every 12 weeks as 45 mg for patients <100 kg body weight and 90 mg for those ≥100 kg body weight; the initial adalimumab dose was 80 mg, the second dose was 40 mg one week after the first dose, and then a 40 mg dose every two weeks interval; 400 mg of sertolizumab dose every two weeks interval; 300 mg of secukinumab dose once a week for the initial five weeks, and then once in every four weeks interval; 160 mg of initial ixekizumab dose, then 80 mg dose every two weeks until week 12; 100 mg dose guselkumab with four weeks intervals (first two doses), then application of 100 mg dosages every eight weeks; and the first two doses of risankizumab were 150 mg every four weeks interval, then 150 mg doses every 12 weeks.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows version 21.0 (SPSS, Chicago, IL, USA). Evaluation of the conformity of the variables to the normal distribution was performed using analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Continuous and discrete variables were presented as mean ± standard deviation and median (minimum-maximum), respectively. The Student's t-test was used to compare the two means of dependent groups. The Kruskal-Wallis test was executed to test the difference in discrete numerical variables in more than two groups. The Spearman correlation coefficient was used to evaluate the relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

Results

Of the 55 patients included in the study, 28 (50.9%) were female, while 27 (49.1%) were male. The mean age was 49.54±1.95 years. The patients were receiving the following therapies: seven patients (12.72%) tumor necrosis factor alpha (TNF-α) inhibitors (six patients adalimumab, one patient certolizumab); nine patients (16.36%) interleukin (IL)-12/23 inhibitor (ustekinumab); 34 patients (61.82%) IL-17 inhibitors (18 patients secukinumab, 16 patients ixekizumab), and five patients (9.1%) IL-23 inhibitors (four patients guselkumab, one patient risankizumab). Table 1 summarizes the demographic features and clinical attributes of the patients.

Table 1. Demographic features and clinical attributes of patients

Gender (female/male), n, (%)	28/27 (50.9/49.1)
Age (mean ± SD)	49.54±1.95
The duration of disease (year) (mean ± SD)	22.1±1.42
Family history (yes/no), n, (%)	36/19 (65.45/34.54)
The nail involvement (yes/no), n, (%)	33/22 (60/40)
Scalp involvement (yes/no), n, (%)	39/16 (70.9/29.1)
Concomitant arthritis (yes/no), n, (%)	20/35 (36.36/63.63)
Received therapy, n (%)	Adalimumab - 6 (10.9) Sertolizumab - 1 (1.81) Ustekinumab - 9 (16.36) Secukinumab - 18 (32.72) Ixekizumab - 16 (29.1) Guselkumab - 4 (7.27) Risankizumab - 1 (1.81)
PASI 0 (mean ± SD)	18.8±11.38
PASI 3rd month (mean ± SD)	1.69±2.81

SD: Standard deviation, PASI: Psoriasis areata severity index

After three months of biological therapy, there was a statistically significant decrease in the neutrophil count, platelet count, NLR, PLR, PCT, and CRP values of the patients (p=0.008, 0.012, 0.017, 0.001, 0.011, 0.009, respectively). However, there was no statistically significant difference between pre- and post-treatment lymphocyte counts and MPV values (p=0.131, 0.097). Table 2 displays the laboratory measures of the patients before and after three months of biological therapy.

The patients were categorized into four groups based on the type of biological therapy they received. These group classifications were as follows: patients receiving IL-12/23 inhibitors in group 1, TNF-α inhibitors in group 2, IL-17 inhibitors in group 3, and IL-23 inhibitors in group 4. There was no statistically significant difference between these four groups considering the changes in neutrophil count, lymphocyte count, platelet count, NLR, PLR, MPV, PCT, and CRP pre- and post-treatment levels. Table 3 displays the pre- and post-treatment laboratory measures of the groups.

The relationship between the changes in NLR, PLR, MPV, PCT, and CRP pre- and post-treatment values and the PASI scores was insignificant. However, there was a statistically significant, albeit low-moderate correlation, between the CRP and NLR pre- and post-treatment value changes (p=0.025, r=0.303), whereas the difference in PLR was statistically significant with a moderate correlation (p=0.000, r=0.525). Table 4 depicts the relationship between pre- and post-treatment changes among NLR, PLR, MPV, PCT, and CRP values.

Discussion

Psoriasis is a chronic inflammatory disease in which T lymphocytes, neutrophils, macrophages, mast cells,

Table 2. Laboratory measures of patients before and after three months of biological therapy

	Pre-treatment (mean ± SD)	Post-treatment (3rd month) (mean ± SD)	p-value
Neutrophil count (x10^3/mL)	4.47±1.54	3.91±1.13	0.012
Lymphocyte count (x10^3/mL)	2.11±0.56	2.25±0.59	0.131
Platelet count (x10^3/mL)	270.27±65.76	257.69±57.2	0.017
NLR	2.22±0.89	1.8±0.66	0.001
PLR	134.42±40.66	120.16±32.92	0.011
MPV	9.51±1.18	9.34±1.23	0.097
PCT	0.25±0.05	0.24±0.05	0.009
CRP (mg/L)	4.06±4.7	2.47±2.04	0.008

Student's t-test was used for analysis. SD: Standard deviation, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, CRP: C-reactive protein

Table 3. Pre- and post-treatment laboratory measures of the groups

	The therapy group	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Pre- and post-treatment difference Median (min-max)	p-value
Neutrophil count (x10^3/mL)	1	4.09±1.36	3.7±1.12	-0.24 (-0.42-2.79)	0.784
	2	4.7±0.80	4.3±0.92	0.26 (-1.10-1.69)	
	3	4.6±1.76	3.9±1.20	0.39 (-3.13-8.31)	
	4	3.9±0.83	3.2±0.78	0.70 (-0.31-1.62)	
Lymphocyte count (x10^3/mL)	1	2.10±0.49	2.30±0.52	-0.01 (-1.25-0.63)	0.262
	2	2.12±0.71	2.40±0.64	-0.21 (-1.24-0.74)	
	3	2.16±0.56	2.16±0.55	-0.04 (-1.27-1.63)	
	4	1.67±0.40	2.46±0.93	-1.10 (-2.84)-(-0.10)	
Platelet count (x10^3/mL)	1	275.44±64.20	259.66±41.50	15.0 (-24-74)	0.672
	2	305.71±74.84	284.14±65.26	15.0 (-8-63)	
	3	258.52±64.21	246.73±58.50	8.5 (-50-177)	
	4	291.20±61.14	291.60±49.18	-4.0 (-53-44)	
NLR	1	1.91±0.66	1.65±0.46	0.25 (-0.19-0.95)	0.31
	2	2.55±1.29	1.89±0.68	0.43 (0.15-2.08)	
	3	2.21±0.89	1.87±0.72	0.28 (-1.14-4.34)	
	4	2.38±0.50	1.43±0.47	0.92 (-0.07-2.43)	

Table 3. Continued

	The therapy group	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	Pre- and post-treatment difference Median (min-max)	p-value
PLR	1	128.71±30.36	117.47±29.32	-1.01 (-19.85-45.27)	0.171
	2	156.26±49.33	122.37±39.90	18.48 (-27.79-127.66)	
	3	124.44±33.24	119.25±32.54	8.08 (-76.54-72.29)	
	4	182.04±55.84	128.05±40.8	20.77 (3.77-177.59)	
MPV	1	9.60±0.97	9.32±0.90	0 (-1.1-0.9)	0.719
	2	9.37±0.60	9.38±0.93	-0.3 (-0.7-1.7)	
	3	9.64±1.34	9.41±1.43	0.25 (-0.8-2.33)	
	4	9.10±1.03	8.92±0.73	0.2 (-0.3-0.6)	
PCT	1	0.25±0.05	0.24±0.03	0.010 (-0.03-0.07)	0.896
	2	0.28±0.06	0.26±0.07	0.006 (-0.02-0.07)	
	3	0.24±0.05	0.23±0.05	0.014 (-0.06-0.16)	
	4	0.26±0.04	0.25±0.04	0.003 (-0.03-0.04)	
CRP	1	5.43±9.48	3.17±2.89	-0.06 (-2.64-25.45)	0.123
	2	5.69±3.73	2.16±1.31	2.13 (-0.3-9.0)	
	3	3.47±2.75	2.59±1.95	0.52 (-3.34-6.2)	
	4	3.37±4.79	0.85±0.91	0.10 (-0.91-10.11)	

Group 1: IL-12/23 inhibitory (ustekinumab for nine patients)
Group 2: TNF alpha inhibitory (adalimumab for six patients, sertolizumab for one patient)
Group 3: IL-17 inhibitory (secukinumab for 18 patients, ixekizumab for 16 patients)
Group 4: IL-23 inhibitory (guselkumab for four patients, risankizumab for one patient)
Kruskal-Wallis test used for analysis.
SD: Standard deviation, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, CRP: C-reactive protein

Table 4. The correlative change between neutrophil lymphocyte ratio, platelet lymphocyte ratio, mean platelet volume, platelet crit, and C-reactive protein values before and after therapy

		Change in CRP	p-value
Spearman's rho	Change in NLR	0.303	**0.025**
	Change in PLR	0.525	**0.000**
	Change in MPV	-0.181	0.186
	Change in PCT	0.063	0.648

Spearman correlation test was used for analysis. NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, PCT: Plateletcrit, CRP: C-reactive protein

dendritic cells, keratinocytes, and various cytokines released from these cells play a role in its pathogenesis (14). Numerous studies have focused on markers that could be used to assess disease activity and therapy response among patients with psoriasis. The literature revealed that various cytokines, including IL-6, TNF-α, IL-17A, IL-23, and adhesion molecules such as E-selectin and intracellular adhesion molecule-1, are at a more elevated level among patients with psoriasis; consequently, they pose potential for use as disease activity markers (1,15). However, these markers are inconvenient tools for clinical practice because of their high cost and labor-intensive study requirements. Therefore, there is a demand for low-cost and straightforward approaches that have the capacity to assess psoriasis disease activity and therapy response.

The complete blood cell count is a laboratory test routinely performed in daily clinical practice and estimates the number of leukocytes, erythrocytes, and platelets in the bloodstream and the indices related to these cells (16). Recent studies have demonstrated that NLR, PLR, MPV, and PCT values acquired from complete blood cell counts are proportionate to the severity of systemic inflammation in cardiovascular diseases, malignancies, and chronic inflammatory diseases (2-6). Various studies have indicated that the mentioned values are higher in patients with psoriasis than in controls (7-13).

Due to its short half-life, CRP, an acute-phase protein, is extremely sensitive to inflammation and is typically employed in the disease follow-up process. Numerous studies have revealed it is higher among patients with psoriasis than in healthy controls, corresponds to the disease severity, and declines with systemic cures (17). The findings of the two separate studies in which patients with psoriasis were analyzed initially and 12 weeks after

etanercept therapy revealed that the CRP levels drastically declined by therapy (18,19). A study focusing on 142 psoriasis patients who received adalimumab therapy because they failed to respond satisfactorily to etanercept, narrowband UVB, and methotrexate therapies reported a substantial decrease in CRP levels at the 16th week of the therapy, concurrently correlated with a drop in PASI score (20). The current study also found a significant decline in CRP levels after 12 weeks of therapy, regardless of the type of biological agent used, establishing a positive correlation between diminished NLR, PLR, and CRP values.

Studies have reported that patients with psoriasis retain higher neutrophil counts and neutrophil activation products in their lesions and peripheral blood (21). Focusing on psoriasis, Yamanaka et al. (22) discovered that neutrophil activity products were lower in the peripheral blood of psoriasis patients who received biological therapy (ustekinumab and infliximab) than those who did not. In addition to promoting hemostasis, platelets contribute significantly to inflammation by releasing proinflammatory cytokines. They seem to have played a critical role in the pathogenesis of psoriasis by escalating the release of inflammatory cytokines by promoting leukocyte migration of activated platelets to the skin (23). Studies have indicated that platelet activation markers are higher in the plasma of psoriasis patients than in the general population, and there is also a correlation between plasma levels of these markers and PASI score (24). As compatible with the findings of this study, the literature review also revealed that several studies investigating psoriasis patients before and after biological therapy revealed a significant decline in neutrophil and platelet counts after therapy (25,26).

Various studies have reported that NLR may pose a potent marker for identifying systemic inflammation (27). Studies have also indicated that NLR is significantly higher among patients with psoriasis and corresponds to disease severity (11,17,28). A study comparing 39 psoriasis patients and 49 healthy controls discovered that the NLR level was more elevated in psoriasis patients than in the control group; however, there was no significant change in NLR values after three months of narrowband ultraviolet B therapy. The authors attributed this outcome to the ineffective reduction of inflammation by phototherapy (29).

As initially depicted in the literature in 2008, studies have reported that PLR is proportional to the degree of systemic inflammation due to thrombocytosis and lymphopenia. The subsequent studies in the forthcoming years further revealed that PLR had the potential to be a critical marker for systemic inflammation in various chronic inflammatory and cardiovascular diseases (30). However, several studies reported that it was more prevalent among patients with psoriasis than in the control groups, correlating it with the PASI score (11,28). Najar Nobari et al. (31) analyzed 80 patients with psoriasis vulgaris who received TNF-α inhibitor therapy for 12 months, indicating that NLR and PLR values significantly reduced with therapy consistent with the decrease in PASI scores.

As compatible with the findings of the current study, the literature review identified the study of Çevirgen Cemil and Ataş (25), who focused on 42 psoriasis patients and analyzed them before and after the third month of therapy with biological agents, reporting a substantial decline in NLR, PLR, and CRP post-treatment values. In another study, regardless of the type of biological used, a significant reduction in NLR, PLR, and CRP post-treatment values was observed in 186 patients with psoriasis vulgaris and 50 patients with psoriatic arthritis who were evaluated before starting therapy and once during the first 12 months of therapy (either 2-4 months, 5-7 months, or 11-12 months) (32).

Similarly, another study focusing on 75 psoriasis patients and analyzing them before receiving therapy and at the 3rd and 6th months of therapy reported a statistically significant decrease, regardless of the type of biological therapy used, in NLR, PLR, and CRP post-treatment levels, posing concurrent findings with the current study (26). This study found a significant relationship, albeit a low-moderate correlation, between the decrease in CRP and NLR levels; however, a significantly moderate positive correlation was found between the PLR levels. There was no significant relationship between PASI and these parameters for the level decrease. Accordingly, it is conceivable to state that NLR, PLR, and CRP are inadequate parameters for monitoring the clinical severity of the disease in psoriasis patients, whereas NLR and especially PLR are effective parameters in the follow-up of systemic inflammation.

The main platelet volume is a potential indicator of platelet function and activation. High MPV values are considered an independent risk factor for acute MI, renal artery stenosis, DM, hypertension, and hyperlipidemia. These values are also high in various systemic inflammatory diseases and are positively related to CRP (18). According to the literature, its level correlates with the PASI score in patients with psoriasis and is higher in patients with arthritis (13,18,33). In a study conducted with 59 patients with psoriasis, Capo et al. (33) scrutinized the pre-treatment and six-month effects of TNF-α inhibitors, identifying a significant decline in post-treatment MPV values and an adverse correlation between the decrease in MPV value and the PASI score. Therefore, they concluded that MPV was an ineffective marker for identifying disease activity (33). Asahina et al. (32) also revealed that MPV was not

an effective marker for systemic inflammation since it was lower among patients with psoriatic arthritis than in patients with psoriasis vulgaris, displayed a negative correlation with CRP, and was elevated after biological therapy. The current study correspondingly identified no substantial difference between pre- and post-treatment MPV values and no correlation between CRP and MPV decline. Therefore, it is viable to claim that MPV is not a reliable marker to demarcate the severity of inflammation.

Plateletcrit refers to the number of platelets in a unit of blood. The MPV X platelet count equation yields PCT. It serves as a marker for platelet aggregation and cardiovascular disease (34). Studies have established that it is associated with the severity of inflammation in Behçet's disease, inflammatory bowel diseases, and malignancies (13). Plateletcrit was typically higher in patients with psoriasis compared to the control group, and its level indicated the severity of the disease (35). Çevirgen Cemil and Ataş (25) assessed the PCT value of psoriasis patients, reporting a significant decline in PCT value after three months of biological therapy. Notwithstanding the therapy agent type, the current study similarly identified a substantial decrease in PCT value after 3-month therapy, albeit establishing no correlation between CRP and PCT decline. Therefore, PCT may also be a potential marker in the follow-up of systemic inflammation among patients with psoriasis; however, further and broad-prospective studies are required to prove it.

Study Limitations

The limitations of this study are that it is retrospective in nature, comprises a limited number of patients, and has a short patient follow-up period. However, assessment of dependent groups, evaluation of patients who have not received biological therapy before, and exclusion of patients with inflammatory and infectious diseases are the main strengths of this study.

Conclusion

Irrespective of the biological therapy category, this study demonstrated that the values of NLR, PLR, PCT, and CRP, the markers for systemic inflammation and cardiovascular morbidity, substantially lowered after therapy, that there was a low-moderate correlation between the CRP and NLR decline, and that there was a moderately positive correlation between the decrease in PLR level. In addition, it established that NLR, PLR, and PCT values obtained from hemogram data, particularly PLR values, can be low-cost and easily accessible parameters to potentially use in analyzing biological therapy effects on systemic inflammation in psoriasis patients. The study findings provided supportive evidence that biological agent therapy lowers the risk of systemic inflammation and cardiovascular morbidity in patients with psoriasis.

Ethics

Ethics Committee Approval: Ethics approval for the study was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Kanuni Training and Research Hospital with decision number 2022/62.

Informed Consent: Written informed consent was waived because of the retrospective nature of this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.K., I.D.O., Concept: S.K., Design: S.K., Data Collection or Processing: S.K., I.D.O., Analysis or Interpretation: S.K., I.D.O., Literature Search: S.K., Writing: S.K.

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The Value of Fetal Cerebro-umbilical Doppler Indices in Predicting Umbilical Blood Gas Abnormalities and Apgar Score in Diabetic Pregnant Women

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Abstract

Aim: There is conflicting data regarding the utility of Doppler indices in patients with diabetes. Our objective was to investigate the value of fetal Doppler parameters on umbilical blood gas abnormalities and Apgar scores in term diabetic pregnancies treated with insulin.

Methods: A total of 120 pregnant women with pregestational or gestational diabetes underwent Doppler screening between 37 and 38 weeks of gestation. The main outcome was to compare the diagnostic performance of the umbilical artery-pulsatility index (UA-PI), middle cerebral artery-PI (MCA-PI), cerebroplacental ratio (CPR), and umbilicocerebral ratio (UCR) in detecting the presence of intrauterine hypoxemia.

Results: From the sample, 18 (15%) had type 1 diabetes mellitus (DM), 40 (33.3%) had type 2 DM, and 62 (51.7%) had GDM A2. The median gestational age at the time of Doppler screening was 37 weeks and 3 days (range 37 weeks to 38 weeks 2 days) and the mean ± standard deviation gestational age at delivery was 38 weeks 4 days ± 3 days. No significant correlations were observed for MCA-PI, UA-PI, CPR, or UCR with any of the measured outcomes. Analysis of Doppler parameters of normal neonates and those with abnormal composite tests showed that Doppler parameters were non-significant in predicting abnormal composite outcomes.

Conclusion: The data obtained from this study show that the low predictive ability of Doppler velocimetry in abnormal neonatal tests results in pregnancies complicated by diabetes.

Keywords: Diabetes mellitus, fetal Doppler, fetal hypoxia, pregnancy, pulsatility index

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that affects more than 21 million births globally every year. Gestational DM is the most common metabolic disorder in pregnancy (1). The worldwide prevalence of all types of DM during pregnancy is estimated at 17% (2). While only a minority of the cases of carbohydrate intolerance during pregnancy represent women with pre-existing diabetes, most cases (~85%) develop or are first recognized during pregnancy (3,4). Diabetes during gestation is associated with an increase in adverse outcomes for the maternal-fetal dyad (5-8). In addition, maternal hyperglycemia can cause fetal hypoxia, which can ultimately lead to fetal respiratory distress syndrome, stillbirth, and neonatal death (9).

Fetal chronic hypoxia leads to persistent modifications in fetal circulation; this hemodynamic adaptation ensures the delivery of oxygen and nutrients to the brain (10). This compensatory phenomenon, the so-called "brain sparing effect", leads to vasodilatation and reduced resistance in the cerebral vessels, and reflects Doppler assessment with a decreased middle cerebral artery-pulsatility index (MCA-PI) and an increased umbilical artery-PI (UA-PI). This results in a change in the cerebroplacental ratio (CPR), i.e., MCA-PI/UA-PI, and the reversal of this ratio, termed the umbilicocerebral ratio (UCR). In recent years, fetal

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Doppler evaluation has become an important screening and surveillance tool in high-risk pregnancies (11). The use of abnormal Doppler indices in pregnancies complicated by placental insufficiency led to improvements in fetal surveillance and adverse perinatal outcomes (12). Moreover, maternal diabetes is also associated with widespread pathologic structural changes, including utero-placental circulation. This pathologic remodeling is associated with increased vascular resistance and tissue hypoperfusion. However, there is conflicting data regarding the utility of Doppler indices in a diabetic cohort. The main purpose of this study was to investigate the role of fetal Doppler parameters on umbilical blood gas abnormalities and Apgar score in term pregestational and gestational diabetic pregnancies treated with insulin.

Materials and Methods

Compliance with Ethical Standards

This study was conducted according to the principles stated in the Declaration of Helsinki. The Clinical Research Ethics Committee of the Medical Faculty of Erciyes University approved the study (KAEK-2016/170). Informed consent forms were obtained from all patients.

Study Design and Participants

This cross-sectional study was designed using the medical data of patients followed up in Erciyes University Faculty of Medicine, Department of Gynecology and Obstetrics with the diagnoses of pregestational diabetes (type 1 DM and type 2 DM) and insulin-treated gestational diabetes (GDM A2) between 2015 and 2016. The enrollment criteria were as follows: maternal age older than 18 years, singleton pregnancy, and morphologically normal fetus. Pregnancies complicated by fetal or severe maternal infections, maternal hypertensive disorders, active smokers, or maternal major medical diseases were excluded from the analyses.

After providing verbal informed consent, low-risk pregnant women routinely underwent blood glucose measurement according to the institutional guidelines at 24-28 weeks of gestation with a 50 g glucose challenge test (GCT). If 50 g of GCT was positive with a 135 mg/dL cutoff point, then a 100 g oral glucose tolerance test (OGTT) was performed according to the diagnostic criteria of Carpenter and Coustan (13). Patients with a spot blood glucose level exceeding 190 mg/dL or two or more values above the threshold levels in the OGTT were regarded as having diabetes. All diabetic pregnant women were assessed with a 1-hour postprandial blood glucose profile, followed by diet counseling (30 kcal/kg) every 2 weeks. Patients were hospitalized at 37 weeks of gestation and monitored by the nonstress test and fetal movement count. In addition, they were evaluated by ultrasound examination in terms of amniotic fluid index, estimated fetal weight, placental localization, and Doppler parameters. All deliveries were performed at 38-39 gestational weeks if the blood glucose levels were regulated and there were no additional risk factors.

