ISSN: 2619-9793 • E-ISSN: 2148-094X

istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 24 • ISSUE 4 • November 2023

Original Articles

istanbulmedicaljournal.org

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Publisher Certificate Number: 14521

Publication Date: November 2023
ISSN: 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published three times in a year.

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Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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İSTANBUL TIP DERGİSİ

CONTENTS

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İSTANBUL TIP DERGİSİ

CONTENTS

2023 Index

İstanbul Med J 2023; 24(4): 328-33
DOI: 10.4274/imj.galenos.2023.36360

Comparison of Post-Intensive Care Syndrome between Patients with and without COVID-19 who had Non-Invasive Mechanical Ventilation Support in the Intensive Care Unit

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ABSTRACT

Introduction: Post-intensive care syndrome (PICS) is defined as "new or deteriorating physical, cognitive, or mental health state after intensive care". This study compared patients with and without a diagnosis of coronavirus disease-2019 (COVID-19) who received non-invasive mechanical ventilation support in the intensive care unit and were monitored for the onset of PICS.

Methods: Retrospective imaging was performed on 50 COVID-positive and 50 non-COVID patients who were over 18 years of age and receiving non-invasive mechanical ventilation. The Mini Mental State test, Beck Depression test, Beck Anxiety test, and Post-Traumatic Stress Disorder test were administered to the patients to evaluate cognitive and psychiatric functioning after contacting them via the hospital system and obtaining the required consents.

Results: Patients with COVID had longer stays in the ICU ($p<0.001$). Patients with COVID were observed to have a more severe depression than patients without COVID ($p=0.019$). Patients with COVID had a higher percentage of moderate and severe anxiety than those without COVID ($p=0.003$). Patients with COVID had a greater incidence of PTSD ($p=0.025$). Although COVID patients were more likely to have severe cognitive dysfunction than non-COVID patients, the difference was not statistically significant ($p=0.184$). Physical dysfunction was significantly higher in the COVID group than in the non-COVID group ($p=0.019$). Longer stays in the ICU were found in patients who had PICS ($p=0.008$).

Conclusion: When we examined the patient groups with and without a diagnosis of COVID, we concluded that PICS is more prevalent among COVID patients receiving non-invasive mechanical ventilator support.

Keywords: Intensive care, anesthesia, COVID-19, post-intensive care syndrome

Introduction

It is now recognized that post-intensive care syndrome (PICS) can have harmful effects on patients' lives, particularly on health-related quality of life. The majority of clinicians who have studied the subject define "PICS" in the literature as "new or worsening physical, cognitive, or mental health state after intensive care" (1). Treatment and care for these patients continue even after discharge. On the other hand, PICS excludes patients with primary nerve injuries, such as traumatic brain damage or cerebrovascular accidents, who are admitted to the intensive care unit (2).

The risk factors associated with the formation of PICS are not well understood, and different studies have identified different risk variables. Risk factors can be broken down into two groups when looked at generally. The first category includes elements such as pre-existing neurological and neuromuscular conditions. The second is the presence of acute respiratory distress syndrome (ARDS), sepsis, dysglycemia, delirium, dose of sedative provided, and other significant comorbidities associated with the critical care unit (3).

In addition, because of improvements in medical technology, a larger percentage of patients are now being released from intensive care units. There are numerous comorbidities because of this growth. After a severe illness, 25% of survivors are believed to experience cognitive impairment on average. The most frequently reported psychiatric problems are Post-Traumatic Stress Disorder (PTSD), depression, and anxiety (4). Numerous PICS symptoms and indicators can linger for months, although healing is feasible (5). Therefore, it is crucial to diagnose PICS early in patients and begin appropriate therapy to lower mortality, morbidity, health care expenses, and workforce loss.

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Cite this article as: Onk D, Taş HG, Subaşı F, Karataş T, Kuyrukluyıldız U. Comparison of Post-Intensive Care Syndrome between Patients with and without COVID-19 who had Non-Invasive Mechanical Ventilation Support in the Intensive Care Unit. İstanbul Med J 2023; 24(4): 328-33.

Received: 11.08.2023
Accepted: 08.10.2023

The goal of this research was to compare the development of PICS in patients with and without a diagnosis of COVID-19 who were followed up with non-invasive mechanical ventilation support in the intensive care unit.

Methods

Following approval from the Erzincan Binali Yıldırım University Local Ethics Committee (approval number: 08/07, date: 21.06.2021), the files of 100 patients (50 COVID positive and 50 non-COVID), over the age of 18, who were followed up on and discharged from our anesthesiology and reanimation intensive care unit with non-invasive mechanical ventilation between April 1, 2020 and May 1, 2021 were retrospectively scanned. The patient files contained information regarding anamnesis, physical examination, length of stay in the intensive care unit, and treatment administered. This study excluded patients with traumatic brain injury, cerebrovascular disease, previous neuropsychiatric disease, and invasive mechanical ventilation support.

This manuscript adhere to the applicable STROBE guidelines. After contacting the patients via the hospital system and obtaining the necessary consents, the Mini Mental State test, Beck Depression test, Beck Anxiety test, and PTSD test were administered to the patients to assess cognitive and psychiatric dysfunction. A detailed history and physical examination were performed to assess physical dysfunction. Patients were asked if they had any limitations in their physical functions after being admitted to the intensive care unit. To assess this, we asked if there was a limitation in their effort capacity, fatigue, and activities that he could do previously, both inside and outside the home. The same researcher conducted all of these tests, and the physical examination and data collection. The test results were scored using the test result scales, and the data were recorded.

Statistical Analysis

For statistical analysis, IBM SPSS 22 (Armonk, NY: IBM Corp.) was used. Categorical variables are presented as numbers and percentages, while continuous variable descriptive statistics are presented as mean ± standard deviation or median (minimum-maximum) value. For categorical variable comparisons in the groups with and without COVID, the chi-square test was used. Depending on the distribution type, continuous variables were analyzed using the Student's t-test or the Mann-Whitney U test. In all statistical tests, cases with $p<0.05$ were considered significant.

Results

When the patients were examined, it was discovered that the average age was 61.1±18.1 (minimum: 20, maximum: 96). While the average age of COVID patients was 67.9±13.6 (minimum: 28, maximum: 96), the average age of non-COVID patients was 54.4±19.7 (minimum: 20, maximum: 94). The mean age of the groups differed statistically ($p<0.001$).

When the length of stay in the ICU was examined, the median length of stay in COVID patients was 6.5 days (2-22); the median length of stay in non-COVID patients was 4 days (2-15). The length of stay in the ICU was longer in COVID patients ($p=0.001$).

It was discovered that 37 of 100 patients did not suffer from depression. Mild depression was observed in 21 people, moderate depression in 39 people, and severe depression in three people. Anxiety was absent in 35 patients, mild in 19, moderate in 40, and severe in 6. In 59 patients, PTSD was found. In 50 patients, cognitive functions were normal. Mild cognitive dysfunction was in 32 patients, moderate cognitive dysfunction in 14 patients, and severe cognitive dysfunction in 4 patients. In 65 of 100 patients, post-ICU syndrome was present.

Depression was not observed in 26% of COVID patients. Mild depression was found in 24% of the participants, moderate depression in 44%, and severe depression in 6%. Depression was not observed in 48% of non-COVID patients, whereas 18% had mild depression and 34% had moderate depression. Non-COVID patients did not have severe depression. Depression was found to be more severe in COVID patients than in non-COVID patients ($p=0.019$) (Table 1, Figure 1).

Anxiety was absent in 22% of COVID patients. Anxiety was mild in 16%, moderate in 50%, and severe in 12% of the participants. While 48% of non-COVID patients do not have anxiety, 22% have mild anxiety, and 30% have moderate anxiety, these patients do not have severe anxiety. When the anxiety levels in the groups were compared, it was discovered

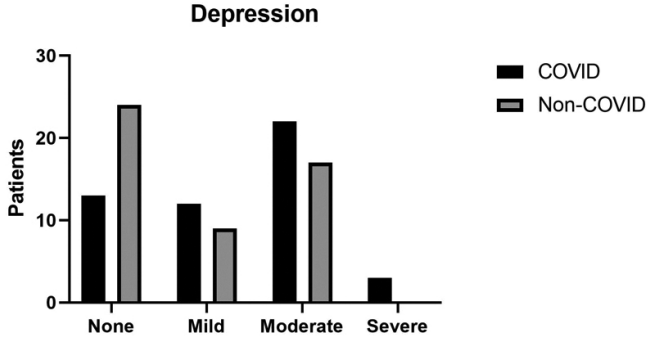

Figure 1. Depression levels in the COVID and non-COVID groups
COVID: Coronavirus disease

Table 1. Depression distribution of the COVID and non-COVID groups

	Depression (n)				
	None	Mild	Moderate	Severe	Total
COVID	13	12	22	3	50
Non-COVID	24	9	17	0	50
Total	37	21	39	3	100

COVID: Coronavirus disease

that patients with COVID had a higher proportion of moderate and severe anxiety than those without COVID (p=0.003) (Table 2, Figure 2).