Data collected included patient demographics, type of diabetes, body mass index (BMI), total daily dose of insulin, glycosylated hemoglobin (HgbA1c) levels, gestational age at the time of sonographic scan and delivery, Doppler parameters of the umbilical and MCAs, neonatal birth weight, umbilical arterial acid-base status, and Apgar score. Gestational age was based on the last menstrual period, unless the first trimester sonogram (crown-rump length measurement) and the maternal report of the last menstrual period showed an inequality exceeding 7 days.

All Doppler examinations were performed by the same experienced high-risk pregnancy specialists (M.S.K.) with a Voluson 730 Pro scanner equipped with a 5-8 MHz convex transabdominal transducer (GE Healthcare, Wauwatosa, WI) in accordance with the International Society of Ultrasound in Obstetrics and Gynecology practice guidelines: the use of Doppler ultrasonography in obstetrics (14). The UA Doppler flow velocity waveforms were obtained from a free-floating cord loop, and MCA Doppler velocimetry was performed in an axial section of the fetal head, at its origin in the circle of Willis. CPR and UCR were computed as the ratios between MCI-PI and UA-PI and, conversely, the ratios between UA-PI and MCA-PI, respectively. Since all of the measurements were performed within the same gestational week (37-38 weeks), we used absolute CPR and UCR values rather than the multiple of the median or Z score, as previously described (15,16).

The main outcome was to compare the diagnostic performance of fetal Doppler parameters (UA-PI, MCA-PI, CPR, and UCR) in detecting the presence of intrauterine hypoxemia. Intrauterine hypoxemia was measured by umbilical arterial gas analysis and Apgar score (pH, base excess, 1 min, and 5 min Apgar score). Abnormal neonatal test results were defined as follows: pH <7.23, base excess more than 6 (mEq/L), 1-min Apgar score <5, 5-min Apgar score 7 (17,18).

Statistical Analysis

The Kolmogorov-Smirnov test and histograms were used to assess the distribution of the data. Categorical variables were expressed as numbers and percentages (%). Normally distributed data were compared with the Student t-test; asymmetrically distributed data were compared with the Mann-Whitney U. A linear regression analysis was implemented to assess the association between UA-PI, MCA-PI, CPR, and UCR and each neonatal

outcome measure. The receiver-operator characteristic curve (ROC) was suggested to investigate applicability for predicting the neonatal composite outcome. SPSS version 23 (SPSS Inc., Chicago, IL) was used for analysis, and a p-value <0.05 was deemed statistically significant.

Results

A total of 120 women with DM met the inclusion criteria and were recruited for the study. Of these, 15% (18/120) had type 1 DM, 33.3% (40/120) had type 2 DM, and 51.7% (62/120) had GDM A2. The mean maternal age and BMI of our sample were 33.25±6.48 years and 33.82±6.26 kg/m^2, respectively. The majority of patients, 107 (89.2%), were multiparous, and the rest, 13 (10.8%), were primigravida. The median (Q1-Q3) gestational age at the time of Doppler screening was 37 weeks and 3 days (range 37 weeks to 38 weeks 2 days), and the mean ± standard deviation (SD) gestational age at delivery was 38 weeks 4 days ± 3 days. The interval between Doppler screening and delivery (mean ± SD) was 6.2±2.1 days. Patient baseline demographic and clinical data are described in Table 1.

Table 2 shows the results of the linear regressions of fetal Doppler parameters for predicting abnormal neonatal test results. According to our results, no significant correlations were observed for MCA-PI, UA-PI, CPR, or UCR with any of the measured outcomes.

Table 3 shows a comparison of Doppler parameters between normal neonates and those with abnormal composite tests. Abnormal composite tests were defined as the combination of pH <7.23, base excess <-6.3, and 5th Apgar score <5. According to the analysis results, Doppler parameters were not significant predictors of abnormal composite outcomes, with the ROC curves of Doppler parameters showing a poor predictive value for each Doppler parameter (Figure 1).

Table 1. The baseline demographic and clinical parameters

Maternal age (years)	33.25±6.48
Body mass index (kg/m^2)	33.82±6.26
Nulliparous	13 (10.8%)
Multiparous	107 (89.2%)
Total daily insulin dose (units)	25 (10-48)
HgbA1c levels	5.67±1.01
The type of diabetes	
Gestationel A2 Type 1 Type 2	62 (51.7%) 18 (15%) 40 (33.3%)
Gestational age at the time of Doppler screening (weeks)	37+3 (37-38+2)
Gestational age at the time of delivery (weeks)	38+4±3
Mode of delivery	
Vaginal delivery Cesarean section	16 (13%) 104 (87%)
UA-PI	0.93±0.29
MCA-PI	1.64±0.43
CPR	1.9±0.7
UCR	0.6±0.23
Newborn weight (g)	3569±543
Apgar score 1st minute	8 (2-8)
Apgar score 5th minute	10 (0-10)
Neonatal pH	7.31±0.7
Neonatal base excess	-4.1±3.8

Values are expressed as n (%), mean ± SD or median (1st-3rd quartiles).
UA: Umbilical artery, PI: Pulsatility index, MCA: Middle cerebral artery, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio

Table 2. Results of linear regressions of fetal Doppler parameters on predicting abnormal neonatal test results. P-values

	pH	Base excess	1st min Apgar	5th min Apgar
UI-PI	0.853	0.481	0.455	0.642
MCA-PI	0.484	0.155	0.661	0.778
CPR	0.976	0.787	0.426	0.632
UCR	0.99	0.452	0.265	0.468

UA: Umbilical artery, PI: Pulsatility index, MCA: Middle cerebral artery, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio

Discussion

Our study, where we investigated the role of fetal Doppler parameters on umbilical blood gas abnormalities and Apgar score, showed that Doppler ultrasonographic scans of MCA-PI, UA-PI, CPR, and UCR were not correlated with neonatal Apgar score or umbilical cord acid-base status in otherwise healthy diabetic patients. In addition,

Table 3. Comparison of Doppler parameters between normal neonates and neonates having abnormal composite tests

Doppler parameters	Normal neonatal tests (n=93)	Composite abnormal neonatal tests (n=27)	p-value
UA-PI	0.85 (0.44-2.22)	0.93 (0.65-1.77)	0.116**
MCA-PI	1.59 (0.65-2.89)	1.70 (0.74-2.54)	0.481**
CPR	1.92±0.68	1.82±0.74	0.501*
UPR	0.54 (0.26-1.35)	0.58 (0.28-1.14)	0.468**

*Student's t-test, Mean ± standard deviation was given for descriptives. **Mann-Whitney U test, Median (minimum-maximum) was given for descriptives.
Combined abnormal neonatal tests included pH pH<7.23, Base excess <-6.3, 5th Apgar score <5, p<0.05, statistically significant difference.
UA: Umbilical artery, PI: Pulsatility index, MCA: Middle cerebral artery, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio

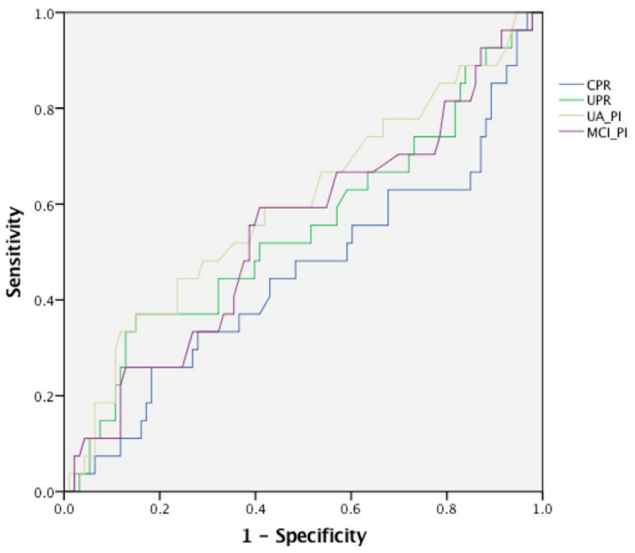

Figure 1. Receiver operating characteristic analyses for predicting abnormal composite outcomes using Doppler parameters

fetal Doppler parameters did not offer a diagnostic tool for predicting abnormal composite neonatal results among patients with diabetes.

The applicability of fetoplacental Doppler sonography in diabetic pregnancies for fetal monitoring is still disputed because previous studies showed incompatible results (15,16,19-23). In the study by To and Mok (20) the PI of UA, the diameter of UV, and the mean maximum velocity of umbilical venous flow were measured. They concluded that umbilical velocimetry at near term was unable to predict abnormal pregnancy outcomes. In parallel with this, Pietryga et al. (19) reported that placental Doppler sonography does not appear to have clinical value for fetal surveillance unless there is an absence of fetal growth restriction and/or preeclampsia. In the prospective single-center cohort study of Ganor Paz et al. (21) in pregnancies affected by GDM, they found that CPR below the 10th percentile was not associated with adverse perinatal outcomes. In a previous study that compared transcranial Doppler indices of fetal brain hemodynamics in diabetic versus normal pregnancies, a higher PI of the MCA was found among the diabetic group; however, they did not provide any information about insulin use or daily insulin dose (22). The importance of UCR is still a subject of debate in estimating fetal hypoxia, and it is currently unclear whether UCR should be preferred over other Doppler indices. In a recent study, Familiari et al. (16) found that MCA-PI and UCR were significantly correlated with a low neonatal pH; however, they only included gestational diabetic patients in their cohort, and most of these pregnancies were regulated by diet. Fetuses of women with insulin-controlled diabetes had poorer neonatal outcomes than those of women treated with dietary control alone (23). Therefore, our cohort reflects the strong metabolic and hemodynamic effects of diabetes on umbilical cord blood gas analysis.

Transcranial Doppler findings have provided valuable predictive models for assessing high-risk pregnancies. in uteroplacental insufficiency, the PI of MCA tends to reduce to increase cerebral perfusion, which is called the brain sparing effect. However, according to our results, there was no correlation between MCA-PI, CPR, and umbilical cord acid-base status, and no cerebroplacental compensation was observed, which is contrary to the situation observed in uteroplacenta insufficiency. There are some possible explanations for this. Although DM is an intrauterine hypoxic condition, the response of the ductus venosus to hypoxia is blunted and the umbilical venous/ductus venosus shunt ratio is lower compared to healthy control (24). Therefore, it may be speculated that the brain sparing effect at the ductus venosus level is less operative in fetus of DM mothers, and this disregulation may propagate to the MCAs with resultant higher MCA-PI in the acidotic fetus of DM mothers. On the other hand, UA-PI is largely dependent on placental vascular surface area and in DM pregnancies, this is known to enlarge due to increased local vascular growth factors with resultant normal UA-PI values (25,26). Therefore, it seems that hemodynamic pathologies and adaptations are not operative in the fetus of diabetic mothers (FODM). Thus, the inefficiency of the cerebral protective mechanism is partly responsible for sudden third trimester fetal distress and loss in FODM (27). Moreover, increased red blood cell mass and viscosity and altered perfusion of fetal liver may further affect cerebral regulation in these cases (28).

The clinical importance of Doppler measurement in fetal growth restriction is well known (29). However, data gathered from this study showed no predictive value for Doppler indices as a screening test for fetal well-being in pregnancies complicated with diabetes. In practice, the non-stress test is still the main clinical tool for the surveillance of diabetic pregnancies. The combination of strict glycemic control and the non-stress test may improve perinatal outcomes.

Study Limitations

The main limitation of the current study is its retrospective design and the inherent bias associated with observational data. A second limitation is the lack of a prestudy power analysis. However, this study also presents some strength. To the best of our knowledge, this study provides the first data for pre- and gestational diabetes cohorts with which the doppler parameters were investigated at term for cases treated with insulin. This stricter study population enabled us to objectively

investigate the metabolic and hemodynamic effects of diabetes on umbilical blood gas abnormalities and Apgar scores. Another important point is that all cases are managed with a single institutional protocol, and all sonographic exams are performed by the same experienced high-risk pregnancy specialists. In addition, we set pH value <7.23 as the threshold to define fetal acidosis, which was related to a 1% false-negativity for neonatal asphyxia (17). Another advantage of the present study is that it includes 85% rate of cesarean section, most of which are operated on an elective basis. This factor largely excludes intrapartum hypoxic events associated with vaginal delivery that affect fetal acid-base status in a fetus with otherwise normal doppler findings at 37 weeks (30).

Conclusion

The data obtained from the present study show that doppler velocimetry is not predictive of abnormal neonatal test results in pregnancies complicated with diabetes. Further prospective studies are needed to confirm the current findings.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of the Medical Faculty of Erciyes University approved the study (KAEK-2016/170).

Informed Consent: Informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.K, M.D Concept: C.C, M.S.K., M.D., Design: M.S.K., T.T., C.C Data Collection or Processing: M.S.K., M.D., Analysis or Interpretation: C.C., M.S.K., T.T., Literature Search: C.C., M.D., T.T., Writing: C.C., M.S.K., T.T.

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Original Article

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Effect of Preoperative Anxiety Level on Postoperative Analgesia Requirement in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Aim: The preoperative anxiety levels of the patients create negative effects in the postoperative period. In this study, we aimed to reveal the relationship between postoperative analgesia needs and preoperative anxiety levels in patients undergoing laparoscopic cholecystectomy.

Methods: This study was organized as a cross-sectional study. The Preoperative Trait And State Anxiety Scales (STAI-T and STAI-S) were applied to 66 patients undergoing elective laparoscopic cholecystectomy between October 2020 and October 2021, and they were divided into two groups of high and low anxiety according to their STAI-S scores. Postoperative anxiety level was considered 0th hour when the patient was able to respond to verbal stimuli and was re-evaluated with the STAI-S scale within the first 4 h. Postoperative pain scores of the patients were recorded with the visual analogue scale at 2nd, 6th, 12th, and 24th hours. Patients who needed additional analgesia doses were recorded.

Results: Sociodemographic characteristics were compared between groups, and no significant difference was found. Although the pain of our patients decreased over time, there was no significant relationship between anxiety levels and postoperative pain scores of the groups.

Conclusion: This study showed that there was no relationship between the preoperative anxiety level and the postoperative analgesia score of the patients.

Keywords: Analgesia, anesthesia, anxiety

Introduction

Undergoing surgery due to health issues is a psychologically challenging situation for individuals. Patients awaiting surgery experience increased anxiety and fears throughout the operation period, considering this period a crisis phase. The evaluation of patients' physical and psychological condition, medications used, previous surgeries, and laboratory results plays a crucial role in determining the anesthesia risk before surgery. Therefore, alleviating anxiety during the pre-operative preparation process holds significant importance. Typically, hospitalized patients exhibit anxiety rates ranging from 10% to 30% (1). Anxiety can have adverse effects on surgical procedures, anesthesia management, and postoperative recovery (2). Various factors contribute to preoperative anxiety, such as separation from loved ones, disruption of daily activities, fear of death, limb or organ loss, dependency on care, fear of job loss, fear of waking up during surgery or not waking up after surgery, and concerns about experiencing pain (3). Providing detailed information to patients based on preoperative assessments can reduce anxiety.

Postoperative pain can negatively impact the patient's quality of life and increase mortality and morbidity rates due to its effects on the respiratory, endocrine, cardiovascular, immune, and gastrointestinal systems (4). While numerous drugs and methods are used for postoperative pain management, no consensus on the gold standard approach has yet been reached. Moreover,

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the side effects of these methods can further deteriorate the already compromised quality of life for patients. In some cases, managing pain during the postoperative period remains challenging. Particularly, pain following laparoscopic procedures poses significant issues during the early stages.

The aim of this study was to evaluate the relationship between preoperative anxiety levels and postoperative analgesia requirements in patients undergoing laparoscopic cholecystectomy. We hope that our findings, along with current and future studies, will contribute to the resolution of this problem.

Methods

Compliance with Ethical Standards

Ethical permission for the study was obtained from Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Traning and Research Hospital (approval number: 2020/190, date: 21.10.2020). The participants were informed that the data would only be used for scientific purposes. Informed consent was obtained from all participants.

Study Design

This study included American Society of Anesthesiologist I-II patients aged between 18 and 60 years who were eligible for elective cholecystectomy and who had the mental state to fill in the scales and questionnaires for evaluation, all of whom were volunteers. Our research was designed as a cross-sectional study. Sociodemographic information about the patients was recorded at the pre-operative anesthesia visit. The Preoperative Trait and State Anxiety Inventory (STAI-T and STAI-S) was applied to 66 patients, and they were divided into two groups based on their STAI-S scores: high and low anxiety. Those with a preoperative STAI-S score of 40 points or less were included in Group L (low), and those above 40 points were included in Group H (high). No sedative medication was administered to the patients in the service on the day of surgery. After premedication with 0.04 mg/kg midazolam, 1-2 mcg/kg fentanyl, 2-3 mg/kg propofol, and 0.6 mg/kg rocuronium were administered for anesthesia induction, the patients were intubated orotracheally.

Anesthesia Procedure

Laparoscopic surgery was performed under inhalation anesthesia with a concentration of sevoflurane of 1-2% in a 40-60% oxygen-air mixture for the maintenance of anesthesia. During the laparoscopic procedure, pneumoperitoneum was created at pressures of 10-12 mmHg. 15 mg/kg acetaminophen and 1-2 mg/kg tramadol were administered to the patients 30 minutes before the end of the surgery. Patients who were taken to the service after the follow-up in the recovery room were administered intravenous 1 g acetaminophen every 8 h and intravenous non-steroidal anti-inflammatory (20 mg tenoxicam) drugs every 12 h, in accordance with the general surgery clinic postoperative analgesia protocol, if there were no contraindications. Patients who needed additional analgesia were recorded. The time when the patients were able to respond to verbal stimuli was accepted as the 0^{th} hour postoperatively, and the pain scores of the patients were recorded at the $2n^{d}$, 6^{th}, 12^{th}, and 24^{th} hours. The STAI-S questionnaire was repeated to measure the state anxiety level in the first 4 hours postoperatively. The preoperative STAI-S scores, postoperative visual analogue scale (VAS) scores, and postoperative analgesic drug needs of the groups were compared.

Statistical Analysis

The Statistical Package for the Social Sciences version 25 (SPSS, IBM Corp., Armonk, NY, USA) program was used. The normal distribution of the variables was checked by the Shapiro-Wilk test and Q-Q plots. The Mann-Whitney U test was used to compare continuous data. Categorical variables were grouped and compared using the χ^2 test or Fisher's exact test. The repeated measurement test was used for the analysis of repeated measurements. The data were analyzed at a 95% confidence level.

Results

The mean age of the 66 patients included in the study was 46.09±11.27 years. While 30 patients (45.5%) had no surgical experience; 36 patients (54.5%) had previous experience with one or more operations (Table 1). The mean preoperative STAI-T score of the participants was 42.2±13.8, the maximum score was 70, the minimum score was 21, and the median was 39; the mean preoperative STAI-S score was 46.4±13, the maximum score was 72, the minimum score was 26, and the median was 42.5; the mean postoperative STAI-S score was 39.7±9.8, the maximum score was 69, the minimum score was 25, and the median was 38.5 (Table 2).

It was determined that the rate of participants with a preoperative STAI-T value of ≤40 was 62.1%, the rate of participants with a preoperative STAI-S value of ≤40 was 39.4%, and the rate of participants with a postoperative STAI-S value of ≤40 was 71.2% (Table 3).

When the demographic characteristics of the groups were examined, the mean age of the group with low preoperative anxiety (Group L) was 44.5±9.5 years, 65.4% were female, 80.8% were married, 38.5% were primary school graduates, and 42.3% had a history of surgery. The mean age of the group with high preoperative anxiety (Group H) was 47.1±12.2 years, 67.5% were female; 80%

were married; 32.5% were primary school graduates; and 62.5% had a history of surgery. No statistically significant difference was found in the comparison of the two groups according to their demographic data (Table 4).

No statistically significant difference was found in the comparison of the additional analgesic dose needs of the groups (Table 5). In the comparison of the VAS values of the groups, it was determined that VAS values decreased statistically significantly over time, but there was no statistically significant correlation between preoperative STAI-S and VAS values (Table 6).

Table 1. Demographic data of patients

Mean age*	**46.09±11.27**
Gender, n (%)	
Male	22 (33.3%)
Female	44 (66.7%)
Marital status, n (%)	
Single	13 (19.7%)
Married	53 (80.3%)
Educational status, n (%)	
Illiterate	2 (3.0%)
Literate	7 (10.6%)
Primary school	23 (34.8%)
Secondary school	12 (18.2%)
High school	14 (21.2%)
University	7 (10.6%)
Graduate of a master' program	1 (1.5%)
Operation history, n (%)	
No	30 (45.5%)
Yes	36 (54.5%)
*Mean ± standard deviation	

Table 2. Maximum, minimum and median distribution of STAI scores

	Preoperative STAI-T score	Preoperative STAI-S score	Postoperative STAI-S score
Maximum	70	72	69
Minimum	21	26	25
Median	39	42.5	38.5

Table 3. STAI score distribution of patients

	n (66)
Preoperative STAI-T, n (%)	
≤40	41 (62.1%)
>40	25 (37.9%)
Preoperative STAI-S, n (%)	
≤40	26 (39.4%)
>40	40 (60.6%)
Postoperative STAI-S, n (%)	
≤40	47 (71.2%)
>40	19 (28.8%)

Discussion

Although many studies have been conducted on the factors affecting the analgesia needs of patients in the postoperative period, postoperative pain remains a problem. We evaluated the preoperative anxiety levels of our patients who participated in our study and examined the relationship between their postoperative VAS scores.

Lichtor et al. (5). evaluated the anxiety levels on the morning of the operation and the day before the

Table 4. Comparison of groups by demographic data

		Preoperative STAI-S score		
	Total	Grup L	Grup H	p-value
Age, mean ± standard deviation		44.5±9.5	47.1±12.2	*0.408
Gender, n (%)				**0.859
Male	22 (33.3%)	9 (34.6%)	13 (32.5%)	
Female	44 (66.7%)	17 (65.4%)	27 (67.5%)	
Martal status, n (%)				**0.939
Single	13 (19.7%)	5 (19.2%)	8 (20.0%)	
Married	53 (80.3%)	21 (80.8%)	32 (80.0%)	
Educational status, n (%)				**0.746
Illiterate	2 (3.0%)	0	2 (5.0%)	
Literate	7 (10.6%)	3 (11.5%)	4 (10.0%)	
Primary school	23 (34.8%)	10 (38.5%)	13 (32.5%)	
Secondary school	12 (18.2%)	5 (19.2%)	7 (17.5%)	
High school	14 (21.2%)	5 (19.2%)	9 (22.5%)	
University	7 (10.6%)	2 (7.7%)	5 (12.5%)	
Graduate of a master' program	1 (1.5%)	1 (3.8%)	0	
Operation history, n (%)				**0.107
No	30 (45.5%)	15 (57.7%)	15 (37.5%)	
Yes	36 (54.5%)	11 (42.3%)	25 (62.5%)	
*Student's t-test, **Chi-square test				

Table 5. Comparison of additional analgesic dose needs of the groups

		Preoperatif STAI-S score		
	Total	**Grup L**	**Grup H**	**p-value**
Analgesic dose need, n (%)				*0.061
No	57 (86.4%)	25 (96.2%)	32 (80.0%)	
Yes	9 (13.6%)	1 (3.8%)	8 (20.0%)	
*Chi-square test				

Table 6. Comparison of VAS values of the groups

Time	Preop STAI-S	VAS (Mean ± SD)	Sphericity	Greenhouse-Geisser (Time-VAS)	Greenhouse-Geisser (VAS-STAI-S)
2nd hour	≤40	5.73±2.49	<0.001	<0.001	0.149
	>40	4.9±2.53			
6th hour	≤40	4.54±1.65			
	>40	4.18±2.07			
12th hour	≤40	4.19±1.96			
	>40	4.08±2.08			
24th hour	≤40	2.88±2			
	>40	3.38±2.65			

VAS: Visual analogue scale, SD: Standard deviation

operation and did not observe any difference between the two time periods (5). We performed a preoperative visit one day before the operation to determine the demographic characteristics of our patients and to measure their preoperative anxiety levels.

The most widely used test for measuring anxiety is the STAI scale, developed by Spielberger et al. (6). In our study, we also used the STAI scale to evaluate the effect of preoperative anxiety on the need for postoperative analgesics. Domar et al. (7) found a mean anxiety score of 45 according to the STAI scale in the pre-operative period in their study. Gönüllü et al. (8) reported a mean anxiety score of 40.76 in their study, which included 83 patients. In our study, we found the preoperative anxiety score of the patients to be 46.4, and we observed that our results were similar to those reported in the literature. Some studies in the literature have observed a relationship between increased anxiety levels and increased education levels, but this relationship has not been observed in some studies (9-11). In our study, we did not find a statistically significant relationship between the education status and preoperative anxiety levels of the patients.

There are studies with different results on the relationship between patient age and preoperative anxiety. Since family responsibility is found to be higher in middle-aged individuals compared to other age groups, higher anxiety levels were obtained in the study conducted by Ossai et al. (12) in this age group. Meyer et al. (13) found the anxiety level to be higher in young individuals due to their level of knowledge. In our study, the mean age of our patients was 46.09 years, and we did not find a significant relationship between age and preoperative anxiety level.

Wagner et al. (9) obtained the result that previous operation experience reduced preoperative anxiety, but Domar et al. (7) concluded that previous operation experience did not affect anxiety. In our study, we did not find a statistically significant difference between the previous surgery of experience and the level of preoperative anxiety in our patients. In their study, Güz et al. (14) evaluated the preoperative anxiety level using the state and trait anxiety scale and found a significant relationship between increased anxiety level and postoperative pain level. In our study, when we compared the preoperative anxiety levels of our patients with their postoperative VAS scores, we observed that the VAS scores decreased over time in both groups, but there was no statistically significant correlation between the anxiety level and postoperative pain scores. In the studies of Caumo et al. (11) and Kashif et al. (15), patients with increased anxiety needed more analgesics due to the increased pain they felt in the postoperative period. In our study, when the preoperative anxiety levels and the need for additional dose analgesia were evaluated, we did not find a significant statistical relationship, and we observed that 3.8% of the patients in the low- and 8% of the patients in the high-anxiety groups needed additional dose analgesia. If we touch on the shortcomings of our study, since we did not record the weight and height of our patients, the effect of body mass index on position-related postoperative pain was not evaluated.

Study Limitations

Our study has some limitations. The first limitation is that the study was conducted at a single center. Additionally, the subjective nature of anxiety assessments may impact the results. Moreover, the patients' body mass indexes were not evaluated, which could influence postoperative pain related to positioning. However, despite these limitations, the study's strengths lie in its prospective design and the examination of a specific group, specifically patients undergoing laparoscopic cholecystectomy.

Conclusion

Although medical and alternative treatment methods are used for treating postoperative pain, there is no consensus on the gold standard treatment. The side effects of the methods used can worsen the already impaired quality of life of patients. We conducted our study to evaluate the relationship between the preoperative anxiety levels of the patients and postoperative pain, and according to the data, we did not observe a relationship between the preoperative anxiety levels of our patients and their pain levels in the postoperative period.

Ethics

Ethics Committee Approval: Ethical permission for the study was obtained from Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Traning and Research Hospital (approval number: 2020/190, date: 21.10.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Original Article

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Opioid-free versus Opioid-Based General Anesthesia in Cesarean Sections: A Cross-sectional Analysis

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Abstract

Aim: Guidelines recommend opioid-free (OF) anesthesia in elective cesarean sections (CS). However, opioids are commonly administered after a baby's delivery for postoperative pain in daily practice. Our aim was to compare OF and opioid-based (OB) general anesthesia in elective surgery (CS).

Methods: The study was a cross-sectional study including patients who had undergone elective CS with OF (Group OF) and OB (Group OB) general anesthesia between June 1, 2022, and November 30, 2022. Intraoperatively administered analgesics for postoperative pain mainly included acetaminophen and non-steroidal anti-inflammatory drugs (NSAID) in Group OF and fentanyl, acetaminophen, and tramadol in Group OB. Non-steroidal anti-inflammatory drugs were administered as analgesics at the maternity ward.

Results: Of 368 patients, 278 were excluded due to regional anesthesia. In 90 patients, 45 were in Group OF and 45 were in Group OB. Group OF received less intraoperative fluid compared with Group OB. Two groups required a similar number of NSAIDs on postoperative day zero. Group OF had more NSAID consumption on postoperative days one and two.

Conclusion: Opioid-free general anesthesia did not change the required number of NSAIDs 24 hours after surgery and necessitated less intraoperative crystalloid fluid. Our study supports Enhanced recovery after surgery protocols, which recommend multimodal analgesics and sparing opioids in CS, and adds to the accumulating evidence that suggests the use of OF general anesthesia in CS.

Keywords: Obstetrics, cesarean section, general anesthesia, opioid analgesics, postoperative pain, perioperative care

Introduction

Cesarean section (CS) is one of the most common surgical procedures, with a rate of 32% of all births and 1.27 million patients annually in the United States (1). Since taking care of two lives-mother and fetus-has gained extra importance, improving patient outcomes has gained extra importance (2). Obstetric mortality reductions in CS are based on regional anesthesia increases and enhancing the safety of general anesthesia (3). Over the last few decades, general anesthesia applications for CS have declined. It was shown that general anesthesia was performed in less than 1% of CSs in a tertiary care facility (4). However, general anesthesia may still be requested by patients, preferred in emergent CS, or used when regional anesthesia is contraindicated due to hemodynamic, neurological, or spinal abnormalities. In both general and regional anesthesia, pregnant women require comprehensive perioperative care.

Enhanced recovery after surgery (ERAS) includes perioperative care to accelerate patient recovery. Enhanced recovery after surgery protocols in obstetrics recommend prescribing multimodal analgesics with a combination of drugs that have different mechanisms of action and sparing opioids (5). Furthermore, newborns are affected by opioids administered during birth. The use of neuraxial or systemic opioids is associated with unpredicted maternal and neonatal outcomes. To decrease fetal opioid exposure, opioids should be minimized or avoided before delivery. However, minimal opioid use can still lead to unwanted outcomes. The side effects of neuraxially administered opioids are significantly lower than those of systemically administered opioids (6,7). Avoiding opioids in general anesthesia will discard the risk of potential maternal and

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fetal opioid side effects. In addition, guidelines suggest encouraging breastfeeding as normal following CS and opioid-sparing anesthesia in breastfeeding women. Immediately after delivery, the intercellular gaps in the milk glands are fully open for immunoglobulin passage to the baby, and during this period, drugs are also freely able to pass into breast milk. Also, they suggest extra caution for infants less than six weeks of age. Recent guidelines recommended using multimodal analgesia with non-opioid drugs for postoperative pain after delivery, including non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen (8).

Even though guidelines recommend opioid-free (OF) anesthesia in elective CS, in daily practice, opioids are commonly administered after the delivery of a baby for postoperative pain. Because of the rarity of applying OF general anesthesia in CS, it has been difficult to determine the perioperative management difference between OF and opioid-based (OB) general anesthesia in CS. In this study, we compared the perioperative management of OF and OB general anesthesia in elective CS.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital (date: 19/12/2022, decision no: E-46059653-050.99).

Study Design

We retrospectively screened patients who had undergone elective CS with general anesthesia from June 1, 2022, to November 30, 2022. All patients with American Society of Anesthesiologists (ASA) II and III who had undergone elective CS with general anesthesia were included in our study. Patients who were ASA IV and had undergone CS with regional anesthesia were excluded. Patients were divided into two groups: 1) patients who were operated under OF general anesthesia (Group OF); and 2) patients who were operated under OB general anesthesia (Group OB).

All patients received anesthesia induction with i.v. propofol (2 mg/kg) and rocuronium (0.6 mg/kg) and were maintained with sevoflurane in a mixture of 50% oxygen and air with a 2 L/min flow rate. The patient's anesthesia depth was recorded by bispectral index (BIS) monitoring while maintaining a value between 40 and 60. Sevoflurane MAC was increased according to the patient's BIS values. Lungs were ventilated with a tidal volume of 6-8 mL/kg and a positive end-expiratory pressure of 5 cm H_2O. End-tidal carbon dioxide was maintained between 35 and 40 mmHg by adjusting the tidal volume and respiratory rate. Group OF and Group OB anesthesiologists were different physicians, and postoperative analgesia management was different in both groups. In Group OF, intraoperatively administered analgesics for postoperative pain included acetaminophen (1000 mg) and NSAID (75 mg diclofenac sodium i.m.) with magnesium (1.5 mg in crystalloid solution) and a single 10 mL 0.5% bupivacaine injection under the skin before wound closure. In Group OB, intraoperative analgesics for postoperative pain after delivery included fentanyl (50 or 100 mcg), paracetamol (1000 mg), and tramadol (100 mg) with ondansetron (4 mg).

Demographic variables were age, body mass index, weight, height, ASA score, previous CS, comorbidities (diabetes mellitus, hypertension, lung disease, thyroid disease), and smoking history. Intra-operative data included pre-operative and post-operative mean arterial pressure (MAP), pre-operative and post-operative heart rate (HR), total amount of administered fluid, surgery time, time difference between start of anesthesia and delivery of the baby, and emergence from anesthesia time (time between end of surgery and transfer to the recovery room). Postoperative data included NSAID consumption, which was administered according to the patient's demand at the maternity ward, on day zero (24 hours after surgery), day one, day two, and the patient's hospital length of stay (LOS). All the data from the two groups was compared.

Statistical Analysis

A power analysis was run to evaluate the size of the sample. To obtain a statistical power of 80 percent with an effect size of 0.6 in the study, we needed to enroll a minimum of 2×21 subjects to detect significant differences between groups. The mean, standard deviation, median, minimum, maximum value, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. The independent sample t-test and Mann-Whitney U test were used for the comparison of quantitative data. The Wilcoxon signed-rank test was used for repeated measurement analysis. The chi-square test was used for the comparison of qualitative data. SPSS 28.0 was used for statistical analyses.

Results

Two hundred and sixty-eight patients who had undergone elective CS between June 1, 2022, and November 30, 2022, were screened. One hundred and seventy-eight patients were excluded due to regional anesthesia. Ninety patients were enrolled in the study (Figure 1). Forty-five patients had OF general anesthesia (Group OF) and 45 patients had OB general anesthesia (Group OB) in elective CS surgeries. There were no

significant differences in the demographic variables of the two groups (Table 1).

In intraoperative variables, there were no significant differences between pre- and postoperative MAP or the variation of MAP between groups. There were significant differences between the pre-operative HR (p=0.025) and post-operative HR (p=0.005) of the groups. There was no significant difference in the variation of HR between

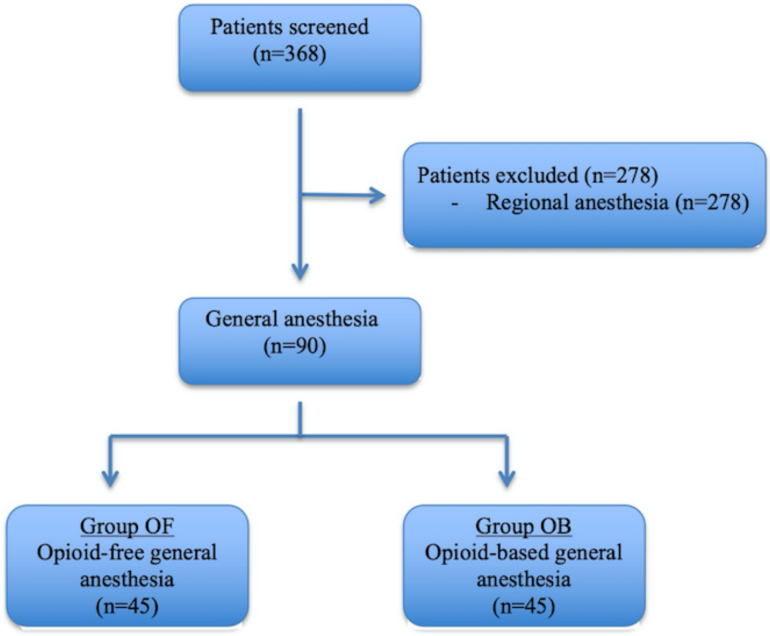

Figure 1. Flow chart
OF: Opioid-free, OB: Opioid-based

Table 1. Demographic variables of all patients

Variables	Overall (n=90)	Group OF (n=45)	Group OB (n=45)	p-value
Age (yr)	28 (25 to 33)	29 (26 to 34)	27 (25 to 32)	0.167[m]
Weight (kg) Height (cm) BMI	76 (70 to 87) 165 (160 to 168) 28 (26 to 31)	80 (69 to 85) 160 (160 to 166) 29 (26 to 31)	75 (70 to 90) 165 (160 to 170) 28 (26 to 32)	0.916[m] 0.172[m] 0.729[m]
ASA II III	 86 (96) 4 (4)	 42 (93) 3 (7)	 44 (98) 1 (2)	 0.616[x2]
Previous CS 0 1 2 3	 17 (19) 49 (54) 22 (25) 2 (2)	 6 (13) 23 (51) 14 (32) 2 (4)	 11 (24) 26 (58) 8 (18) 0 (0)	 0.178[x2]
Comorbidities HT DM Asthma Thyroid disease	 1 (1) 6 (7) 1 (1) 10 (11)	 1 (2) 4 (9) 1 (2) 5 (11)	 0 (0) 2 (4) 0 (0) 5 (11)	 0.494[x2] 0.398[x2] 1.000[x2] 1.000[x2]
Smoking Never Current Former	 78 (87) 7 (8) 5 (5)	 38 (84) 5 (11) 2 (5)	 40 (89) 2 (4) 3 (7)	 0.535[x2]

Data are presented as the median (interquartile range) or absolute number (percentage).
[m]: Mann-Whitney U test; [X2]: Chi-square test
P-values in bold represent statistically significant results (p<0.05).
BMI: Body mass index, CS: Cesarean section, HT: Hypertension, DM: Diabetes mellitus

groups. Intraoperatively administered fluids were all crystalloids and significantly different between groups (p=0.012). There was no significant difference in surgery time, time between the start of anesthesia and delivery of the baby, or emergence from anesthesia time between the groups (Table 2).

In postoperative variables, there was no significant difference in postoperative day zero NSAID consumption between the groups. The mean NSAID consumption on postoperative days one (p=0.001) and two (p=0.031) was significantly different between groups. On postoperative day one, the mean NSAID use was 1.1±0.5 in Group OF and 0.7±0.7 in Group OB. On postoperative day two, the mean NSAID use was 0.8±0.4 in Group OF and 0.6±0.5 in Group OB. Hospital LOS was not significantly different between the groups (Table 2).

Discussion

In this study, we compared OF and OB general anesthesia in elective CS. We found differences in intraoperative crystalloid fluid amount, NSAID consumption on postoperative days one and two between the two groups.

Systemic opioids are used in the general anesthesia of CS after the delivery for pain relief. However, opioids have many side effects, including hypotension, which could result in administering more intraoperative fluid than necessary. The results showed that OF general anesthesia in CS patients received less intraoperative fluid than OB general anesthesia (1075 vs. 1217 mL). Iatrogenic overload side effects have not been reported so far, but hypervolemia was associated with endothelial damage (9). Literature supports our results by finding better outcomes in abdominal surgery patients who had restrictive fluid management compared to conventional fluid management during surgery (10).

Our other result was the amount of NSAIDs consumed on postoperative day zero, which was not significantly different between Group OF and Group OB. Our data are consistent with the literature, which showed that

Table 2. Peri-operative variables of all patients

Variables	Overall (n=90)	Group OF (n=45)	Group OB (n=45)	p-value
Mean arterial pressure (mmHg)				
Preoperative	91 (86 to 97)	90 (86 to 95)	91 (86 to 98)	0.532[m]
Postoperative	85 (80 to 93)	83 (80 to 93)	87 (80 to 93)	0.585[m]
Variation	-5 (-12 to -2)	-6 (-11 to -1)	-4 (-12 to -2)	0.684[t]
Heart rate (per min)				
Preoperative	92 (84 to 104)	95 (88 to 105)	87 (81 to 98)	**0.025[m]**
Postoperative	91 (80 to 100)	100 (89 to 107)	90 (70 to 115)	**0.005[m]**
Variation	2 (-11 to -12)	1 (-10 to -15)	2 (-14 to -9)	0.876[t]
Crystalloid fluid (mL)	1146±272	1075±200	1217±315	**0.012[m]**
Times (min)				
Surgery	65 (55 to 76)	63 (52 to 78)	66 (55 to 75)	0.802[m]
Difference between anesthesia start and baby delivery	7 (5 to 9)	7 (6 to 9)	7 (5 to 8)	0.265[m]
Emergence from anesthesia	5 (5 to 10)	5 (5 to 8)	5 (5 to 10)	0.226[m]
Post-operative day zero NSAID				
Mean	1.1±0.8	1.2±0.7	1±0.8	0.305[m]
0	25 (28)	9 (20)	16 (36)	
1	34 (38)	20 (44)	14 (31)	0.218[x2]
2	31 (34)	16 (36)	15 (33)	
Post-operative day one NSAID				
Mean	0.9±0.6	1.1±0.5	0.7±0.7	**0.001[m]**
0	22 (24)	3 (7)	19 (42)	
1	58 (64)	36 (80)	22 (49)	**<0.001[x2]**
2	8 (9)	5 (11)	3 (7)	
3	2 (2)	1 (2)	1 (2)	
Post-operative day two NSAID				
Mean	0.7±0.5	0.8±0.4	0.6±0.5	**0.031[m]**
0	28 (31)	9 (20)	19 (42)	
1	60 (67)	35 (78)	25 (56)	**0.023[x2]**
2	2 (2)	1 (2)	1 (2)	
Hospital LOS (day)	3.2±1	3.3±1.4	3.1±0.6	0.266[m]

Data are presented as the mean ± SD, median (interquartile range), or absolute number (percentage).
[m]: Mann-Whitney U test, [X²]: Chi-square test
P-values in bold represent statistically significant results (p<0.05).
NSAID: Non-steroidal anti-inflammatory drug, LOS: Length of stay

NSAIDs were equally effective 24 hours after surgery compared with opioids (11,12). Toleska and Dimitrovski (13) found that patients who had OF general anesthesia in laparoscopic cholecystectomy operations needed less postoperative analgesia in 24 hours compared to the OB group. In addition, Fletcher and Martinez (14) published a meta-analysis about opioid-induced postoperative hyperalgesia. They showed that high-dose intraoperative opioid use was associated with increased opioid use in the postoperative 24 hours. Moreover, it was recommended as Grade A to use OF multimodal analgesia for postoperative analgesia in CS, including acetaminophen and NSAIDs (8).

As an adjuvant for postoperative pain management, we used i.v. magnesium in Group OF. Magnesium is an NMDA receptor antagonist and plays many important roles in nociception. Likewise, our results and the meta-analysis by De Oliveira et al. (15) showed that perioperative systemic magnesium administration minimizes postoperative pain. In addition, it was shown that intravenous maternal magnesium therapy is not expected to affect serum magnesium levels in breastfed infants (16).

Non-steroidal anti-inflammatory drugs consumption on postoperative days one and two was significantly different between groups. Ninety percent of two groups were required to take one or two NSAIDs on postoperative day one, and 98% of two groups were required to take one or two NSAIDs on postoperative day two. The maximum dose of diclofenac sodium was 150 mg, and all of our patients received less than 150 mg per day. Ostensen and Musby (17) showed no drug in patients' colostrum after receiving 150 mg of diclofenac sodium following CS in 48 h. Diclofenac sodium IM injections were found to be safe at repeated doses and a good analgesic to use alone for postoperative pain in CS (18).

Lastly, we injected 10 ml of 0.5% bupivacaine under the skin before wound closure in Group OF for postoperative pain. Supporting us, it was recommended as Grade A to use single-shot local anesthetic wound infiltration for reducing postoperative pain in CS (19). Our findings on bupivacaine injection to the wound area agree with those reported by Gurbet et al. (20), who showed lower postoperative pain scores and lower analgesic consumption in 24 h in patients who received wound infiltration with 10 mL of 0.5% bupivacaine.

Even patients who received low-dose intrathecal opioids experienced bradypnea (21) at least once and were recommended to schedule respiratory monitors every 2 hours for 12 hours (22). Opioids could be very hazardous in systematic use after CS for patients and infants.

Study Limitations

Our study had several limitations. First, it was a retrospective study with a limited number of patients in the groups due to the lower use of OF general anesthesia in CS. Second, patients did not have any records about previous CS, intraoperative diuresis, sevoflurane MAC value, or postoperative pain scales, such as NRS or VAS. Despite these limitations, including CS patients with OF general anesthesia, which is recommended but less practiced in daily use, is one of the strengths of the study.

Conclusion

Opioid-free general anesthesia did not change the required number of NSAIDs 24 hours after surgery and necessitated less intraoperative crystalloid fluid. Our study supports ERAS protocols, which recommend multimodal analgesics and sparing opioids in CS, and adds to the accumulating evidence that suggests the use of OF general anesthesia in CS. Our cohort included a limited number of patients. Therefore, larger prospective studies with longer follow-up are needed to establish the perioperative management of OF general anesthesia in CS.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital (date: 19/12/2022, decision no: E-46059653-050.99).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.O., B.S., E.A., N.B., Design: E.O., B.S., E.A., N.B., Data Collection or Processing: E.O., B.S., Analysis or Interpretation: E.O., B.S., E.A., N.B., Literature Search: E.O., B.S., E.A., N.B., Writing: E.O., B.S., E.A., N.B.

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

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Original Article

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Correlations of Temporal Changes of CT Severity Scores and Laboratory Parameters in COVID-19 Hospitalized Patients

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Abstract

Aim: It has been reported that the increased neutrophil/lymphocyte ratio (NLR) is associated with a poor prognosis in Coronavirus disease-2019 (COVID-19) patients. We aimed to correlate three consecutive computed tomography severity score (CT-SS) values with simultaneous NLR and other laboratory parameters and investigate their temporal changes effects on the prognosis of COVID-19 patients.

Methods: This single-center cross-sectional study included 99 (aged ≥18 years) COVID-19 patients hospitalized between March 1, 2021, and June 30, 2021. Demographic data, laboratory findings, and intensive care unit (ICU) admissions were obtained from electronic medical records. We divided patients into two groups: ICU and non-ICU patients A radiologist calculated three consecutive chest CT-SSs using a 25-point visually semiquantitative system. Spearman's rho correlation was used to evaluate correlations between CT-SSs and laboratory parameters in ICU and non-ICU patients.