While the rate of PTSD was found to be 70% in those with COVID, it was 48% in those without COVID. COVID patients had a higher rate of PTSD (p=0.025) (Table 3, Figure 3).

Normal cognitive function was present in 44% of COVID patients, whereas mild cognitive dysfunction was present in 34%, moderate cognitive dysfunction in 14%, and severe cognitive dysfunction in 8% of patients. Patients with normal cognitive function comprised 56% of non-COVID patients, whereas those with mild and severe cognitive impairment comprised 30% and 14%, respectively. In these patients, no serious cognitive dysfunction was observed. Although COVID patients were more likely than non-COVID patients to experience severe cognitive dysfunction, the difference was not statistically significant (p=0.184) (Table 4, Figure 4).

Physical dysfunction was not found in 67 patients; however, it was found in 33. Physical dysfunction was found in 44% of COVID patients but only in 22% of non-COVID patients. The COVID group was shown to have statistically considerably a more physical dysfunction than the non-COVID group (p=0.019).

In those with COVID, the rate of PICS formation was 78%, compared with 52% in people without COVID. Patients with COVID showed a higher percentage of PICS development (p=0.006). The mean age was 44.8±15.2 in patients who did not develop PICS, compared to 69.9±12.8 in people who did. In patients who had PICS, the mean age was greater (p<0.001). Patients with PICS were reported to have a median length of stay in the ICU of 6 days (2-22), compared with 3 days for patients without PICS (2-15). Patients who acquired PICS were observed to have longer stays in the ICU (p=0.008) (Table 5, Figure 5).

Discussion

In this study, patients with COVID had a PICS formation rate of 78%, compared with 52% in the non-COVID patient group. While patients who acquired PICS were found to have a higher mean age, they were also found to have longer stays in the ICU. It was discovered that patients diagnosed with COVID had greater rates of depression, anxiety, PTSD,

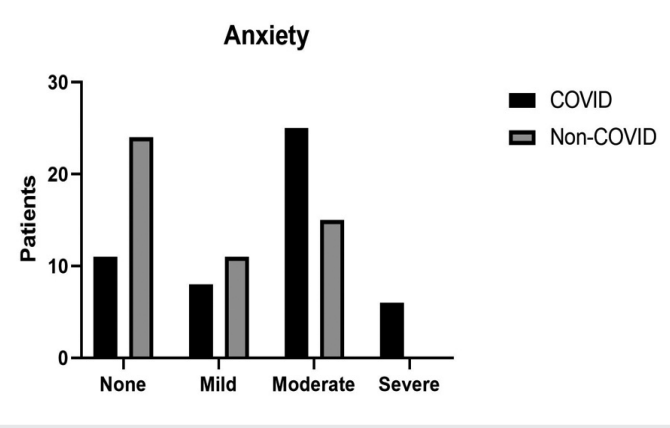

Figure 2. Anxiety levels in the COVID and non-COVID groups
COVID: Coronavirus disease

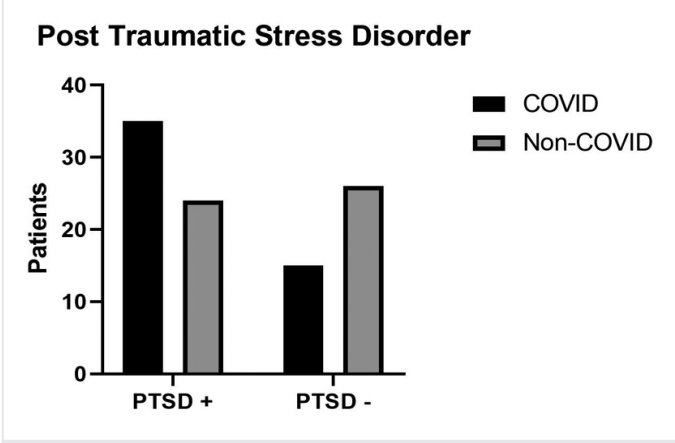

Figure 3. Post-Traumatic Stress Disorder levels in the COVID and non-COVID groups
COVID: Coronavirus disease

Table 2. Anxiety distribution of the COVID and non-COVID groups

	Anxiety (n)				
	None	Mild	Moderate	Severe	Total
COVID	11	8	25	6	50
Non-COVID	24	11	15	0	50
Total	35	19	40	6	100

COVID: Coronavirus disease

Table 3. Post-Traumatic Stress Disorder distribution of the COVID and non-COVID groups

	Post-Traumatic Stress Disorder (n)		
	Positive	Negative	Total
COVID	35	15	50
Non-COVID	24	26	50
Total	59	41	100

COVID: Coronavirus disease

Table 4. Cognitive dysfunction distribution of the COVID and non-COVID groups

	Cognitive dysfunction (n)				
	None	Mild	Moderate	Severe	Total
COVID	22	17	7	4	50
Non-COVID	28	15	7	0	50
Total	50	32	14	4	100

COVID: Coronavirus disease

Table 5. Post-intensive care syndrome distribution of the COVID and non-COVID groups

	Post-intensive care syndrome (n)		
	Positive	Negative	Total
COVID	11	39	50
Non-COVID	24	26	50
Total	35	65	100

COVID: Coronavirus disease

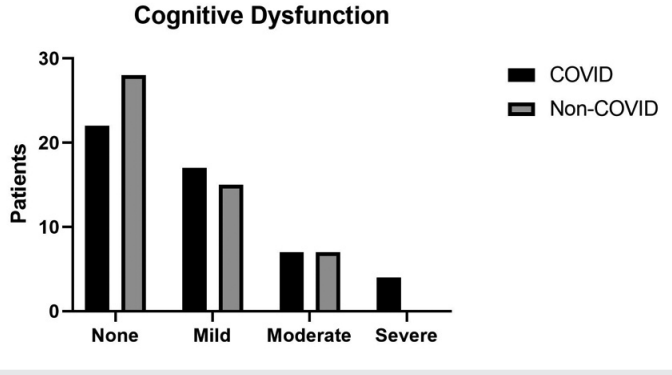

Figure 4. Cognitive dysfunction levels in the COVID and non-COVID groups
COVID: Coronavirus disease

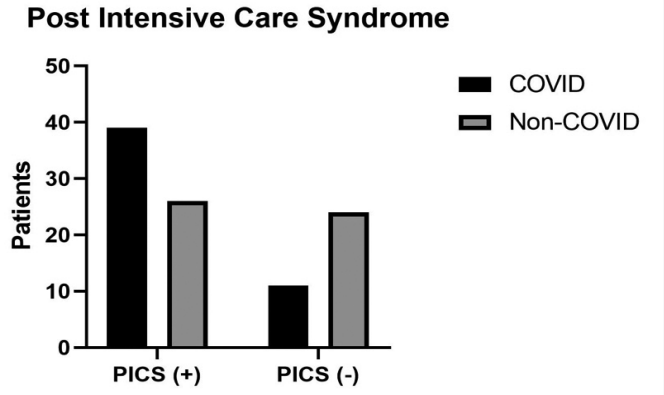

Figure 5. Post-intensive care syndrome levels in the COVID and non-COVID groups
COVID: Coronavirus disease

and cognitive dysfunction. Similar to PICS, individuals with a diagnosis of COVID had a higher mean age and longer stays in the intensive care unit.

According to our analysis of the literature, investigations on PICS are typically published as review articles. In addition, it is notable that the few studies that have looked into the connection between COVID and PICS have all focused on COVID patients who have been intubated and are mechanically ventilated (6,7). The non-invasive ventilated patient population in the intensive care unit is the subject of our study, which is the first of its kind.

Patients with cognitive dysfunction have issues such as trouble concentrating, difficulties focusing, forgetfulness, a loss of problem-solving skills, an inability to articulate oneself properly, and irregularity in performing obligations. This circumstance produces significant issues and disturbances in the patient's entire life, particularly in their post-discharge professional lives (8). According to previous studies, cognitive dysfunction increases the risk of delirium in the intensive care unit. In a different study, patients who were being released from the intensive care unit had delirium between 30% and 80% of the time. In addition to delirium, other issues that could have been discovered before admission to intensive care include hypoglycemia, illiteracy, and low IQ (9). Those with COVID were more likely to have cognitive dysfunction and severe cognitive dysfunction than those without COVID.