Results: The study population included 99 patients with a mean age of 61.17±14.36 years. Significant associations were found between the third-highest values of CRP (p=0.005), D-dimer (p=0.007), lactate dehydrogenase (p=0.027), and ICU admission. While there was no statistical significance between the first and second CT-SS and ICU admissions, there was a significant relationship between the third CT-SS and ICU admissions (p=0.013). Moderate positive correlations between the first NLR and CT-SS (p=0.025, r=0.488) and the second NLR and CT-SS (p=0.001, r=0.650) were found in ICU patients.

Conclusion: Our results demonstrate the importance of late follow-up chest CT and laboratory parameters for the prognosis and ICU admissions of COVID-19 patients.

Keywords: COVID-19, coronavirus, CT severity score, neutrophil/lymphocyte ratio, NLR, intensive care unit

Introduction

The Coronavirus disease-2019 (COVID-19) has caused a major challenge for the global health system, with the mortality of patients being related to the healthcare burden (1,2). The rapid increase in the number of COVID-19 patients worldwide has made treatment in intensive care units (ICUs) a major challenge. Therefore, triaging patients as early as possible is essential for the early recognition of severe forms of COVID-19 (3).

COVID-19 can cause critical respiratory symptoms, especially in elderly patients and those with comorbidities. In some patients, it may progress to a serious disease with significant pulmonary changes that can be seen with imaging techniques. Computed tomography (CT) has been reported to have a high sensitivity in COVID-19 patients showing signs of pneumonia; therefore, it is largely used to aid patient management (4).

Although clinical symptoms such as fever, cough, and shortness of breath are characteristic of COVID-19, some biomarkers such as lymphopenia, neutrophilia, a high neutrophil/lymphocyte ratio (NLR), elevated C-reactive protein (CRP), and D-dimer concentrations may also indicate this infection (3,5).

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According to previous studies, changes in hematological parameters are more pronounced in severe COVID-19 patients than in non-severe patients (3). In particular, increased NLR, lactate dehydrogenase (LDH), and D-dimer and CRP concentrations are closely related to the poor prognosis of COVID-19 (6,7).

Chest CT findings and CT severity score (CT-SS) have been shown to be important independent prognostic factors in patients with COVID-19 (8). However, it can cause death and serious fatal complications such as fulminant myocarditis or disseminated intravascular coagulopathy, even in younger individuals without an underlying disease. It is critical to evaluate clinical and laboratory tests that may indicate a possible poor prognosis. In our study, unlike the literature, we assessed the three consecutive CT-SS values, the simultaneous NLR, and other laboratory parameters and their effects on the need for ICU treatment.

In our study, we aimed to correlate three consecutive CT-SS values with simultaneous NLR and other laboratory parameters and to investigate the effects of their dynamic changes on the prognosis of COVID-19 patients. Our second objective was to investigate the effectiveness of NLR and CT-SS in predicting the prognosis of COVID-19 patients.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the Non-Invasive Clinical Research Ethics Committee of the Amasya University Faculty of Medicine (date: 02.12.2021, approval no: 153) and was conducted according to the Declaration of Helsinki and Good Clinical Practice. Because the study was retrospective, patient information was obtained from the electronic records of the hospital, and the ethics committee did not require written informed consent from the patients.

Study Population and Data Collection

Our study was a single-center cross-sectional study of COVID-19 patients who were hospitalized at our hospital. The study included patients with confirmed severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infections who were hospitalized between March 1, 2021, and June 30, 2021. We included patients with positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing and at least three chest CT scans. We excluded patients with at least 3 negative RT-PCR tests, pediatric patients, and pregnant women from our study (Figure 1).

Data on the patients' demographic characteristics, comorbidities, laboratory findings, and chest CT results were extracted from electronic medical records.

Laboratory Procedures

Reverse transcriptase-polymerase chain reaction for SARS-CoV-2 was performed on the nasal and pharyngeal swab specimens of all patients according to WHO guidance. Laboratory tests involving a complete blood count, serum biochemical tests such as LDH, inflammatory markers such as CRP and ferritin, and coagulation markers such as D-dimer were recorded in the hospital records. We calculated the NLR by dividing the absolute neutrophil count by the total lymphocyte count.

Computed Tomography Protocol

Non-contrast chest CT scans were performed using a 128-slice CT scanner (GE Medical Systems; Milwaukee, WI) in a supine position. The acquisition and reconstruction parameters were as follows: tube potential, 120 kV; tube current, 100-450 mA; gantry rotation, 0.4 seconds; acquisition direction, caudocranial; reconstruction kernel, standard; beam collimation, 64 mm×0.625 mm; beam pitch, 1.375; slice thickness, 0.625 mm; and section overlap, 0.625 mm. All chest CT scans were assessed at a lung window of 1500 WW and -450 WL. A non-contrast chest CT was obtained at the end of inspiration whenever possible.

Image Analysis

A radiologist with more than 10 years of experience in chest CT imaging evaluated all CT images individually, blinded to patients' clinical data and laboratory indicators. A chest CT-SS was calculated using a visually semiquantitative CT-SS (9) by evaluating the percentage

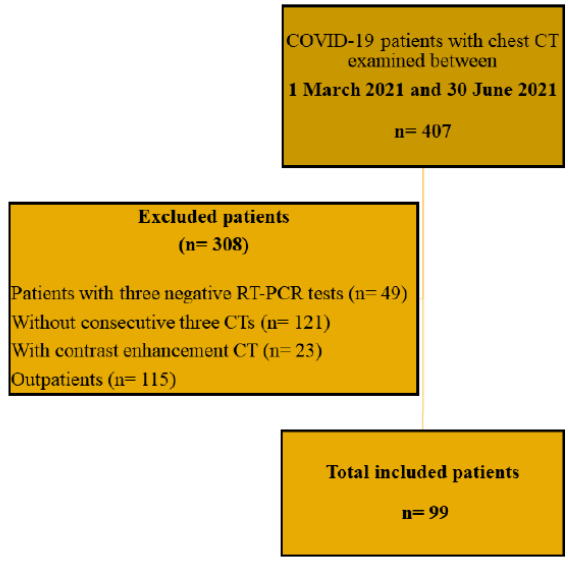

Figure 1. Flowchart of study
COVID-19: Coronavirus disease-2019, RT-PCR: Reverse transcriptase-polymerase chain reaction, CT: Computed tomography

of involvement of each of the five lobes. It was calculated as: score 0, 0% involvement; score 1, <5% involvement; score 2, 5% to 25% involvement; score 3, 26% to 49% involvement; score 4, 50% to 75% involvement; and score 5,> 75% involvement. Scoring from 0 to 5 was made for each lobe, and the total CT-SS was between 0 and 25.

Statistical Analysis

All statistical analyses were performed using IBM SSPS statistical software (version 22.0) (IBM Corp., Released 2017). Armonk, NY). Categorical data were calculated as numbers (percentages) and compared using the chi-square test. Median (25^{th} and 75^{th} percentiles) values were calculated using the Mann-Whitney U test for data with a non-normal distribution. Spearman's rho correlation was used to evaluate the relationship between CT-SS and laboratory parameters in ICU and non-ICU patients. In Spearman's rho correlation analysis, the correlation between two variables is expressed by the letter r and a number ranging from -1 to +1. Zero means no correlation; where 1 is ±1, it means perfect correlation. When the r value is negative, it means that there is an inverse relationship between the variables (10). P<0.05 was considered statistically significant.

Results

Patients who had at least three chest CT scans during clinical follow-up were included in the study. In this study, we analyzed 99 patients who were hospitalized due to COVID-19. The mean age of the patients was 61.17±14.36. 54/99 (54.5%) of the patients were male. The most common comorbidities in the study population were hypertension (45/99; 45.45%) and diabetes mellitus (36/99; 36.36%). There was a significant association between the presence of chronic pulmonary disease and ICU admission (p=0.025) (Table 1).

In our study, negative associations were found between second and third lymphocyte values (p=0.010, p=0.021) and ICU admission. In addition, significant associations were found between the third highest median values of CRP (p=0.005), D-dimer (p=0.007), LDH (p=0.027), and ICU admission. While there was no statistical significance in the first and second CT-SS values between ICU admission, there was a significant relationship between the third mean CT-SS and ICU admission (p=0.013) (Figure 2, Table 2).

In Spearman's rho correlation analysis, there was a moderate positive correlation between the second NLR and CT-SS (p<0.001, r=0.400) and a weak positive correlation between the third NLR and CT-SS (p=0.044, r=0.229) in non-ICU patients. In the ICU patients, there were moderately positive correlations between the first

Table 1. Comorbid diseases of all COVID-19 patients

		Non-ICU		ICU		
		n	(%)	n	(%)	p-value
Diabetes mellitus	Absent	50	64.10	13	61.90	0.853
	Present	28	35.90	8	38.10	
	Total	78		21		
Hypertension	Absent	44	56.40	10	47.60	0.473
	Present	34	43.60	11	52.40	
	Total	78		21		
Cardiovascular disease	Absent	53	67.90	12	57.10	0.355
	Present	25	32.10	9	42.90	
	Total	78		21		
Chronic pulmonary disease	Absent	63	80.80	12	57.10	0.025
	Present	15	19.20	9	42.90	
	Total	78		21		
Cerebrovascular diseases*	Absent	75	96.20	20	95.20	0.999
	Present	3	3.80	1	4.80	
	Total	78		21		

Chi-square or (*) Fisher's exact tests were used to compare comorbidities according to ICU admission
COVID-19: Coronavirus diseases-2019, ICU: Intensive care unit

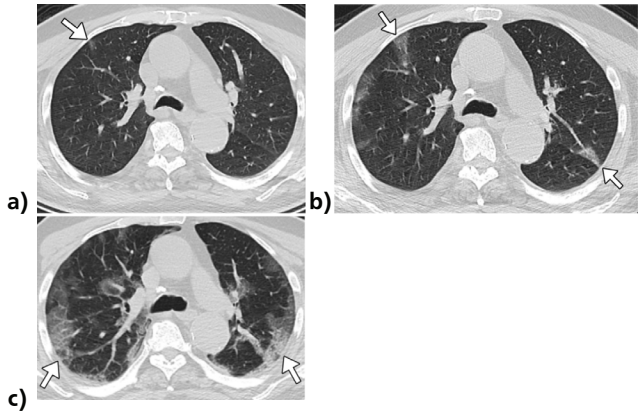

Figure 2a-c. A 76-year-old man with a positive RT-PCR test. He died after 16 days of treatment in the intensive care unit. **a)** Axial lung window of first non-contrast chest CT shows peripheral localized nodular ground glass opacity (GGO) in the upper lobe of the right lung (arrow). CT-SS_1 =2; neutrophil/lymphocyte ratio $(NLR)_1$: 2.25. **b)** Axial lung window of second chest CT shows bilateral peripheral localized GGOs (arrows). CT-SS_2 =9; NLR_2:3.19. **c)** Axial lung window of third chest CT shows increased bilateral peripheral localized GGOs (arrows). CT-SS_3 =20; NLR_3:24.58
RT-PCR: Reverse transcriptase-polymerase chain reaction, CT-SS: Computed tomography severity score, NLR: Neutrophil/lymphocyte ratio

Table 2. Comparison of the first, second and third median values of laboratory parameters and CT severity scores according to the non-ICU and ICU groups

		N	Mean	SD	Min.	Max.	Median	25th	75th	p-value
Age	Non-ICU	78	59.62	14.46	32	88	59.5	48.5	71.25	0.037
	ICU	21	66.95	12.67	43	89	66	56.5	78	
	Total	99	61.17	14.36	32	89	61	50	72	
First CT-SS*	Non-ICU	78	7.62	7.52	0	25	8	0	11.25	0.556
	ICU	21	8.43	8.08	0	25	7	1	12	
	Total	99	7.79	7.61	0	25	8	0	12	
Second CT-SS*	Non-ICU	78	14.88	7.78	0	25	15	9.75	22	0.817
	ICU	21	14.05	9.01	0	25	16	6	22.5	
	Total	99	14.71	8.01	0	25	16	9	22	
Third CT-SS*	Non-ICU	78	14.09	8.14	0	25	14.5	10	20.25	0.013
	ICU	21	19.29	5.15	8	25	20	16	24	
	Total	99	15.19	7.88	0	25	17	10	21	
NLR1	Non-ICU	78	4.05	3.66	0.81	22.48	2.83	1.84	5.11	0.337
	ICU	21	10.71	30.94	1.18	145.33	3.71	2.18	5.71	
	Total	99	5.46	14.61	0.81	145.33	2.88	2.03	5.27	
NLR2	Non-ICU	78	8.36	7.48	1.32	42.43	6.59	3.42	10.78	0.108
	ICU	21	11.65	10.72	1.71	47.37	9.36	3.45	15.42	
	Total	99	9.05	8.32	1.32	47.37	6.78	3.44	12.40	
NLR3	Non-ICU	78	7.84	8.58	0.05	52.54	5.90	2.56	10.41	0.085
	ICU	21	22.48	36.81	1.43	164	6.87	4.19	25.64	
	Total	99	10.94	19.25	0.05	164	6.27	2.89	11.20	
Neutrophil_1	Non-ICU	78	4.71	2.78	1.58	14.06	3.98	2.90	5.39	0.336
	ICU	21	8.66	18.35	1.68	87.20	3.95	2.62	5.60	
	Total	99	5.54	8.80	1.58	87.20	3.95	2.74	5.40	
Neutrophil_2	Non-ICU	78	7.88	4.12	1.76	25.61	7.29	5.11	9.39	0.227
	ICU	21	6.70	3.19	1.88	14.21	5.96	4.29	8.81	
	Total	99	7.63	3.95	1.76	25.61	6.92	4.86	9.24	
Neutrophil_3	Non-ICU	78	8.40	4.29	2.32	24.17	7.64	4.70	10.83	0.783
	ICU	21	8.71	5.09	1.69	22.96	8.69	5.09	12.17	
	Total	99	8.47	4.44	1.69	24.17	7.64	4.88	11.12	
Lymphocyte_1	Non-ICU	78	1.47	0.76	0.29	4.64	1.27	1.02	1.71	0.513
	ICU	21	1.34	0.86	0.57	4.10	1.10	0.75	1.59	
	Total	99	1.44	0.78	0.29	4.64	1.25	0.93	1.70	
Lymphocyte_2	Non-ICU	78	1.28	0.74	0.26	4.71	1.11	0.80	1.62	0.010
	ICU	21	0.88	0.54	0.30	2.14	0.67	0.50	1.18	
	Total	99	1.20	0.72	0.26	4.71	1.03	0.64	1.59	
Lymphocyte_3	Non-ICU	78	2.43	7.67	0.25	69.00	1.45	0.93	2.13	0.021
	ICU	21	1.02	0.89	0.14	3.48	0.70	0.37	1.40	
	Total	99	2.13	6.84	0.14	69.00	1.29	0.82	2.03	
D_Dimer_1	Non-ICU	78	0.84	1.96	0.03	16.79	0.40	0.22	0.90	0.98
	ICU	21	0.85	0.67	0.13	2.62	0.68	0.41	1.27	
	Total	99	0.85	1.76	0.03	16.79	0.46	0.23	1.01	
D_Dimer_2	Non-ICU	78	0.99	1.56	0.03	8.53	0.46	0.27	0.95	0.409
	ICU	21	1.31	1.52	0.20	5.38	0.58	0.42	2.12	
	Total	99	1.06	1.55	0.03	8.53	0.49	0.28	0.97	

Table 2. Continued

		N	Mean	SD	Min.	Max.	Median	25th	75th	p-value
D_dimer_3	Non-ICU	78	0.78	0.79	0.03	3.42	0.44	0.22	1.04	0.029
	ICU	21	1.23	0.98	0.28	3.43	0.88	0.56	1.86	
	Total	99	0.87	0.85	0.03	3.43	0.55	0.27	1.21	
CRP_1	Non-ICU	78	35.73	37.74	0.50	140	17.77	6.87	60	0.469
	ICU	21	42.82	46.64	1.03	145.25	19	10.29	76	
	Total	99	37.23	39.65	0.50	145.25	19	8.00	61	
CRP_2	Non-ICU	78	55.16	55.24	0.50	245	34.49	11.25	91.09	0.39
	ICU	21	66.84	54.14	0.56	178.35	51.02	16.91	119.38	
	Total	99	57.64	54.95	0.50	245	41.44	12.78	93	
CRP_3	Non-ICU	78	47.56	58.81	0.40	291	20.14	3.38	85.41	0.012
	ICU	21	85.69	68.20	1.30	256.75	96	17.34	123.5	
	Total	99	55.65	62.55	0.40	291.00	27.42	5.04	96.10	
LDH_1	Non-ICU	78	288.01	94.61	166	550	259	219	342.25	0.304
	ICU	21	328.24	168.55	134	706	286	189.5	418.5	
	Total	99	296.55	114.47	134	706	261	218	346	
LDH_2	Non-ICU	78	317.63	110.96	169	745	296.5	242.75	349.75	0.377
	ICU	21	343.29	140.57	175	727	313	230	416	
	Total	99	323.07	117.55	169	745	300	240	380.5	
LDH_3	Non-ICU	78	322.40	105.01	163	745	291	252.5	378	0.019
	ICU	21	386.95	126.15	226	679	367	283.5	452	
	Total	99	336.09	112.32	163	745	308	265	398	

The independent t-test or (*) Mann-Whitney U tests were used to compare continuous variables according to ICU admission
CT: Computed tomography, ICU: Intensive care unit, SD: Standard deviation, Min.: Minimum, Max.: Maximum, CT-SS: Computed tomography severity score, NLR: Neutrophil/lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase

NLR and CT-SS (p=0.025 and r=0.488) and the second NLR and CT-SS (p=0.001 and r=0.650). In the ICU group, there were positive correlations between the first CT-SS and D-dimer (p=0.023, r=0.495), CRP (p=0.006, r=0.579), ferritin (p=0.017, r=0.514), LDH (p<0.01, r=0.806), and a negative correlation with lymphocyte count (p=0.017, r=-0.513). Also, there were positive correlations between the second CT-SS and the second white blood cell (WBC) (p=0.001, r=0.653), neutrophil (p<0.001, r=0.708), and LDH values (p=0.001, r=0.650), and a negative correlation with lymphocyte count (p=0.047, r=-0.439). Also, significant correlations were found between laboratory parameters and CT-SSs, especially in the second evaluation in the non-ICU group (Table 3).

The relationship of consecutive CT-SS values between ICU and non-ICU patients was compared with the Wilcoxon test. There was a statistically significant increase between the first CT-SS and the second CT-SS values in ICU and non-ICU patients, respectively (p=0.002; p<0.001). There was also a significant increase between the second and third CT-SS in the ICU group (p=0.02) (Table 4, Figure 3).

Discussion

In our study, hospitalized COVID-19 patients who had at least three chest CTs and concomitant serum hematological parameters were investigated. We divided the patients into two groups: ICU patients and non-ICU patients. We compared serum hematological parameters and three CT-SS between both groups and investigated the importance and necessity of follow-up examinations. While there was no statistically significant difference between the first and second high CT-SS values and ICU admission, we found a significant relationship between the third high CT-SS and ICU admission. Also, significant associations were found between the third highest median values of CRP, D-dimer, LDH, and lower second and third lymphocyte counts with ICU admission. Our results show moderately positive correlations between the second NLR and CT-SS and between the third NLR and CT-SS in non-ICU patients. In addition, moderately positive correlations were found between the first and second NLR values and simultaneous CT-SSs in the ICU patients.

In the literature, CT-SS scores were found to be higher in severe or critical patients who were treated in the ICU and needed ventilation (8,11,12). We found no significant association between the first and second CT-SS and ICU

Table 3. Spearman's Rho correlations among laboratory parameters and CT severity scores

		Non-ICU			ICU		
		CT-SS$_1$	CT-SS$_2$	CT-SS$_3$	CT-SS$_1$	CT-SS$_2$	CT-SS$_3$
NLR (1)	r-value	0.135			0.488		
	p-value	0.239			0.025		
NLR (2)	r-value		0.400			0.650	
	p-value		<0.001			0.001	
NLR (3)	r-value			0.229			0.203
	p-value			0.044			0.377
Neutrophils (1)	r-value	0.016			-0.020		
	p-value	0.892			0.933		
Neutrophils (2)	r-value		0.278			0.708	
	p-value		0.014			<0.001	
Neutrophils (3)	r-value			0.135			0.016
	p-value			0.237			0.944
Lymphocyte (1)	r-value	-0.128			-0.513		
	p-value	0.266			0.017		
Lymphocyte (2)	r-value		-0.275			-0.439	
	p-value		0.015			0.047	
Lymphocyte (3)	r-value			-0.221			-0.276
	p-value			0.052			0.225
CRP (1)	r-value	0.554			0.579		
	p-value	<0.001			0.006		
CRP (2)	r-value		0.330			-0.085	
	p-value		0.003			0.714	
CRP (3)	r-value			0.198			0.171
	p-value			0.082			0.460
D-dimer (1)	r-value	0.256			0.495		
	p-value	0.024			0.023		
D-dimer (2)	r-value		0.242			0.399	
	p-value		0.033			0.073	
D-dimer (3)	r-value			0.218			-0.025
	p-value			0.055			0.915
Ferritin (1)	r-value	0.405			0.514		
	p-value	p<0.001			0.017		
Ferritin (2)	r-value		0.511			0.218	
	p-value		<0.001			0.344	
Ferritin (3)	r-value			0.440			-0.094
	r-value			<0.001			0.685
LDH (1)	p-value	0.351			0.806		
	r-value	0.002			<0.001		
LDH (2)	p-value		0.489			0.0768	
	r-value		<0.001			<0.001	
LDH (3)	p-value			0.225		0.028	0.226
	r-value			0.048			0.324

Correlation coefficient: r-value
CT: Computed tomography, ICU: Intensive care unit, CT-SS: Computed tomography severity score, NLR: Neutrophil/lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase

admission in our study. We found a statistical relationship between the third-higher CT-SS and ICU admission. While there was a minimal decrease in the third CT-SS in the non-ICU group compared with the second, there was an increase in the third CT-SS in the ICU group compared with the second. In addition, significant associations were found between the third-highest median values of CRP, D-dimer, LDH, and ICU admission. Our results demonstrate the importance of late-stage follow-up chest CTs and laboratory parameters for the prognosis of patients. The lymphocyte count in the second evaluation showed significant differences between the two groups. The significant difference in lymphopenia between the two groups in the second evaluation indicates that lymphopenia is an early prognostic factor compared with other parameters.

In the initial period, the clinical symptoms of the patients may be milder, and peripheral laboratory findings

Table 4. The relationship of consecutive CT-SS values between ICU and non-ICU patients was compared with the Wilcoxon test

		N	Mean rank	Sum of ranks	p-value
Non-ICU					
Second CT-SS First CT-SS	Negative ranks	7[a]	28.64	200.50	**<0.001**
	Positive ranks	63[b]	36.26	2284.50	
	Ties	8[c]			
	Total	78			
Third CT-SS Second CT-SS	Negative ranks	36[d]	34.58	1245.00	0.507
	Positive ranks	31[e]	33.32	1033.00	
	Ties	11[f]			
	Total	78			
ICU					
Second CT-SS First CT-SS	Negative ranks	2[a]	2.50	5.00	**0.002**
	Positive ranks	13[b]	8.85	115.00	
	Ties	6[c]			
	Total	21			
Third CT-SS Second CT-SS	Negative ranks	5[d]	7.40	37.00	**0.020**
	Positive ranks	14[e]	10.93	153.00	
	Ties	2[f]			
	Total	21			

a. Second CT-SS < First CT-SS
b. Second CT-SS > First CT-SS
c. Second CT-SS = First CT-SS
d. Third CT-SS < Second CT-SS
e. Third CT-SS > Second CT-SS
f. Third CT-SS = Second CT-SS

ICU: Intensive care unit, CT-SS: Computed tomography severity score

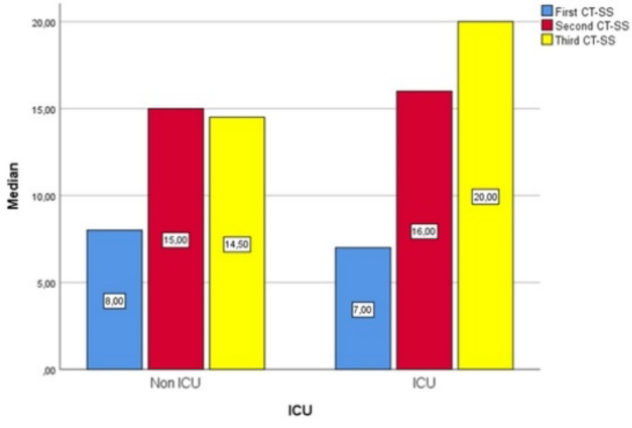

Figure 3. The statistical graphic shows the mean values of three consecutive CT-severity scores in ICU and non-ICU subgroups
CT: Computed tomography, ICU: Intensive care unit

may show normal or mild changes (13). In previous studies, when chest CT imaging was performed within the first 2 days after the onset of symptoms, nearly half of the patients had normal CT imaging findings, which was termed an early period (9). The fact that more laboratory parameters were correlated with CT-SS in the ICU group in the first evaluation compared with the other group may indicate that this patient group applied to the hospital later. Pneumonia often accompanies inpatients due to COVID-19 disease. Because pneumonia develops due to inflammatory processes, a correlation between inflammatory markers and the CT-SS is expected (14-16). In past studies that divided the patient groups into severe and non-severe groups according to the clinical symptoms of the patient, a significant difference was found between the two groups in terms of WBC, neutrophil, lymphocyte count, NLR, CRP, and D-dimer (17,18). However, in some studies, while significant differences were observed in WBC, CRP, LDH, and ferritin parameters in asymptomatic and symptomatic patient groups, no statistically significant difference was observed in neutrophil, lymphocyte count, or D-dimer parameters (14).

In previous studies, a positive correlation was found between CT-SS and NLR, D-dimer, and ferritin (14-16). El Hussini et al. (15) reported that NLR, CRP, and D-dimer values were significantly higher in severe COVID-19 patients. Çil et al. (16) divided COVID-19 patients into 3 groups according to their CT-SS values. They reported that NLR was significantly higher in patients with severe COVID-19 and was the most important factor determining CT-SS (16). Sejópoles et al. (19) reported that COVID-19 patients' serum leukocyte, neutrophil, and lymphocyte counts and NLR values at hospital admission have shown satisfactory accuracy and sensitivity in predicting patients at higher risk of death. While other studies analyzed the CT-SS and laboratory values at the time of administration, in our study, we examined the temporal changes and correlation of simultaneous NLR and other laboratory parameters with three consecutive CT-SS values and investigated their effects on ICU admission. In our study, moderately positive correlations were found between the first NLR and CT-SS and the second NLR and CT-SS in the ICU patients. Also, negative associations were found between the second and third lymphocyte values and ICU admission, and positive associations were found between the third higher median values of CRP and LDH and ICU admission. Because of the evaluation of the laboratory results of our study patients, we observed that deterioration in laboratory values in the late period, as in CT-SS, was more associated with the poor prognosis of COVID-19 patients.

Study Limitations

There were several limitations to our study. First, our study was a single-center retrospective study. Second, we do not have any information about the period between the first evaluation made at the time of admission and the onset of symptoms. Another limitation is that the three evaluations could not be made in a standard day or week interval. Despite these limitations, our study contributes to the literature as it is the first to associate three consecutive CT-SS values with simultaneous NLR and other laboratory parameters and to investigate their relationship with ICU admission.

Conclusion

Our study results demonstrate the importance of late follow-up chest CT and laboratory parameters for the prognosis and ICU admissions of COVID-19 patients.

Ethics

Ethics Committee Approval: This study was approved by the Non-Invasive Clinical Research Ethics Committee of the Amasya University Faculty of Medicine (date: 02.12.2021, approval no: 153) and was conducted according to the Declaration of Helsinki and Good Clinical Practice.

Informed Consent: Because the study was retrospective, patient information was obtained from the electronic records of the hospital, and the ethics committee did not require written informed consent from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.D., A.T.K., B.A., Design: S.D., A.T.K., Data Collection or Processing: A.T.K., Analysis or Interpretation: S.D., A.T.K., B.A., B.T., Literature Search: S.D., B.A., Writing: S.D., B.A.

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

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Original Article

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Prolonged Elevation of D-dimer Levels In The Post-Covid-19 Period

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Abstract

Aim: D-dimer elevation is observed during acute Coronavirus disease-2019 (COVID-19) and the post- COVID-19 period. It is not known how long the D-dimer remains elevated in the post-COVID-19 period. The aim of the study was to determine how long the D-dimer level remained elevated in the post-COVID-19 period.

Methods: This study was conducted as a cross-sectional study, a type of observational study, at the University of Health Sciences Turkey, Darica Farabi Training and Research Hospital Cardiology Outpatient Clinic between March 1, 2022, and December 1, 2022. Past medical histories, examination notes, and laboratory results were extracted from standard electronic medical records. Patients were also categorized as those over 50 years old and those under 50 years old. Age-adjusted D-dimer levels were used when analyzing the D-dimer values of patients over 50 years old.

Results: Three hundred twenty two patients were included in this study. Two hundred nineteen (68%) patients were women. Two hundred twenty-three (69%) patients were under the age of 50. Elevated D-dimer levels were present in 77 (23.91%) patients, and age-adjusted elevated D-dimer levels were present in 22 (6.80%) patients. The median duration from the time the patient's reverse transcription-polymerase chain reaction (RT-PCR) test resulted in a positive result to the time of admission was 6 (1-24) months. The highest number of patient admissions to the cardiology outpatient clinic occurred in the 12th month after the RT-PCR test resulted in a positive.

Conclusion: We investigated how long the D-dimer remained elevated in the post-COVID-19 period. We examined the time distribution of D-dimer elevation and calculated age-adjusted D-dimer values. The highest number of patients whose D-dimer level was elevated on admission occurred in the 3rd-4th month after the RT-PCR test resulted positively.

Keywords: COVID-19, D-dimer, age-adjusted D-dimer level

Introduction

The World Health Organization declared Coronavirus disease-2019 (COVID-19) a pandemic on March 11, 2020 (1). Among the complaints of patients with COVID-19 are chest pain, palpitations, and shortness of breath. These cardiac complications occur both during COVID-19 treatment and after the treatment is completed. COVID-19 can directly cause cardiac and vascular injuries. These conditions are arrhythmias, heart failure, myocarditis, pericarditis, myocardial infarction, and thromboembolic events (2). Several previous studies have shown that patients with acute COVID-19 are in a hypercoagulable state and therefore have an increased risk of adverse thromboembolic events (3-5). Elevated D-dimer levels are associated with worse clinical outcomes, such as deep vein thrombosis and pulmonary embolism (6,7). D-dimer levels increase during COVID-19.

How long the D-dimer level remains elevated in these patients after the initial diagnosis is unknown. There is no consensus on how long anticoagulant therapy should be administered to patients. In this study, our aim was to determine when patients apply to the cardiology outpatient clinic after an initial diagnosis of COVID-19 and how long the D-dimer level stays elevated in the post COVID-19 period.

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Methods

Compliance with Ethical Standards

Permission for the research was obtained from the Ministry of Health of the Republic of Turkey. Approval was obtained from the Clinical Studies Ethics Committee of Kocaeli Derince Training and Research Hospital (approval number: 2022/6; approval date: February 24, 2022). This study was conducted at the University of Health Sciences Turkey, Darica Farabi Training and Research Hospital Cardiology Outpatient Clinic. The study was conducted between March 1, 2022, and December 1, 2022. The study was conducted in accordance with the rules of the Declaration of Helsinki.

Study Design

This study was conducted as a cross-sectional study, a type of observational study. Past medical histories, examination notes, and laboratory results were extracted from standard electronic medical records. Demographic features of the patients age, gender, chronic diseases [diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL), documented coronary artery disease (CAD)], impaired fasting glucose, atrial fibrillation, mitral valve prolapse, bicuspid aorta, rheumatic valve disease, hypothyroidism, hyperthyroidism, and metallic valve prosthesis were recorded. Laboratory findings, i.e., D-dimer, C-reactive protein (CRP), high-sensitive cardiac troponin T, hemoglobin, white blood cells, creatinine, alanine aminotransferase, thyroid stimulating hormone, thyroxine, low-density lipoprotein, triglyceride, N terminal pro B type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR) were recorded on admission, and they were evaluated as normal or abnormal according to the reference range of the laboratory assays. Estimated glomerular filtration rate was assessed by the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). The CKD-EPI was calculated electronically using age, gender, and race parameters. An eGFR under 60 mL/min/1.73 m^2 was defined as chronic renal failure. Anemia was defined as a hemoglobin level below 12.0 g/dL in women and <13.0 g/dL in men. If the plasma fasting glucose was between 100 and 126 mg/dL, it was defined as impaired plasma fasting glucose. Patients were also categorized as those over 50 years old and those under 50 years old. To discuss the D-dimer elevation in patients over 50 years of age, we used age-adjusted D-dimer levels. The patients whose D-dimer level was above the cut-off value according to age-adjusted D-dimer level at the time of admission were determined.

Electrocardiography (ECG) was performed by cardiology outpatient clinic nurses. Normal sinus rhythm and atrial fibrillation were recorded on the ECGs of the patients. Transthoracic echocardiography was conducted by the cardiologists at the Cardiology Outpatient Clinic. The left ventricular ejection fraction (LVEF) was recorded. LVEF below 50% was defined as systolic heart failure.

A chest contrast-enhanced computed tomography (CT) angiography scan was performed in the pulmonary phase in patients with severe dyspnea, tachycardia, and high D-dimer levels. The reports were interpreted by the radiology department.

Inclusion Criteria

Patients over the age of 18, who applied to the cardiology outpatient clinic between January 3, 2021, and December 31, 2021, had a positive RT-PCR test, completed COVID-19 treatment, wanted to have a heart control, or had heart complaints such as chest pain, shortness of breath, palpitations, backache, and fatigue, were included in the study. The patients were consecutively included in the study.

Exclusion Criteria

Patients under 18 years of age, hospitalized patients, patients with systolic heart failure, acute renal failure, chronic kidney disease, patients on hemodialysis or peritoneal dialysis, pregnant women, patients with acute deep vein thrombosis, chronic deep vein thrombosis, acute pulmonary embolism, chronic pulmonary embolism, patients with known coagulation disorders, pneumonia, urinary tract infections, and other system infections were excluded from the study.

Statistical Analysis

The statistical analyses were performed using SPSS software (version 26.0, SPSS Inc., Chicago, IL, USA). The normality of the parameters was assessed by the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median [interquartile range (IQR)] where appropriate. Categorical variables were expressed as numbers and percentages.

Results

Consecutively, 322 adult patients diagnosed with COVID-19 with RT-PCR positivity and admitted to the Cardiology Outpatient Clinic after completion of COVID-19 treatment were included in the study. Of the patients, 219 (68%) were women and 103 (32%) were men. Of the patients, 223 (69%) were under 50 years old, and 99 (31%) were over 50 years old. Of the patients over 50 years of age, 59 (59.6%) were women and 40 (40.4%) were men. The median age was 44 (18-92) years. The accompanying comorbidities of all the patients were as follows: DM 48 (14.90%), HT 65 (20.2%), HL 62 (19.30%), CAD 31 (9.60%), impaired

fasting plasma glucose 79 (24.50%), atrial fibrillation 11 (3.40%), metallic valve prosthesis 1 (0.003%), bicuspid aorta 2 (0.006%), rheumatic valve disease 1 (0.003%), hypothyroidism 3 (0.009%), hyperthyroidism 3 (0.009%) (Table 1).

Table 1. Basic clinical characteristics of the patients	
The total number of patients	322
>50-year patients (n) (%)	99 (30)
Gender (female/male) (n) (%)	219/103 (68/32)
Age (median) (IQR) years	44 (18-92)
>50 years (female/male) (n) (%)	59/40 (59.60/40.40)
Follow-up (median) (IQR) months	6 (1-24)
Hypertension (n) (%)	65 (20.2)
Diabetes mellitus (n) (%)	48 (14.90)
Hyperlipidemia (n) (%)	62 (19.30)
Coronary artery disease (n) (%)	31 (9.60)
Impaired fasting glucose (n) (%)	79 (24.50)
Atrial fibrillation (n) (%)	11 (3.40)
Mitral valve prolapse (n) (%)	1 (0.003)
Bicuspid aorta (n) (%)	2 (0.006)
Rheumatic valve disease (n) (%)	1 (0.003)
Hypothyroidism (n) (%)	3 (0.009)
Hyperthyroidism (n) (%)	3 (0.009)
Metallic valve prosthesis n (%)	4 (1.20)
n: Number, IQR: Interquartile range	

Laboratory findings of the patients on admission are shown in Table 2. Elevated hs-cTn was present in 3 (0.90%) patients; elevated NT-proBNP was present in 11 (3.40) patients; elevated D-dimer was present in 77 (23.90%) patients; and age-adjusted elevated D-dimer was present in 22 (6.80%). A chest contrast-enhanced CT angiography scan was performed in 12 patients. A pulmonary embolism was not found in any patient.

Figure 1 shows the frequency of application and the months after the initial diagnosis. Figure 2 shows the distribution of patients by month, and Figure 3 shows the distribution of patients by month.

Discussion

In this study, we included adult patients diagnosed with COVID-19 with RT-PCR positivity and admitted to the cardiology outpatient clinic after completion of COVID-19 treatment for cardiac control or due to cardiac complaints. The majority of patients were female and under 50 years of age.

When the literature is reviewed, it is seen that HT and DM are the leading chronic diseases accompanying COVID-19. However, in our study, the most common co-morbidity was impaired fasting plasma glucose, seen in

Table 2. Laboratory findings of the patients on admission		
Glucose (mg/dL) median (IQR)	97.00 (73.00-495.00)	74-106 mg/dL
Creatinine (mg/dL) median (IQR)	0.70 (0.17-1.26)	0.5-0.9 mg/dL
Glomerular filtration rate (mL/min/1.73 m²) median (IQR)	106 (61-157)	-
Alanine aminotransferase (U/L) median (IQR)	17.50 (6-95)	0-33 U/L
CRP (mg/L) median (IQR)	2.60 (0.14-39.30)	0-5 mg/L
Thyroid stimulating hormone (mIU/L) median (IQR)	1.57 (0.07-34.91)	0.35-4.94 mIU/L
Thyroxine (T4) (ng/dL) median (IQR)	0.96 (0.61-1.92)	0.70-1.48 ng/dL
White blood count (10^3/mL) median (IQR)	6.69 (0.32-14.30)	3.98-10.04 10^3/mL
Hemoglobin (g/dL) means SD	13.18 1.66	11.7-16.0 g/dL
High sensitive cardiac troponin T (ng/L) median (IQR)	1.00 (1.00-66.00)	0-14 ng/L
D-dimer (mg/mL) median (IQR)	0.31 (0.10-4.51)	0-0.5 µg/mL
Age-adjusted D-dimer (mg/mL) median (IQR)	1.24 (0.55-3.40)	>0.50
NT-proBNP (pg/mL) median (IQR)	14.50 (5.00-2176.00)	0-125 pg/mL
Low-density lipoprotein mg/dl means SD	124±35.97	0-130 mg/dL
Triglyceride mg/dl median (IQR)	123 (33-729)	0-150 mg/dL
Ejection fraction percentage median (IQR)	60 (50-65)	50-72
Anemia n (%)	23 (17.40)	
Elevated D-dimer n (%)	77 (23.90)	
Age-adjusted elevated D-dimer n (%)	22 (6.80)	
Elevated high sensitive cardiac troponin T n (%)	3 (0.90)	
Elevated NT-ProBNP n (%)	11 (3.40)	
bpm: Beats per minute, IQR: Interquartile range, n: Number, SD: Standard deviation, mg/dL: Milligram/deciliter, pg/mL: Picogram/milliliter, NT-proBNP: N terminal Pro B type natriuretic peptide, CRP: C-reactive protein, ng/L: Nanogram/liter, U/L: Unit/liter		

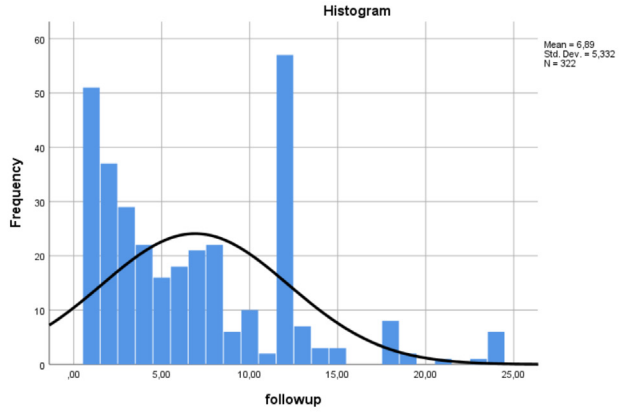

Figure 1. Distribution of all patients by month

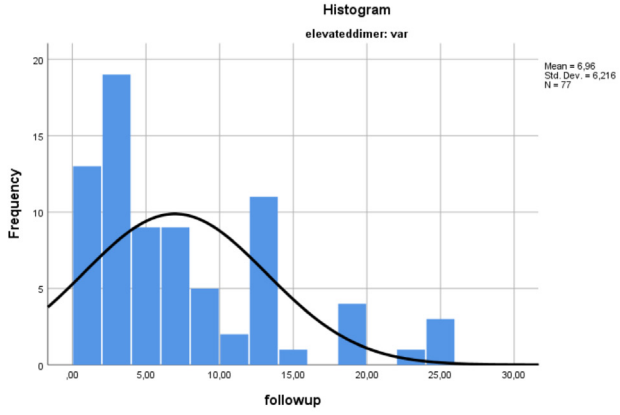

Figure 2. Distribution of all patients with elevated D-dimer values by months

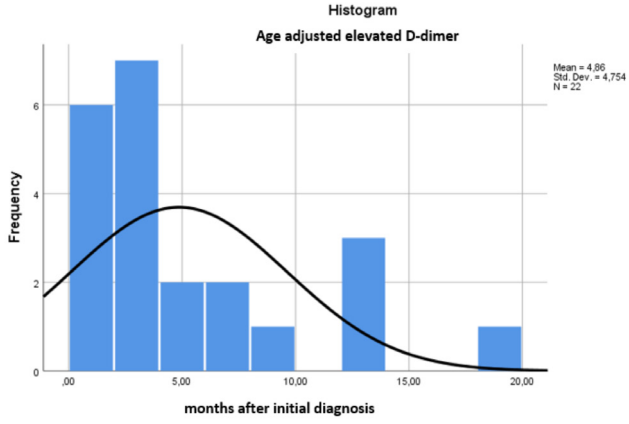

Figure 3. Distribution of patients over 50 years of age with elevated D-dimer values by months

79 (24.50%) patients. In the literature, few articles have examined the relationship between COVID-19 and plasma glucose. Huang et al. (8) found a relationship between plasma fasting glucose and mortality in a study they conducted on non-diabetic patients. Cai et al. (9) found that patients with DM with COVID-19 had a worse prognosis. Alahmad et al. (10) found a correlation between the increase in fasting plasma glucose and follow-up in the intensive care unit.

Anticoagulants are used in the treatment because there is a predisposition to coagulopathy in this disease (11-14). Elevated D-dimer as an independent predictor for mortality and complications (15). There are many articles showing the relationship between D-dimer level and morbidity. However, there are very few studies studying how long the D-dimer level stays high. Townsend et al. (16) conducted a study involving 150 patients. They followed the patients for a median of 80 days. Elevated D-dimer levels were observed in 25.30% of patients up to four months after the initial diagnosis. Compared to this study, the number of patients in our study was higher, and the proportion of women participating was higher (56.7% vs. 68%). The elevated D-dimer ratio was similar (25.30% vs. 23.90%), and the mean age of the study participants was similar (47.3 vs. 44 years), but the age-adjusted D-dimer was not mentioned in this study either.

Meisinger et al. (17) conducted a study with similar issues. A total of 411 participants (178 males, or 43.3%) were included in the study, with a mean age of 46.8 years. Sixty-one patients (15%) showed increased plasma D-dimer concentrations (≥500 µg/L) after a median of 255 days after the acute infection; of these, 17 individuals had even higher D-dimer values ≥1000 µg/L. Compared to this study, the number of patients was higher, the proportion of men participating was higher (43.3% vs. 32%), and the elevated D-dimer ratio was lower (15% vs. 23.90%). The mean age of the study participants was similar (46.8 vs. 44 years). Age-adjusted D-dimer was not mentioned in this study either.

Lehmann et al. (18) measured D-dimer values 3 months after hospitalization in patients recovering from COVID-19. They included 129 patients (median age 48.8 years; range 19-91 years) in this study. They evaluated D-dimer levels after a median (IQR) of 94 days (64-130) following COVID-19. D-dimer elevation was found in 15% (19/129) and was significantly more common in patients who had experienced a severe severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection that required hospitalization compared with patients with mild disease (p=0.049). The number of patients in this study was less than in our study (129

vs. 322), and the elevated D-dimer ratio was lower than in our study (15% vs. 23.90%). However, this study was a prospective study. They detected acute pulmonary embolism in one patient and chronic thromboembolic pulmonary HT in another.

In our study, the highest number of patients admitted to the cardiology outpatient clinic occurred in the 12th month after the post-SARS-CoV-2 infection. We attributed this result to the continuation of the pandemic and increased knowledge about the cardiac effects of COVID-19. Television, the media, and the internet contributed positively to the increase in awareness of pandemics. When Figures 2 and 3 are examined, it is observed that the D-dimer level decreases after the 3rd and 4th months. It is noteworthy that there was an increase again in the 12th month. The reasons for this increase are: 1) The highest number of applications was made in the 12th month; 2) Patients may be infected with SARS-CoV-2 again one year later, but they are not aware of the situation because RT-PCR testing is not done; 3) Most of the patients are vaccinated; they remain asymptomatic in case of re-infection, but the inflammatory process continues in the body.

In our study, we examined both the time distribution of patients on admission and the time distribution of D-dimer elevation. When similar studies in the literature were examined, there was no study that made a detailed examination like ours. It is unclear in which month the patients applied for these studies. On the other hand, in our study, we determined how many patients applied in which month and in which month the D-dimer of the patients was high. When other studies in the literature were examined, figurative scatter plots were not found.

In addition, we calculated age-adjusted D-dimer values in our study. When other studies in the literature were examined, it was seen that the age-adjusted D-dimer level was not calculated. While D-dimer elevation was detected in 77 (23.9%) of the patients included in our study, only 22 (6.80%) patients had age-adjusted D-dimer elevation. Thanks to this corrected calculation, unnecessary coagulopathy research was avoided. In addition, unnecessary anticoagulant treatment was prevented.

Patients who apply to the hospital with complaints such as weakness, malaise, and shortness of breath in the post-COVID-19 period should be evaluated for long-term COVID. Discussions continue about the duration of thromboprophylaxis after discharge in long-term COVID cases. Anticoagulant therapy should be given to patients with high D-dimer values (19).

We detected elevated hs-cTn levels in 3 (0.90%) patients. None of the patients with high troponin levels had an acute coronary syndrome. Troponin-level increases may occur in conditions other than acute coronary syndrome (20). The common feature of the three patients with high troponin in this study was that they were hypertensive.

We detected elevated NT-proBNP levels in 11 (3.40%) patients. N terminal pro B type natriuretic peptide levels increase in heart failure (21), chronic kidney disease (22), and cirrhosis (23). We did not include patients with these diseases in our study. Therefore, elevated NT-proBNP levels cannot be attributed to these diseases.

Study Limitations

This study has several limitations. First, our study might have had selection bias because it was a single-center and retrospective study. Second, inpatients and outpatients were not compared. Despite these weaknesses, we examined how many months after the positive RT-PCR test patients came to the control and in which months the D-dimer value was high. We used age-adjusted D-dimer levels when analyzing the D-dimer values of patients over 50 years old. There was no study in the literature that was designed in this way before.

Conclusion

In our study, we found that the highest rate of D-dimer elevation was in the 3rd and 4th months of the post-COVID-19 period. The D-dimer level should be studied in patients who have experienced COVID-19 and applied to the Cardiology Outpatient Clinic with chest pain, shortness of breath, palpitation, fatigue, and weakness. Individuals over the age of 50 should be evaluated separately. Patients may have a long-term COVID-19 status as well as the possibility of re-infection. Reverse transcription-polymerase chain reaction can be performed in these patients, and a chest contrast-enhanced CT angiography scan can be performed in patients with severe symptoms. Anticoagulant therapy should be given to patients with elevated D-dimer levels.

Ethics

Ethics Committee Approval: Permission for the research was obtained from the Ministry of Health of the Republic of Turkey. Approval was obtained from the Clinical Studies Ethics Committee of Kocaeli Derince Training and Research Hospital (approval number: 2022/6; approval date: February 24, 2022).

Informed Consent: Informed consent from was not obtained because it was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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The Impact of Hounsfield Unit-related Variables on Retrograde Intrarenal Surgery Outcomes in Isolated Lower Pole Kidney Stones

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Abstract

Aim: The Hounsfield unit (HU) value can predict the stone-free status of retrograde intrarenal surgery (RIRS) for kidney stones. The purpose of this study was to investigate the effect of HU and HU-related variables on RIRS outcomes in isolated lower pole kidney stones.

Methods: This single-center cross-sectional study was conducted between January 2017 and March 2023. One hundred thirty-three patients who underwent RIRS for lower pole kidney stones were evaluated. These were divided into stone-free (Group 1) and remnant (Group 2) groups, and the effects of the HU-related variables on RIRS outcomes were investigated.

Results: One hundred-five (78.9%) patients in Group 1 and 28 (21.1%) in Group 2 were enrolled in the study. Significant differences were observed between the groups in terms of mean stone area (p=0.003), stone size (p<0.001), use of the ureteral access sheath (p=0.013), and operative time (p<0.001). The mean HU values were 795.09±287.55 in Group 1 and 927.64±302.6 in Group 2 (p=0.034). The mean HU density and HU intensity values were not significantly different between the groups (p=0.432 and p=0.207, respectively). The HU value was not identified as a dependent variable in the regression analysis.

Conclusion: Hounsfield unit value, HU density, and HU intensity are not predictive of stone-free rates after RIRS in isolated lower pole kidney stones.

Keywords: Hounsfield unit, kidney stone, lower pole, retrograde intrarenal surgery

Introduction

The essential objective for treating urinary stone disease is to achieve maximum stone-free status with minimal morbidity. However, the presence of lower pole stones poses a unique challenge due to the anatomical considerations involved in their management and treatment. The development of thin, flexible ureteroscopes (f-URS) with high image quality has facilitated access to every point of the kidney, while retrograde intrarenal surgery (RIRS) for lower pole stones has been facilitated by advances in laser and stone removal instrument technology (1,2). Prospective randomized controlled trials have reported RIRS success rates of 74-95% in isolated lower pole kidney stones (3,4).

The European Association of Urology (EAU) guidelines recommend percutaneous nephrolithotomy (PCNL) as the first-step treatment in isolated lower pole kidney stones >20 mm in size and RIRS or shock wave lithotripsy (SWL) in stones <10 mm. In the case of stones larger than 10 mm but <20 mm in size, RIRS is recommended for first-step treatment in the presence of unfavorable factors. The EAU guideline describes these unfavorable factors as a steep infundibular-pelvic angle, a long calyx, a long skin-to-stone distance, a narrow infundibulum, and shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine) (5).

Non-contrast computed tomography (NCCT) is widely employed in the diagnosis of urolithiasis (6). In addition to providing information concerning the stone size, multiplicity, and location, the presence of anatomical anomalies, and skin-to-stone distance, this method is also capable of evaluating the stone density in Hounsfield

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units (HU) values. The HU value determined using NCCT is associated with tissue or stone density. The degree of hardness increases in line with the HU value. These values have been used to predict the type and opacity of stones during diagnosis, and their efficacy has been assessed using therapeutic methods (7). For example, the EAU does not recommend SWL for patients with stone HU values >1,000 (5). Previous studies have assessed the use of HU values in SWL, PCNL, ureterorenoscopic ureterolithotripsy, and medical expulsive treatment in urinary stone disease (7-9). However, no previous studies have examined the predictive role of HU scores in RIRS outcomes in lower pole kidney stones. The primary aim of this study was to identify the association between HU-related variables and RIRS in these stones. The secondary aim was to evaluate our RIRS outcomes in lower pole kidney stones and to present our findings in light of the current literature.

Materials and Methods

The data for patients undergoing RIRS using f-URS due to lower pole kidney stones between January 2017 and March 2023 were then retrospectively evaluated in this cross-sectional study.

Compliance with Ethical Standards

The current study was approved by the Samsun Training and Research Hospital, Clinical Research Ethics Committee (date: 15.03.2023, and approval no: SUKAEK/2023/5/11).

Study Population

The patients were divided into two groups based on their stone-free rate (SFR) status: stone-free (Group 1) and remnant (Group 2).

Inclusion Criteria

- Age over 18, and,
- With a single lower pole stone.

Exclusion Criteria

- Age under 18,
- Who underwent pre-stenting RIRS,
- With isolated non-lower pole kidney stones,
- Undergoing bilateral surgery in the same session,
- Undergoing different kidney stone operations together with RIRS (such as open nephrolithotomy, PCNL, ureterolithotripsy, and antegrade intrarenal surgery) and,
- With a solitary kidney were excluded from the study.

Surgical Technique

All procedures were performed with the patient in the dorsal lithotomy position and under general anesthesia. The bladder was first emptied with a 12 Fr feeding catheter, after which a 0.035-inch safety guidewire was inserted into the ureter under cystoscope-assisted fluoroscopy. A second guidewire was then inserted through the ureteral orifice using a 7 Fr semi-rigid ureterorenoscope (Karl Storz Endoscopy, Tuttlingen, Germany). The ureter was examined endoscopically, and potential distal or middle ureter pathologies were excluded. Balloon dilation was performed in patients with distal ureteral strictures. A second guidewire was then inserted into the ureter. A 7.5 Fr superslim f-URS (Flex-X2, Karl Storz Endoscopy, Tuttlingen, Germany) was then slid over the second guidewire under fluoroscopic control and inserted into the proximal ureter or ureteropelvic region. A 10.7 Fr ureteral access sheath (Cook®, Bloomington, IN, USA) was installed in cases with stones of 15 mm or larger or in which we predicted potential prolongation of the procedure. The stone was identified endoscopically, and stone fragmentation was carried out with a laser lithotriptor in line with the dusting method (Figure 1). Stone fragmentation was performed using a 270 or 365 µm holmium:YAG laser probe in the 1.0-1.5 J and 5-10 Hz energy ranges. In cases in which it is difficult to disintegrate stones in the lower renal pole, the stone can be displaced into a more accessible calyx and fragmented there. Because prolonged operative times are associated with increased complication rates in ureteroscopy, every effort should be made to ensure that surgery lasts no longer than 90 minutes (5). Reasons for the conclusion of RIRS were operative time (>90 min), the

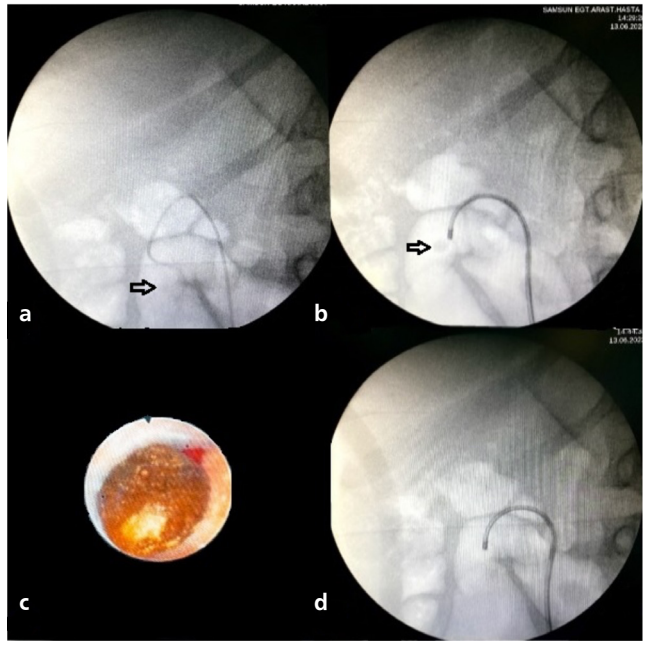

Figure 1. The different stages of retrograde intrarenal surgery. (a) Advancement of the guidewire into the kidney (arrow: Radiological image of the semi-opaque stone); (b) Insertion of a flexible ureteroscope into the kidney with the guidewire; (c) Endoscopic view of the lower pole stone; (d) Stone-free status after laser lithotripsy

removal of the stone, bleeding preventing visualization, or residual fragments <2 mm. A double-J catheter was installed in all patients at the end of the procedure. These were removed 2-4 weeks after surgery, following checking with direct urinary tract imaging (KUB). Patients' third postoperative month stone-free status was evaluated using NCCT. Stone-free status was defined as the absence of stone at NCCT or as residual stone ≤2 mm within three months postoperatively. The urine cultures of all patients were sterile before RIRS.

Postoperative Evaluation

The urethral catheter was removed, and the patient was discharged on postoperative day one. Demographic data, laboratory values, stone-related characteristics, operative characteristics, HU values, and HU-related variables were compared between the groups.

Stone length, stone area, and HU values were calculated automatically from axial and coronal views using the free draw measurement technique from our hospital's electronic records system (Figure 2). Whichever figure was higher for stone length, stone area, and HU value calculated on axial or coronal sections, that value was employed. Hounsfield unit-related variables were calculated using the method first described by Moon et al. (9). HU density was determined by dividing the HU value by the stone length, and HU intensity was determined by dividing the HU value by the stone area.

All patients signed detailed forms agreeing to their clinical details being used in scientific research, a formal requirement under our hospital's regulations.

Statistical Analysis

Normality and variance were evaluated by applying the one-sample Kolmogorov-Smirnov and Shapiro-Wilk tests for each variable. Quantitative data were expressed as mean plus standard deviation and qualitative data as frequency and percentage. The comparisons were completed using an independent sample t-test. Nominal variables were evaluated using the chi-square test. Regression analysis was employed to evaluate the correlation between the data. All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 20.0 software. Statistical significance was set at $p<0.05$.

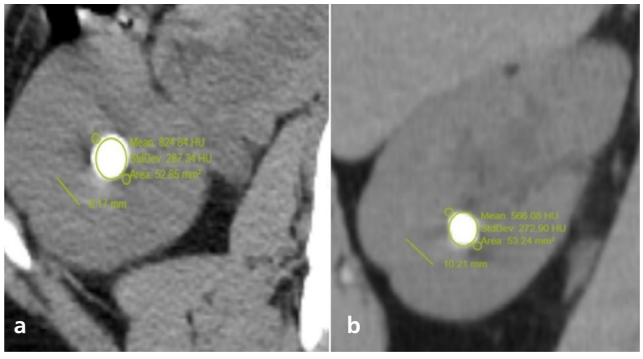

Figure 2. Automatic calculation of renal stone Hounsfield units, stone length, and stone area from coronal (a) and axial (b) views using the free draw measurement technique

Results

One hundred thirty-three patients (48 females and 85 males) with a mean age of 52.84±12.95 years were included in the study. The mean stone area was 87.73±96.94 mm^2 and the mean surgical time was 64.92±16.57 min. The mean American Society of Anesthesiologists score was 1.95±0.6, the ureteral access sheath use rate was 33.1%, the mean length of hospital stay was 2.33±1.08 days, and the SFR was 78.9%.

Mean body mass index values in groups 1 and 2 were 28.11±3.75 and 30.02±3.86 kg/m^2, respectively ($p=0.019$). The mean stone areas were 75.07±90.57 mm^2 in Group 1 and 135.21±106.7 mm^2 in Group 2 ($p=0.003$). Significant differences were found between the groups in terms of stone size ($p<0.001$), ureteral access sheath use ($p=0.013$), and operative time ($p<0.001$). The patient group demographic features, stone characteristics, and peri- and postoperative outcomes are listed in Table 1.

Mean HU values were 795.09±287.55 in Group 1 and 927.64±302.6 in Group 2, and the difference was statistically significant ($p=0.034$). The mean HU density and HU intensity values were not statistically significant ($p=0.432$ and $p=0.207$, respectively). Hounsfield unit-related variables are shown in Table 2. Regression analysis was used to evaluate the HU value correlation. Hounsfield unit values were not considered dependent variables ($p=0.581$).

Grade 2 and higher complications, according to the Clavien-Dindo classification system, developed in 12 patients (9%). These were antibiotics (Grade 2) in eight patients, double J stent placement due to the stent not being in situ (Grade 3a) in two, endoscopic ureter stone surgery (Grade 3b) in one, and sepsis (Grade 4b) in one. There was no difference between the groups in terms of complication rates ($p=0.443$). No patients developed nephrectomy or died of surgical or anesthesia-related complications.

Discussion

HU values measured using NCCT are associated with the density of the tissue. When the radiodensity of water is defined as 0, fat has a negative HU value, while blood and other tissues exhibit positive HU values. Hounsfield unit values can also be employed to evaluate the NCCT density of urinary tract stones. These values are now a highly useful diagnostic tool not only in terms of predicting the

Table 1. Demographics, stone, procedure characteristics of groups			
Variables	**Group 1 (n=105)**	**Group 2 (n=28)**	**p**
Age (years)	52.34±13.65	54.71±9.85	0.391*
Male (n, %)	65 (61.9%)	20 (71.4%)	0.385Ω
Body mass index (kg/m^2)	28.11±3.75	30.02±3.86	0.019*
ASA score	1.93±0.6	2.03±0.57	0.426*
SWL history (n, %)	31 (29.5%)	6 (21.4%)	0.275Ω
Laterality (right)	48 (45.7%)	16 (57.1%)	0.297Ω
Hydronephrosis (n, %)	23 (21.9%)	7 (25)	0.8Ω
Radio opacity (n, %)	78 (74.3%)	22 (78.6%)	0.807Ω
Stone size (mm)	9.48±3.19	12.71±4.38	<0.001*
Stone area (mm^2)	75.07±90.57	135.21±106.7	0.003*
Operation time (min)	61.85±16.02	76.42±13.4	<0.001*
Ureteral access sheath (n, %)	29 (27.6%)	15 (53.6%)	0.013Ω
Hospital stay (day)	2.32±1.1	2.39±1.03	0.766*

*Independent Samples t-test, ΩChi-square test.
ASA: American Society of Anesthesiologists, SWL: Shock wave lithotripsy

Table 2. The groups' HU, HU density, and HU intensity values			
Variables	**Group 1 (n=105)**	**Group 2 (n=28)**	**p***
HU	795.09±287.55	927.64±302.61	0.034
HU density (HU/mm)	85.6±35.34	80.07±21.86	0.432
HU intensity (HU/mm^2)	16.73±10.48	13.9±10.58	0.207

*Independent Samples t-test.
HU: Hounsfield unit

type of stone but also for determining the optimal form of treatment (7).

HU is a frequently employed method for the treatment of urinary system stone disease. According to the EAU guideline, an HU value exceeding 1000 in lower pole stones 10-20 mm in size is an unfavorable factor in terms of success (5). In their 20-center, 4208-patient study comparing RIRS and laser lithotripsy, Keat et al. (8) divided their patients into two groups: one with HU values above 1000 and another with values below 1000. These authors reported that the stones with HU values lower than 1000 were soft stones. In a review study examining the effect of HU on SWL, Garg et al. (7) found that HU<750 was associated with SWL success, while HU values over 1000 were strongly associated with a likelihood of failure. However, Moon et al. (9) reported no relationship between HU and PCNL success.

Lower pole kidney stones represent approximately 35% of all renal stones and are completely asymptomatic in many cases. However, their treatment is problematic because fragments are difficult to eliminate and have limited anatomical access to the inferior renal calyx (10). The American Urological Association and EAU have both issued guidelines and recommendations concerning the management of such stones (5,11). However, since all individuals' renal anatomy differs, the two guidelines differ slightly from one another and both involve deficiencies for treating lower pole kidney stones (12). For example, while the EAU explicitly describes those patients for whom SWL should not be performed, it says nothing specific about which individuals are suitable for RIRS (5).

Previous studies have described anatomical factors such as infundibulopelvic angle, pelvicalyceal height, and infundibular length and stone-related factors such as size and opacity as independent factors affecting the success of RIRS in lower pole kidney stones (13-15). The present study investigated the effect of HU values, HU density, and HU intensity in such stones on the effect of RIRS. Hounsfield unit values were significantly higher in Group 2, whereas no difference was observed between the two groups in terms of HU density or intensity. All three parameters were found not to constitute an independent factor for SFR in RIRS for lower pole kidney stones. Moon et al. (9) investigated the effects of the HU value and its variants on PCNL and concluded that while HU score and HU density were not factors in SFR in PCNL, HU intensity was an independent risk factor for SFR in that procedure. Li et al. (16) concluded that the HU value is not an independent risk factor for SFR in RIRS and PCNL but that it is closely associated with surgical time in RIRS. In their randomized, prospective, controlled study, Gucuk et al. (17) reported that the HU value had no effect on SFR in RIRS performed

due to lower pole kidney stones. Although the present study involved isolated lower pole kidney stones, from that perspective, our results are similar to those of other kidney stone studies.

Prospective randomized controlled trials have also reported SFR between 74% and 95% in isolated lower pole kidney stones (3,4,17). Similar to this research, retrospectively designed studies have reported SFR values of 62.5% to 93.8% (18-21). The SFR value in the present research was 78.9%. In terms of SFR, our research is thus consistent with previous studies in the literature.

The general complication rate of RIRS for treating lower pole kidney stones was as high as 40% in previous studies, although the majority of these complications were minor and required no intervention. Severe complications such as ureteral avulsion, arteriovenous fistulae, and severe kidney injuries have been reported in the following f-URS, but are unusual (10). Mortality rates are low in ureteroscopy for stone disease, with 72 cases having been reported in the literature (22). Rates of Grade 2 or higher complications associated with RIRS in lower renal pole kidney stones of 6.67%, 7%, and 9.9% were reported in three different prospective studies (16,17,23). The grade 2 and higher complication rate in this study was 9%. The most feared complication, sepsis, was observed in one patient (0.07%) but was successfully treated. Our study is also consistent with previous research in terms of complication rates.

Study Limitations

There are some limitations to this study. One is specific to its retrospective and single-center character. The patient number was also low. In addition, because we investigated the degree of stone hardness, anatomical factors involving the pelvicalyceal structure, such as infundibular height and length, infundibular pelvic angle, and infundibular width, were not included in this study. Finally, we excluded the analysis of stone composition. Despite these limitations, there are also some strengths to this study. These include the low number of previous studies on the subject, the fact that it focused specifically on the lower pole alone, and the fact that it is one of the first studies to compare HU and HU-related variables in RIRS.

Conclusion

Stone density measured in terms of HU values was significantly higher in patients with residual stone fragments in this study. Our findings suggest that HU and HU-associated variables are capable of predicting SFR of RIRS in the renal lower pole. We anticipate that subsequent multicenter prospective studies will confirm that HU and HU-associated variables are capable of application as a useful tool in determining the SFR of ureteroscopic surgical procedures.

Ethics

Ethics Committee Approval: The current study was approved by the Samsun Training and Research Hospital, Clinical Research Ethics Committee (date: 15.03.2023, and approval no: SUKAEK/2023/5/11).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Original Article

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Comparison of the Efficacy of Fosfomycin Trometamol and Ciprofloxacin in Transrectal Ultrasound-Assisted Prostate Biopsy Prophylaxis: Clinical Results of A Tertiary Referral Center

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Abstract

Aim: Although infectious complications after a prostate biopsy are uncommon, they may have fatal outcomes. An efficient prophylaxis plan has not been defined in the current literature to reduce these problems. In this study, we aimed to compare the use of ciprofloxacin (CIP) and fosfomycin trometamol (FT) for prophylaxis in terms of infectious complications and morbidity-related parameters in patients who underwent transrectal ultrasound-guided prostate biopsy (TRUSPB).

Methods: The study included 104 patients who received FT for TRUSPB prophylaxis (group 1) between May 2021 and May 2022 and 113 patients who received CIP for TRUSPB prophylaxis between April 2020 and April 2021 (group 2). All patients were instructed to visit our hospital if they had any complaints relevant to the procedure, and outpatient control visits were scheduled one month after the procedure. Post-procedure infectious or non-infectious complications within one month were identified by screening the patients' electronic records and medical charts belonging to their inpatient, outpatient, or emergency department visits.

Results: After the biopsy procedures, the rates of lower urinary tract symptom development, positive urine cultures, and the requirement of hospitalization for parenteral antibiotic treatment were found to be significantly lower in group 1 than in group 2 (p=0.048). In the analyses performed independently of the prophylaxis regimen, it was observed that an increase in the Charlson Comorbidity Index of the patients caused a significant increase in the rates of both urosepsis (p=0.024) and the requirement of hospitalization for parenteral antibiotic treatment (p<0.001).

Conclusion: We observed that the use of FT for prophylaxis in TRUSPB was superior to the use of CIP in terms of reducing infectious complications.

Keywords: Complications, hospitalization, mortality, prophylaxis, prostate biopsy

Introduction

Prostate cancer is the second most common cancer in men worldwide and occurs mostly when men are active in their lives (1,2). Prostate biopsy is currently the gold standard diagnostic tool for prostate cancer diagnosis, and it can be performed via the transperineal or transrectal approach (3). Although over 2 million procedures are performed annually in the United States and Europe, complications, some of which can be life-threatening, continue to be a significant challenge (4). Frequent complications of transrectal biopsies have been defined as hematospermia, hematuria, and rectal bleeding. A minority of patients who have undergone transrectal ultrasound-guided prostate biopsy (TRUSPB) face infectious complications, including

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cystitis, epididymitis, orchitis, prostatitis, and urosepsis (5). Mortality after a prostate biopsy is extremely rare and is mostly due to urosepsis (4). Various antibiotic prophylaxis protocols are used to reduce infectious complications, and clinics regularly update their antibiotic preferences according to the published results of the new regimens. Fluoroquinolones have been traditionally used for the antibiotic prophylaxis of TRUSPB. However, the overuse and misuse of fluoroquinolones have increased fluoroquinolone resistance (6). A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in cases of fluoroquinolone resistance or augmented prophylaxis (combination of two or more different classes of antibiotics), the common recommendation in the literature was targeted therapy (7). However, no standard antibiotic prophylaxis protocol is used worldwide because of regionally different antibiotic resistances. A meta-analysis of three randomized clinical trials reported that fosfomycin trometamol (FT) was superior to fluoroquinolones (relative risk: 0.49, 95% confidence interval: 0.27-0.87) (7), but the routine general use of this agent remains controversial due to the infectious complications reported to date (8).

The aim of this study was to compare FT prophylaxis with ciprofloxacin (CIP) prophylaxis in terms of their efficacy in preventing infectious complications.

Methods

Compliance with Ethical Standards

The present study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine (approval number: 488788, date: 22.09.2022).

Study Design

The records of all patients who underwent TRUSPB with two different prophylactic antibiotic regimes (FT and CIP) in our institution between April 2020 and May 2022 were retrospectively evaluated. Group 1 consisted of patients who received 3 g of oral FT 12 h before and 24 h after TRUSPB. Group 2 consisted of patients who received oral CIP for three days prophylactically, starting the day before TRUSPB. Only patients who were followed up for more than three months were included in the study. Patients who had used fluoroquinolones or FT for any reason within the last three months, had known resistance or allergies, had missing data, or did not attend follow-up visits were excluded from the study. To assess the data more homogenously, we also excluded patients who underwent TRUSPB under parenteral antibiotic prophylaxis due to resistant susceptibility testing results. Patients who were admitted to the hospital with conditions unrelated to the biopsy procedure were excluded from the final analysis.

Biopsy Procedure

Biopsies were performed in the endoscopy suite of our institution by experienced urologists with more than five years of experience in prostate biopsies. Antibiotic prophylaxis was started for the patients in both groups one day before the procedure, and the patients were instructed to apply a self-administered sodium phosphate enema the evening before the procedure. Before the procedure, the patients' comorbidities, urine culture results, prophylaxis status, blood coagulation parameters, antiaggregant or anticoagulant drug use, and the presence of specific symptoms of infection (i.e., fever, chills, urgency, frequent urination, or suprapubic tenderness) were questioned in detail by urologists. For the patients whose antiaggregant or anticoagulant therapy was not regulated, those who had symptoms of urinary tract infection (UTI), and those with positive urine culture results, the biopsy procedures were postponed. Patients with positive urine cultures were treated with antibiotics, and a negative microbiological control after therapy was required before biopsy. 3 g FT was administered prophylactically before and within 24 to 48 h after the procedure, as specified in the prostate biopsy prophylaxis section of the current European Association of Urology (EAU) prostate cancer guideline (3). Patients who received CIP for prophylaxis received a three-day prophylactic course of medication beginning the day before their procedure. The patients were placed in the left lateral decubitus position, and lubricant sterile gel with lidocaine (Lubagel Plus, Yasemin Medika, Istanbul, Turkey) was applied via the rectal route. A digital rectal was examined, and the findings were recorded in the patient's file. A 6.5-MHz transrectal ultrasound probe (Siemens Medical Systems, Inc., Issaquah, WA, USA). Prostate volume was calculated using the prostate ellipsoid formula: volume (V)=0.52 (L x W x H), where L is the cephalocaudal diameter, W is the width, and H is the anteroposterior diameter. A periprostatic block was applied with a combination of lidocaine and bupivacaine using a 20-cm-long, 22-gauge needle (Chiba Biopsy Needle with Echogenic Tip, Argon Medical Devices Inc., Dallas, USA) for both sides under the guidance of transrectal ultrasonography. Transrectal ultrasound-guided prostate biopsy was performed using a disposable 18-gauge × 25-cm biopsy needle (Argon Pro-Mag Biopsy Needle, Argon Medical Devices Inc., Dallas, USA). According to the standard biopsy protocol, 12 core biopsies were taken. If the calculated prostate volume was larger than 60 cc, four additional cores were added. If a suspicious lesion was detected on multiparametric prostate magnetic

resonance imaging (MRI) before the procedure, three subsequent additional core biopsies per lesion were taken using an MRI fusion biopsy device (UroNav, Invivo-Philips, Gainesville, FL, USA).

Follow-up

All patients were advised to present to our hospital if there were any severe rectal or urinary bleeding, urinary retention, fever, chills, or lower urinary tract symptoms. We scheduled visits within one month after TRUSPB as a cut-off to capture only infections that could be related to the prostate biopsy. Any events that occurred more than one month after the prostate biopsy were considered unlikely to have been related to TRUSPB. All symptomatic patients who presented to the hospital underwent a physical examination and urinalysis. Similar to the criteria described by Fahmy et al. (9), urine cultures were taken from the patients who presented with fever, fatigue, any lower urinary tract symptom (i.e., urgency, frequency, dysuria, or suprapubic tenderness), bacteriuria [$\geq 10^4$ colony-forming units (CFUs)/mL], and pyuria (>5 leucocytes/high-power field). Hemocultures and blood tests were collected from the patients with a body temperature of >38 °C and/or in the presence of a septic status. Patients who were considered to have febrile UTIs and required parenteral antibiotics were admitted to the inpatient clinic. In our study, we screened for sepsis using the quickSOFA (qSOFA) score, in which each of the following three criteria is assigned one point: A low systolic blood pressure (≤100 mmHg), a high respiratory rate (≥22 breaths per minute), or altered mental status (Glasgow Coma Scale score <15). (10) Those who scored two out of three in the screening were further evaluated by an infectious diseases specialist in terms of sepsis.

Statistical Analysis

SPSS v. 20 (IBM Corp. Released 2011, IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) statistical program was used for the evaluation of the data. The assumption of normality was tested using the Shapiro-Wilk test. The two groups were compared with the Independent sample t-test and the Mann-Whitney U test. The relationship between categorical variables was analyzed with Fisher's exact and chi-square tests. P<0.05 was considered significant.

Results

Patient characteristics for both groups are shown in Table 1. Group 1 consisted of 104 (47.92%) patients, and group 2 consisted of 113 (49.77%) patients. The two groups were similar in terms of median age, prostate volume, the number of biopsy cores, and presence of urethrorrhagia and rectorrhagia. The median Charlson Comorbidity Index (CCI) and prostate-specific antigen (PSA) values of the patients in group 2 were significantly higher than those of the patients in group 1 (p=0.004). The median number of biopsy cores was significantly higher in group 1 than in group 2 (p=0.007). The number of patients presenting with lower urinary tract symptoms after the biopsy was 16 (15.38%) in group 1 and 39 (34.51%) in group 2 (p<0.001). We detected six (5.76%) post-procedure positive urine cultures in group 1 and 20 (17.69) in group 2 (p=0.007). Eight (30.76%) of these patients were treated with oral antibiotics (Table 2). In group 1, five patients were hospitalized for parenteral antibiotic treatment. Extended-spectrum beta-lactamase (ESBL)-positive *Escherichia coli (E. coli)* > 100.000 CFU/mL was detected in the urine cultures of four of these patients, and meropenem was administered in accordance with susceptibility testing. We detected *Pseudomonas aeruginosa* in the remaining patient and treated it with amikacin monotherapy according to the susceptibility testing results. In group 2, ESBL (+) *E. coli* >100.000 CFU/mL was detected in the urine cultures of 11 of the 13 patients, of whom nine were treated with meropenem and two with ertapenem in line with susceptibility testing. In the remaining patient, *Enterococcus* spp. >100.000 CFU/

Table 1. Patient characteristics

	FT (group 1)	CIP (group 2)	p value
Patients, n (%)	104 (47.92)	113 (52.07)	
Age, median (IQR25-IQR75)	65 (58-71.75)	65 (59-69.5)	0.581♠
Diabetes mellitus, n (%)	32 (30.76)	41 (36.28)	0.39♥
CCI, median (IQR25-IQR75)	3 (1-5)	4 (2-5)	**0.004**#
PSA, ng/mL, median (IQR25-IQR75)	7.5 (5.2-12)	10 (6.24-26)	**0.007**#
Prostate volume, cm^3, median (IQR25-IQR75)	50 (37.63-65.75)	50 (35-65)	0.901#
Number of biopsy cores, mean (IQR25-IQR75)	16 (15-18)	14 (12-16)	**0.000**#
Urethrorrhagia, n (%)	16 (15.38)	16 (14.15)	0.799♥
Rectorrhagia, n (%)	16 (15.38)	27 (23.89)	0.108♦

♠Independent samples t-test, #Mann-Whitney U test, ♦Fisher's exact test, ♥Chi-square test
FT: Fosfomycin trometamol, CIP: Ciprofloxacin, CCI: Charlson Comorbidity Index, PSA: Prostate-specific antigen

mL ampicillin resistant were detected in urine cultures, and teicoplanin treatment was started according to susceptibility testing (Table 3). Two patients, both in group 2 and both with CCI >7, were evaluated for urosepsis according to the qSOFA screening criteria. ESBL (+) *E. coli* >100.000 CFU/mL was detected in the first patient's urine culture 14 days after the biopsy. Empirical meropenem treatment was started as soon as blood cultures were obtained when clinical signs appeared. Blood cultures remained sterile, and meropenem was continued based on urine culture results. In the second patient, *Enterococcus spp.* >100.000 CFU/mL were detected in the urine culture 8 days after the biopsy, while his blood cultures were sterile. Teicoplanin was initiated empirically upon Gram staining results and continued according to susceptibility testing. Due to the development of urosepsis, both patients were transferred to the intensive care unit. Despite timely and prompt parenteral antibiotics and vasopressor therapy, the patients succumbed to urosepsis.

Discussion

The results of our study showed that FT prophylaxis was superior to CIP prophylaxis in terms of lower urinary tract symptoms, urine culture positivity, infections requiring hospitalization, and urosepsis after TRUSPB. Although TRUSPB is generally considered a safe outpatient procedure, infectious complications carry the risk of death. The incidence of bacteriuria and urosepsis following transrectal prostate biopsy was reported to be 17.1% and 5.7%, respectively, in a recent study (11). This circumstance appears to be very extraordinary and concerning. Also, with the increasing number of men on active surveillance worldwide, there has also been an increase in the number of repeat biopsies that have a higher risk of infectious complications than primary biopsies. To prevent infectious complications, fluoroquinolones, which are effective in the *Enterobacteriaceae* family, are commonly used in patients undergoing TRUSPB worldwide. However, due to increasing fluoroquinolone resistance in recent years, fluoroquinolones are no longer the most effective alternative for prophylaxis (12-14). In particular, the European Commission has imposed stringent limits on fluoroquinolones and prohibited their use for prostate biopsy prophylaxis (6). Other alternatives to CIP include parenteral antibiotics, which are not endorsed as prophylaxis according to the EAU guidelines. Despite the increasing resistance to CIP in Turkey, this antibiotic is still widely used for various clinical cases, and yet there is no regulatory rule to limit its use for prophylaxis. Since we encountered challenging infective complications under CIP prophylaxis more frequently, we started to use FT prophylaxis, recommended by the EAU guidelines, in our clinical practice and compared the outcomes of these two prophylaxis agents in the current study. A study by Ongün et al. (15) compared the outcomes for 620 patients under FT- or fluoroquinolone-based TRUSPB prophylaxis, and the results showed that FT prophylaxis reduced the rates of fluoroquinolone-resistant infections requiring hospitalization. In a meta-analysis published by Pilatz et al. (7) in 2020, data obtained from 59 randomized controlled trials and 14,153 patients were examined, and it was emphasized that FT prophylaxis was a good alternative for prophylaxis with low infection rates, especially in countries where the use of CIP was restricted. In comparison to fluoroquinolone, a recent meta-analysis suggested that

Table 2. Patients were treated with oral antibiotics

	FT (group 1)	CIP (group 2)	p value
Presence of LUTS symptoms after biopsy, n (%)	16 (15.38)	39 (34.51)	**<0.001**♥
Positive urine culture, n (%)	6 (5.76)	20 (17.69)	**0.007**♥
Treatment with oral antibiotics, n (%)	1 (0.96)	7 (6.19)	0.067♦
Hospitalization and treatment with parenteral antibiotics, n (%)	5 (4.8)	13 (11.5)	**0.048**♥
Urosepsis, n (%)	0 (0)	2 (1.76)	0.49♦
Mortality, n (%)	0 (0)	2 (1.76)	0.49♦

♦Fischer's exact test, ♥Chi-square test
FT: Fosfomycin trometamol, CIP: Ciprofloxacin, LUTS: Lower urinary tract symptoms

Table 3. Urine culture results of the patients treated with parenteral antibiotics

	FT (group 1)	CIP (group 2)
Escherichia coli (ESBL), n (%)	4 (80)	11 (84.6)
Pseudomonas aeruginosa, n (%)	1 (20)	0
Staphylococcus aureus, n (%)	0	1 (7.7)
Enterococcus spp. *n (%)*	0	1 (7.7)

FT: Fosfomycin trometamol, CIP: Ciprofloxacin, ESBL: Extended-spectrum beta-lactamase

FT or the combination of FT and fluoroquinolone may have a similar preventive impact on UTIs after TRUSPB, and FT may be a good option considering the increase in fluoroquinolone resistance (16). However, Carignan et al. (8), who examined the data of 9,391 patients who had undergone TRUSPB in a nested case-control non-randomized study, reported that the risk of infection increased with FT prophylaxis compared to CIP prophylaxis and that this risk could not be reduced by administering a second dose of FT. Similar to the studies of Ongün et al. (15) and Pilatz et al. (7), we found fewer infective complications in our FT prophylaxis group. Urosepsis development after TRUSPB is a serious, life-threatening complication. When the current literature is reviewed in terms of urosepsis rates, Morin et al. (12) examined the results of prostate biopsies performed in Canada between 2012 and 2015 and found that only 1.1% (12/1090) of patients who received CIP prophylaxis and 0.2% (2/1197) of those who received CIP + FT prophylaxis developed urosepsis, and the rate of urosepsis development was lower in the CIP + FT combination. In a study conducted in Italy in 2015, Cai et al. (17) retrospectively evaluated the data of 1,109 patients who underwent TRUSPB and found that 0.3% (2/632) of the patients in the FT group and 1.8% (9/477) of those in the CIP group developed urosepsis. We evaluated our patients for urosepsis according to the qSOFA criteria as recommended by the EAU urological infection guidelines (10,3). We found the rate of urosepsis to be 1.76% in the CIP group, whereas urosepsis was not observed in any of the patients in the FT group. Our results seem to be consistent with the literature. Positive urine culture results, with or without systemic findings of infection requiring hospitalization after TRUSPB are becoming a more significant problem in current medical practice. When our series was examined, ESBL (+) *E. coli* growth was detected in 83.33% of our hospitalized patients, and *Staphylococcus aureus, Enterococcus spp.*, and *Pseudomonas aeruginosa* growth was observed in one patient each. In the current literature, ESBL (+) *E. coli* growth is reported in a wide range from 56% to 100% (18-20). According to the risk distribution map of the 2019 global antimicrobial resistance evaluation study, the rate of fluoroquinolone-resistant *E. coli* in the general population of Turkey was 40-50%, and the rate of third-generation cephalosporin-resistant *E. coli* was 20-30% (21). In light of these data, the rate of multidrug resistance reflects current epidemiology. Comorbidities often lead to poor outcomes, and therefore patients' comorbidities should be evaluated before TRUSPB. Charlson Comorbidity Index is widely used to evaluate patients' comorbidities and assess mortality risks. In our study, an increase in CCI increased both the requirement for hospitalization for parenteral antibiotic treatment and the rate of urosepsis. However, CCI is rarely used in studies comparing different prophylaxis protocols in the literature. In a 2016 study, Cai et al. (17) compared FT and CIP in TRUSPB prophylaxis and found that a CCI of more than 1 increased the likelihood of symptomatic UTIs. Based on our similar results, we consider that CCI should be evaluated before the procedure and that more effective prophylaxis protocols should be applied for prophylaxis in patients with a CCI of more than 1. Mortality is rarely seen after TRUSPB. In a large-scale population-based study evaluating mortality rates within the first four months after TRUSPB, the data of 22,175 patients was evaluated, and it was reported that 279 (1.3%) patients died during this period (22). In addition, the mortality rate was found to be 0.7% in patients with a CCI of 0 and 2.2% in those with a CCI of 3 or 4. In our study, there was no patient loss in the FT group, but two (1.7%) patients who underwent prophylaxis with CIP died due to urosepsis and related complications after the procedure. The first of these patients was a 71-year-old male who had no known additional disease but had metastatic disease of an unknown primary on admission. The CCI for this patient was determined to be 9. Since his total PSA was 15 ng/dL, a transrectal prostate biopsy was performed. He presented with chills and a fever four days after the biopsy. Extended-spectrum beta-lactamase positive *E. coli* was detected in the urine culture, and his qSOFA score was 3 on clinical assessment. The patient was transferred to the intensive care unit and followed up with positive inotropes for 5 days, but died despite all efforts. The second patient was a 72-year-old man with diabetes mellitus, mitral valve regurgitation, and congestive heart failure. He had a CCI value of seven. Considering that the total PSA level was 16 ng/mL, a transrectal prostate biopsy was performed. One day after the biopsy, he presented to our clinic with a deterioration in his general condition. The qSOFA score was calculated to be 3, and he was transferred to an intensive care unit. *Enterococcus spp.* >100.000 CFU/mL were detected in his urine culture, and teicoplanin was started empirically and continued as targeted therapy according to susceptibility testing. He died after six days of follow-up in the intensive care unit. There was no patient loss in the FT group. The high CCI scores of both patients who died indicate the importance of evaluating patient comorbidities before TRUSPB.

Study Limitations

There are some limitations to our study. Rectal swab cultures to screen for multidrug resistance in the rectal flora were not obtained from the patients before the biopsy procedure. A controversial issue emphasized in the literature is that different patterns of resistance may exist among the rectal flora of the same patient and

may be overlooked in screening cultures. Routine rectal washing with povidone-iodine was also not undertaken during the procedure. Lack of randomization in assigning patients to the prophylaxis groups and the higher mean CCI score of the patients in the CIP arm are among the major limitations of our study. Laboratory analyses for control were also not requested for patients who did not develop any symptoms during the follow-up period. The number of fusion biopsies performed was higher in the FT group. Finally, it should be noted that Germany has withdrawn the use of FT for prostate biopsies because its manufacturers failed to provide the required pharmacokinetic data (3).

Conclusion

It was observed that the use of FT for prophylaxis in TRUSPB was superior to the use of CIP in terms of reducing infectious complications. We recommend that more effective prophylaxis protocols be applied to lower the rates of infectious complications related to TRUSPB.

Ethics

Ethics Committee Approval: The present study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine (approval number: 488788, date: 22.09.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H.G., M.F.S., Concept: M.H.G., S.B.O., Design: M.H.G., I.I.B., M.F.S., B.O., A.E., Data Collection or Processing: G.K., K.C.S., Analysis or Interpretation: M.H.G., G.K., K.C.S., Literature Search: M.H.G., G.K., S.B.O., Writing: M.H.G., S.B.O., I.I.B., M.F.S., B.O., A.E.

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Case Report

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Guillain-Barré Syndrome Presenting with Facial Diplegia Due to SARS-CoV-2 Infection: A Case Series and Current Literature Review

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Abstract

The coronavirus disease-2019 (COVID-19) infection was first detected at the end of December 2019. Encephalitis, ischemic stroke, ataxia, and peripheral nerve diseases were reported in patients after the COVID-19 infection. Guillain-Barré syndrome (GBS) and cranial nerve involvement are also frequently observed. We report five patients with GBS after the COVID-19 infection. Four of them had facial diplegia. Electromyography of the three patients mentioned having acute motor and sensory axonal neuropathy, whereas two had demyelinating and mixed types. Mixed types were more frequent in studies, and a significant relationship was found with the demyelinating type. The high rate of facial diplegia in our cases suggests that more research should be conducted on the cranial nerve involvement in GBS patients with COVID-19 infection. Our aim was to focus on cranial nerve involvement in COVID-19 patients.

Keywords: Guillain-Barré syndrome, facial diplegia, SARS-CoV-2

Introduction

The coronavirus disease-2019 (COVID-19) infection was first detected at the end of December 2019. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the agent responsible for this disease. It is spreading rapidly around the world as a cause of high mortality and morbidity. Cardiopulmonary effects of the disease are predominant, but neurological involvement is also seen. Headaches, a lost sense of taste and smell, and dizziness are the most common neurological symptoms. Encephalitis, ischemic stroke, ataxia, and peripheral nerve diseases were observed in patients after the COVID-19 infection (1). Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculopathy. In particular, it appears in the 1-4 week period after upper respiratory and gastrointestinal tract infections. Guillain-Barré syndrome generally presents with ascending weakness. However, variants of disease such as Miller Fisher syndrome, the pharyngocervicobrachial variant, facial diplegia, paresthesia, and pure sensory neuropathy are seen clinically (2). During the disease, the patient may develop respiratory distress and need an intensive care unit. Even death can occur. Therefore, it is important to keep GBS in mind as a differential diagnosis in patients with COVID-19 infection. We present five patients diagnosed with GBS after the COVID-19 infection. We contribute to the literature with a case series that presents GBS with cranial nerve involvement after COVID-19 infection.

Case Report

This was a single-center case series study, and the data on the patients were obtained retrospectively from their medical records. Five GBS patients after COVID-19 infection from March 2020 to October 2021 in the neurology clinic were described. Thorax computed tomography (CT) and COVID-19 reverse transcriptase-polymerase chain reaction (PCR) were used for the diagnosis of COVID-19 infection, and every patient was consulted with an infectious diseases specialist. The muscle strength of the patients was evaluated according to the Medical Research Council (MRC) scale, and lumbar puncture (LP) and electromyography (EMG)

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were performed at the diagnosis stage. The Brighton Collaboration GBS Working Group criteria were used for the diagnosis of GBS. Disability was calculated according to the Hughes Scale as: 0, healthy; 1, minor symptoms and can run; 2, can walk 10 m or more without help but can't run; 3, can walk 10 m with help; 4, bedridden or chair bound; 5, requiring ventilation for at least part of the day; 6, dead (3). Three of the patients were male, and two were female. Their mean age was 45.6 years [minimum (min) 32, maximum (max) 69]. The oropharyngeal COVID-19 swab sample of four patients was positive, and one of them was negative. Clinical features and thoracic CT were all compatible with COVID-19. The mean time between COVID-19 symptoms and the development of GBS was 11.4 days. (min 2, max 18 days). Facial diplegia was observed in addition to weakness in the extremities on the neurological examination of our four patients. Patients were investigated for metabolic disorders and other polyneuropathy causes, but no explanation for their clinical state was found. Lumbar puncture was performed, and albuminocytological dissociation was observed in all of them. COVID PCR of cerebrospinal fluid was negative. Ganglioside antibodies could not be studied. Electromyography was performed for all five patients. Acute motor and sensory axonal neuropathy (AMSAN) was reported in three patients' EMGs. The other two cases were evaluated as acute inflammatory demyelinating polyneuropathy (AIDP). They received 0.4 g/kg/day intravenous immunoglobulin for five days. The clinical and diagnostic findings of the patients are in Table 1.

Discussion

Guillain-Barré syndrome cases with the COVID-19 pandemic were seen after the SARS-CoV-2 infection. It was also mentioned that several neurological involvements existed. Symptoms and signs occur with damage to tissues in the peripheral and central nervous systems. The direct effect on cells, hypoxia, and immune effects on systems are the main mechanisms of this damage. It spreads to the nervous system with the involvement of the olfactory nerve and other cranial nerves. Secondary damage occurs because of the immune-mediated response, which has been supported by the finding of antibodies such as antiganglioside antibodies in some patients. In addition, mechanisms related to the angiotensin-converting enzyme 2 receptor have also been mentioned (4).

We presented five cases of diagnosed GBS after COVID-19 infection. Three of the patients were male, and two were female. The gender distribution was similar to the literature (5,6). The mean time between COVID-19 symptoms and the development of GBS was 11.4 days (min 2, max 18 days). The median range varies between 11 and 13 days (2). In a multicenter study in Italy, 20% of the patients were diagnosed with GBS after the COVID-19 infection, 80% of the patients were diagnosed with GBS while the current infection symptoms continued (3). Four of our patients' COVID PCR results were positive, but the patient whose symptoms persisted had a negative result. In the United Kingdom data, there was no increase in the number of GBS cases after the pandemic, and even a decrease was observed in March-May 2020. The use of masks and isolation was assumed to be the cause of the decrease, which was due to a decline in viral infections. In contrast, Filosto et al. (3) reported an increase in patients, according to their publication. Following COVID-19, GBS patients described a more serious course, increased autonomic dysfunction, and admission to an intensive care unit, with an apparent experience of the COVID-19 symptoms (3). According to several studies, there was not a significant increase in intensive care rates compared to the pre-covid period, and patients' clinical responses are good following GBS treatment (6,7). Clinical improvement was seen in our patients, but two of them had more severe COVID symptoms, which resulted in longer hospital stays and higher disability ratings. There are many reasons for bilateral facial paralysis. Trauma, infections like syphilis, metabolic diseases, acute leukemia, and autoimmune disorders like sarcoidosis can be expressed. Brainstem lesions such as pontine gliomas or hemorrhage may also be causes. Bilateral facial weakness is frequently observed in neuromuscular junction diseases. However, in these patients, there are other symptoms, such as bulbar symptoms and ophthalmoplegia, that are helpful in the diagnosis (8). GBS is a cause of bilateral facial paralysis. The rate of facial nerve involvement in GBS is 27-50%, and half of them are bilateral. The isolated facial paralysis variants are rare. Cranial nerve involvement is more common in patients with COVID-19 infection in the literature, similar to our cases (9). Three of the cases had AMSAN, and two had AIDP found in the EMG. In research, mixed and demyelinating types were more common, and a significant relationship with the demyelinating type was discovered (3,6). However, we observed axonal-type GBS dominance. Sedaghat and Karimi (10) also reported a patient with bilateral facial paralysis with AMSAN after COVID-19 infection, which had similar EMG and clinical findings to the patients in our study. The fact that the axonal type is more common in the normal GBS population in Asian countries may have led to this result (11). The assessment is also impacted by the size of our small group.

Table 1. Clinical and diagnostic findings of GBS patients after COVID-19 infection

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	**69**	**32**	**46**	**40**	**41**
Gender	Male	Male	Female	Male	Female
Medical history	Familial Mediterranean Fever	None	None	None	None
Symptoms of admission	Cough, hypoesthesia of lower extremities.	Weakness of the lower extremities.	Hypoesthesia of the fingers and toes and weakness of lower extremities.	Malaise and muscle aches.	Numbness in the left side of the face, difficulty in closing eyes and weakness in the lower extremities.
COVID-19 RT- PCR	Positive	Negative	Positive	Positive	Positive
CT chest findings	Pneumonic infiltrations with glass densities.	Patch-style glass densities.	Patch-style glass densities.	Consolidations ground-glass opacity.	Patch-style glass densities.
Neurological examination	Upper extremities 5/5 and lower extremities proximal muscles 4/5 and distal muscles 3/5 with MRC. DTR could not be obtained bilaterally in lower extremities, hypoactive in upper extremities. Plantar reflexes were bilaterally unresponsive.	He had facial diplegia. Upper extremities 4/5 and lower extremities 2/5 with MRC. DTR was hypoactive in all extremities. Plantar reflexes were bilaterally unresponsive.	She had facial diplegia. Upper extremities 4/5, proximal lower extremities 3/5 and distal lower extremities 5/5 with MRC. DTR was normoactive in the upper extremities and absent in the lower extremities. Plantar reflexes were bilaterally unresponsive. She had bilateral facial paralysis.	He had facial diplegia. Upper extremities 4/5, proximal lower extremities 5/5 and distal lower extremities 5/5 with MRC. DTR was hypoactive in the upper extremities and absent in the lower extremities. Plantar reflexes were bilateral flexors.	She had dysphagia, severe dysarthria, and facial diplegia. Upper extremities were 4/5, proximal lower extremities 3/5 and distal lower extremities 2/5 with MRC. DTR was normoactive in the upper extremities and absent in the lower extremities. Plantar reflexes were bilaterally unresponsive.
Duration between COVID-19 and GBS symptoms (days)	2	12	10	18	15
CSF findings	No cell, prt:182 mg/dL	No cell, prt: 180 mg/dL	No cell, prt: 243 mg/dL	No cell, prt: 148.7 mg/dL	No cell, prt: 125 mg/dL
EMG findings	AIDP prolonged DL and decrease in CV of median, tibial and peroneal nerves decreased F response frequency.	AMSAN low CMAP amplitude in peroneal nerve, absent sural sensory response.	AMSAN reduced CMAP amplitude in the ulnar and tibial nerves, reduced ulnar sensory amplitude.	AIDP prolonged DL and decrease in CV of tibial and peroneal nerves decreased F response frequency.	AMSAN low CMAP amplitude in tibial and peroneal nerves, absent sural sensory response.
Disability score at first month (Hughes scale)	4	1	2	1	3

DL: Distal latency, CV: Conduction velocity, CMAP: Compound muscle action potential, AMSAN: Acute motor and sensory axonal neuropathy, CSF: Cerebrospinal fluid, RT-PCR: Reverse transcriptase-polymerase chain reaction, DTR: Deep tendon reflex, COVID-19: Coronavirus disease-2019, EMG: Electromyography, GBS: Guillain-Barré syndrome, CT: Computed tomography

Conclusion

The COVID-19 infection has been in our lives for about two years, and its short- and long-term effects are not fully known yet. The impacts on the nervous system must be considered. We presented five GBS cases presenting with facial diplegia after the COVID-19 infection. In our cases, the axonal type was seen more frequently. But demyelinating is more common in the literature. It is thought that the predominance of this type in the normal GBS population in Asia may be a factor in the results. Also, four of the five patients (80%) had bilateral facial nerve involvement. This rate is higher than the normal GBS

population, but we had a small group for evaluation. More research on the cranial nerve involvement with COVID-19 infection is needed, as evidenced by the high occurrence of facial diplegia in our cases.

Ethics

Informed Consent: Consent information was obtained from the patient's family.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.K.A., Concept: K.G.K., Design: A.A., I.K.A., Data Collection or Processing: K.G.K., A.A., Analysis or Interpretation: M.F.P., E.G., Literature Search: K.G.K., Writing: K.G.K.

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

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Case Report

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Tuberculosis Pleurisy in a Case of Burkitt Lymphoma Secondary to Rituksimab Treatment

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Abstract

Non-Hodgkin's lymphoma (NHL) accounts for 60% of childhood lymphomas and is the fourth most common childhood malignancy. Burkitt's lymphoma (BL) accounts for 40% of NHLs. Burkitt's lymphoma is mostly of abdominal origin and has the highest cell count doubling rate. Tuberculosis (TB) is one of the chronic diseases caused by the *Mycobacterium tuberculosis* bacillus, which has high morbidity and mortality and occurs most frequently in the lung. In this case report, we present a patient with a previous diagnosis of BL who developed pleural effusion while under rituximab-ifosfamide carboplatin etoposide treatment, and TB polymerase chain reaction (PCR) was revealed to be positive in the TB PCR screening test of the pleural fluid. To our knowledge, there is no previous study of the coexistence of BL and TB pleurisy in the literature. When pleural effusion develops in patients with BL under chemotherapy treatment, it should be kept in mind that TB may be present, and anti-TB treatment should be started as soon as the diagnosis is made. There is limited information in the literature about the frequency of tuberculous pleurisy in patients with BL.

Keywords: Burkitt's lymphoma, tuberculosis, pleural effusion, tuberculous pleurisy, rituksimab

Introduction

Non-Hodgkin's lymphoma (NHL) are mostly fast-growing, high-stage tumors. It is more common in boys (1). NHL is divided into approximately 60 subtypes based on morphological, immunophenotypic, genetic, and clinical features. Some deoxyribonucleic asid (DNA) and ribonucleic acid (RNA) viruses play a role in disease development. Epstein-Barr virus (EBV) is the most common virus among them. It has been observed that 90% of Burkitt's lymphoma (BL) cases are associated with EBV infection (2).

Burkitt's lymphoma accounts for 40% of NHLs. Burkitt's lymphoma is mostly of abdominal origin and has the highest cell count doubling rate (3). Burkitt's lymphoma, which is the fastest-growing human tumor with a doubling time of approximately 12-24 hours, is an aggressive B-cell neoplasia. It usually occurs as an extranodal disease and is epidemiologically divided into three types: endemic, non-endemic, and associated with immune deficiency. Endemic type; jaw (most common), liver, adrenal glands, stomach, intestine, pancreas, salivary glands, thyroid, testis, and heart; non-endemic type: abdomen (most common), and 15-20% of the chin; and the type associated with immunodeficiency often involves the lymph nodes (4).

Tuberculosis (TB) is one of the oldest known chronic diseases in human history. It is caused by the *Mycobacterium tuberculosis* bacillus, develops slowly and insidiously, has high morbidity and mortality, and occurs most frequently in the lung (5). While the TB point prevalence rate in Turkey was 25 per hundred thousand in 2009, it was 63 per hundred thousand in the World Health Organization European Region and 201 per hundred thousand worldwide (6). The rate of new cases in 17,402 patients was 91.6% (n=15,943), and 62.7% (n=10,906) of the patients diagnosed with TB showed lung involvement (7).

Case Report

In this case report, we present a patient who was previously diagnosed with BL, who developed pleural effusion while under rituximab-ifosfamide carboplatin

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etoposide (R-ICE) treatment, and who had a positive TB PCR for the test from the pleural fluid. To our knowledge, there is no previous study of the coexistence of BL and TB pleurisy in the literature.

A 9-year-old male patient applied to an external center because she had abdominal pain and occasional vomiting for 2 months. A heterogeneous solid mass lesion with a size of 137x130x80 mm, starting from the upper paraumbilical area and covering the pre-subumbilical area, was observed in the entire abdominal ultrasound radiography of the patient. As a result, the patient was admitted to the emergency department of University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, and to the pediatric surgery service after the first evaluation. In the follow-up of the patient, whose CA-125 was 46.5 in the first blood examination, a tru-cut incisional biopsy performed from the solid mass lesion was CD20 positive, CD3 negative, PanCK negative, NSE negative, synaptophysin negative, chromogranin negative, S100 negative, and Ki-67 proliferation index negative. In the applied immunohistochemical study, CD10-positive cells were detected in the neoplastic cells. Our patient was diagnosed with BL stage 3 according to the anamnesis, examination, and biopsy results. The patient was started on the NHL chemotherapy protocol with the 1st A4 course, followed by the 1st B4 course, the 2nd A4 course, the 2nd B4 course, and the 1st Cc course. However, in the interim evaluation made before the 2nd CC, it was decided to start R-ICE treatment due to the rapid growth of the patient's mass and the positive CD20 in positron emission tomography. It was planned to take the R-ICE2 course after the R-ICE1 cycle.

However, due to dyspnea and a decrease in right lung breath sounds on auscultation, X-ray screening of the lung was performed, and widespread opacity consistent with pleural effusion was observed in the right lung (Figure 1). A contrast-enhanced thorax computed tomography report taken on the same date was interpreted as a diffuse effusion with an anterior-posterior diameter of 7 cm on the right (Figure 2). Diagnostic and excretory thoracentesis were performed by the pediatric surgeon. 350-400 cc of serohemorrhagic fluid were drained. TB-DNA PCR and pleural fluid culture were performed on the drained pleural fluid. On the thorax ultrasound X-ray taken on December 24, 2020, a pleural effusion with a thickness of 1.5 cm in the thickest part of the right hemithorax was observed. In the lung X-ray screening, the opacity in the right lung was resolved, and the sinuses were opened (Figure 3).

In the follow-ups, 8 mm thick pleural fluid was observed in the right hemithorax on thorax ultrasound radiography. The TB-DNA PCR screening test of the pleural fluid was positive. The culture of pleural fluid was negative for microbiological tests. The patient's medical history revealed no close contact with TB. It was thought that there might be TB activation after rituximab treatment. The patient consulted the pediatric infection unit, and anti-TB treatment was initiated according to recommendations with isoniazid, rifampicin, ethambutol, and pyrazinamide. Because rituximab could activate TB, instead of R-ICE, ICE treatment was preferred.

Discussion

Burkitt's lymphoma is the most aggressive form of NHL. The high proliferation rate is approximately 100% due to the doubling time in cells at 24 h and the presence of the celluler-MYC proto-oncogene, especially from cytogenetic-specific changes (8). Obstructive jaundice has been reported in some BL cases with pancreatic and hepatic lymph node involvement.

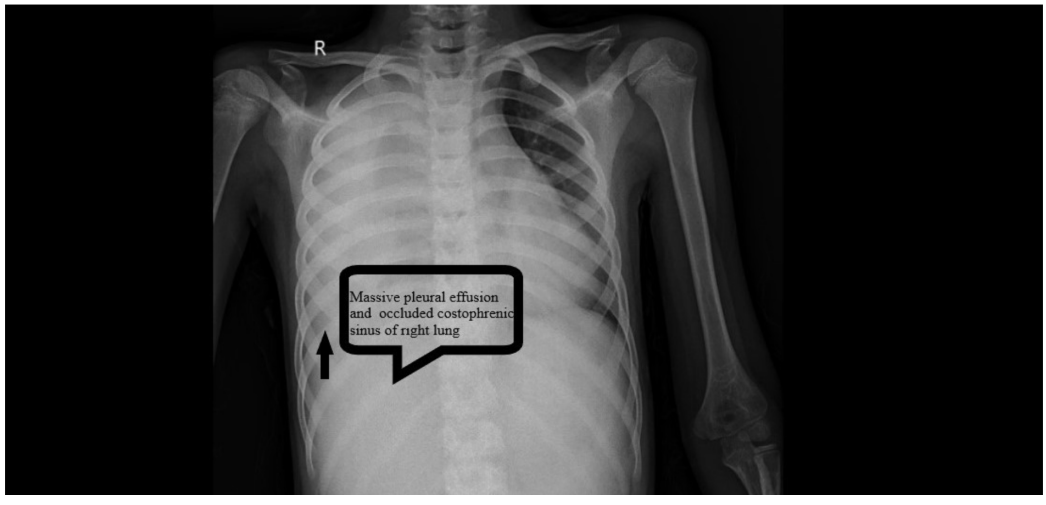

Figure 1. Widespread opacity consistent with pleural effusion was observed in the right lung. The right lung sinus is closed

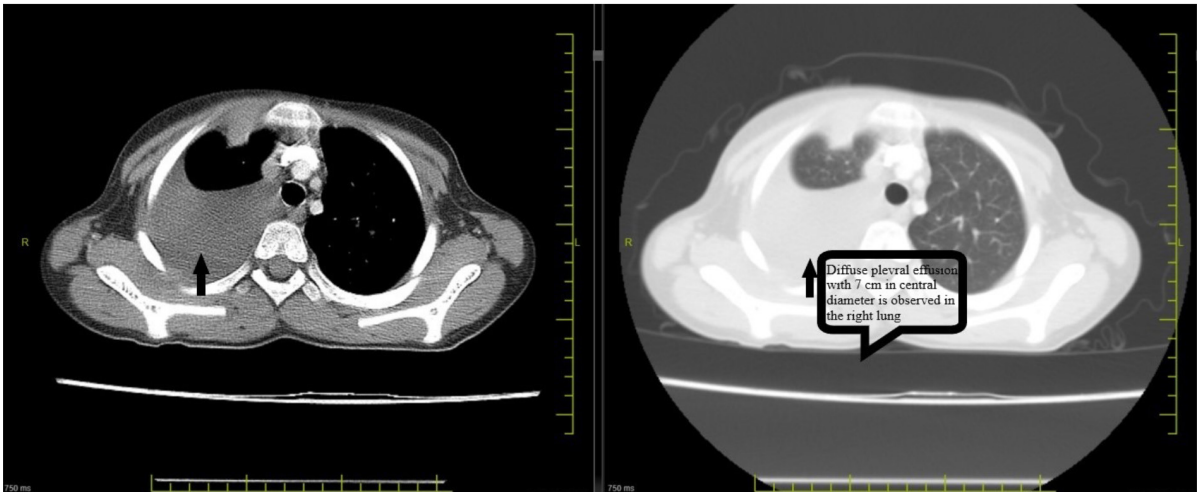

Figure 2. Computerized tomography image of the thorax with contrast. A diffuse pleural effusion with a central diameter of 7 cm is observed in the right lung

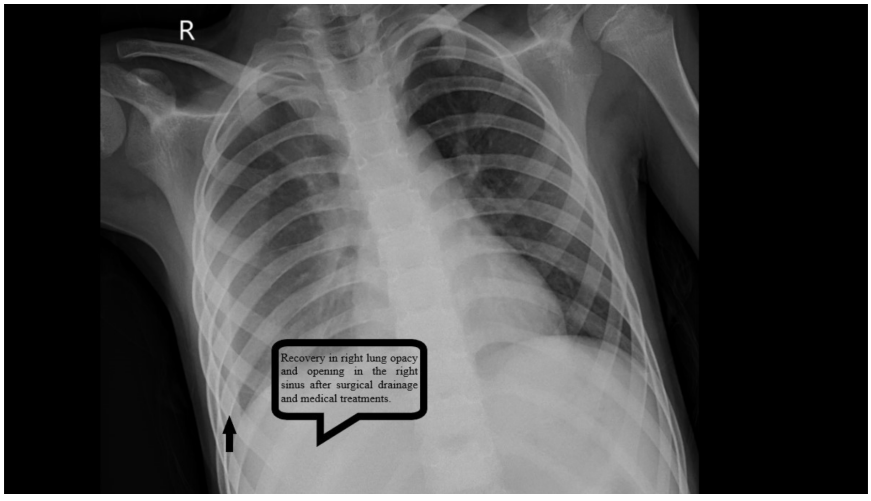

Figure 3. Recovery in right lung opacities and an opening in the right sinus are observed in X-ray screening of the lung after surgical drainage and medical treatments

Burkitt's lymphoma is classified as endemic (e.g., childhood type in Africa), sporadic (with AIDS), and subendemic. Endemic BL is a rapidly growing malignancy. The most common site of the disease is the face (primarily the mandible and often other facial bones), and 55-75% of patients have facial involvement. Involvement in the form of "bulky disease" is often seen in the abdomen.

Rituximab has shown efficacy in adults with B-cell cancers, including diffuse large B-cell lymphoma and BL, and is considered to be the standard of care in addition to chemotherapy in most patients with high-grade B-cell NHL.

Tuberculosis can affect pulmonary and extrapulmonary foci, and treatment and prognosis may vary according to the affected organ. Although TB pleurisy can generally be considered a form of extrapulmonary TB, it is common with pulmonary TB. The disease results from the opening of the subpleural caseous focus in the lung or the foci in the adjacent lymph node and bone to the pleura 6-12 weeks after the primary infection. It can be seen as a complication of primary pulmonary TB, with a rate of 2-38% (9).

Birlutiu et al. (10) reported a case of HIV-TB and BL with central nervous system involvement. This report is similar to our case; immunodeficiency conditions promote infections like TB.

In the Hu et al. (11) study, a 20-year-old female after kidney transplantation presented abdominal pain and multiple nodules throughout the body diagnosed on lung histopathology, and lung histopathology specimens tested positive for the *TB* gene. Additionally,

BL was diagnosed as metastatic after the completion of a liver and bone marrow biopsy. After diagnosis of TB, the patient received intensification of anti-tubercular therapy, and for BL, rituximab, cardioprotection, hepatoprotection, and alkalinization of urine were added. These data show us that, as in our case, TB can be provocative in BL patients, and immunomodulatory drugs can worsen it (11).

Gulleroglu et al. (12) retrospectively evaluated 78 pediatric renal transplant recipients for the occurrence of infectious disease. Eighteen transplant patients received rituximab therapy for various causes. The study revealed that rituximab treatment may be associated with a high risk of infectious disease (12). However, there is no other unique report in the literature of pediatric BL with TB pleurisy that is provoked by rituximab treatment of BL.

Conclusion

When pleural effusion develops in patients with BL under chemotherapy treatment, particularly rituksimab treatment, it should be kept in mind that TB may be present, and anti-TB treatment should be started as soon as the diagnosis is made. Drug interactions should also be considered while preparing the treatment protocol.

Ethics

Informed Consent: Consent for publication have been taken from the patients' parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.A.S., S.A., D.O.Y., O.T., A.A., Design: H.A.S., S.A., D.O.Y., O.T., A.A., Data Collection or Processing: H.A.S., S.A., D.O.Y., O.T., A.A., Analysis or Interpretation: H.A.S., S.A., D.O.Y., O.T., A.A., Literature Search: H.A.S., S.A., D.O.Y., O.T., A.A., Writing: H.A.S., S.A., D.O.Y., O.T., A.A.

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

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Erratum

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The changes made in the article titled "The Predictive Value of the Systemic Immune Inflammation Index for one-year Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Coronary Artery Disease" in the Original Research section published in HTB 2023;61(1) are as follows:

Page 103

The mistake and the correction of the aforementioned article have been demonstrated in the following list:
The expression of the title on page 103 of the article is written as follows inadvertently.

Published title;

The Predictive Value of the Systemic Immune Inflammation Index for one-year Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Coronary Artery Disease

Reported correction of the title;

The Predictive Value of the Systemic Immune Inflammation Index for one-year Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Coronary Artery Disease **who Underwent Carotid Stenting**