We discovered that individuals with COVID had higher rates of depression, but patients without COVID never experienced severe depression. Similarly, patients with a diagnosis of COVID had higher rates of PTSD diagnosis. The general consensus is that a young age, traumatic experience in the intensive care unit, exposure to sedative hypnotics, and intensive care-related psychiatric disorders are also associated with anxiety, depression, and PTSD (4,10-13). Anxiety and loneliness are followed by PTSD, according to a multicenter British study (14). Similar to this, having terrible memories while in the intensive care unit, being sedated for a long time, taking an opiate, having nightmares, and feeling like you can't breathe all increase the risk of developing PTSD (15-17).

In patients diagnosed with COVID, psychiatric symptoms are more prevalent in the older age group, according to our analysis of the study's data. We believe that COVID is to blame for this outcome. When the literature is searched, it is discovered that mechanical ventilator support

is connected to psychological disorders, the majority of which are brought on by depression and anxiety (11). According to a nationwide database registry of more than 24,000 patients on mechanical ventilation, 1% of patients had recently been diagnosed with a psychiatric condition (most commonly anxiety and depression), and 19% were taking psychoactive medications.

In-depth analysis of PICS revealed that risk factors for the condition include neuromuscular disorders, cognitive decline, psychiatric disorders, comorbid ailments, functional regression, mechanical ventilation, severe delirium, sepsis, and ARDS. Due to socioeconomic variables such as poor care and follow-up and the onset of dementia in these individuals, PICS is known to be more prevalent, particularly in older people (18). Parallel to these results, we also found that COVID and PICS are more prevalent in older people.

On the other hand, immobility and social isolation time increase with the length of hospital stay. According to the results of our investigation, PICS incidence increases with patient duration of stay.

Muscle weakness, weight loss, insomnia, anorexia, respiratory problems, and being unable to get up or walk far in the hallway are all signs of physical dysfunction. Another sign is dysphagia (19). Physical dysfunction can make it difficult for patients to go about their daily lives and may even require regular pharmacological therapy. In this study, we analyzed patients who received non-invasive mechanical ventilator support and found that the COVID patient group had a higher prevalence of physical impairment.

Study Limitations

There are some limitations to our study. In our single-center study, the number of patients was limited by the number of admissions. A larger study by performing power analysis can provide more accurate results.

Conclusion

We believe that patients who receive noninvasive mechanical ventilation assistance, those who are intubated and monitored while sedated, and those who receive mechanical ventilator support all fall into the category of patients who are at risk for developing PICS. We believe that PICS is more common in COVID patients receiving noninvasive mechanical ventilator support when we compare the patient group with a diagnosis of COVID with the patient group without a diagnosis of COVID.

Acknowledgments: The generous assistance and direction provided to the researchers at each stage of the study is applauded. The participants in this study who were actively engaged are acknowledged and thanked by the researchers.

Ethics Committee Approval: The study was approved by the Erzincan Binali Yıldırım University Ethics Committee (approval number: 08/07, date: 21.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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Supplement Link: http://glns.co/vr9ph

İstanbul Med J 2023; 24(4): 334-9
DOI: 10.4274/imj.galenos.2023.59908

The Role of Interleukin-20 in Paclitaxel-Associated Peripheral Neuropathy in Non-Metastatic Breast Cancer Patients Receiving Chemotherapy

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ABSTRACT

Introduction: This study investigated the relationship between serum interleukin-20 (IL-20) levels and paclitaxel-associated neuropathy in patients with non-metastatic breast cancer. Paclitaxel-induced peripheral neuropathy (PIPN) is a significant side effect of paclitaxel chemotherapy, and the exact mechanism underlying PIPN is not fully understood.

Methods: This prospective observational study was conducted with non-metastatic breast cancer patients between January 2022 and November 2022. Neuropathy symptoms were evaluated using the QLQ-CIPN20 questionnaire, and serum IL-20 levels were measured at three time points: before chemotherapy, on the 7th day after the first paclitaxel treatment, and after the last treatment. Univariate and multivariate logistic regression analyses were performed to identify factors predicting PIPN.

Results: This study was completed with 59 female patients. During the study, 47 patients (79.6%) reported any degree of neuropathy, whereas 12 patients (20.4%) had no neuropathy. Univariate analysis to predict neuropathy measured on day 7 after first paclitaxel administration demonstrated that age, body mass index, 7th-day serum IL-20 level, and last cycle serum IL-20 level were predictive for PIPN.

Conclusion: This study demonstrated the relationship between serum IL-20 levels and paclitaxel-related neuropathy in breast cancer patients. Further research targeting the function of IL-20 is needed to investigate potential strategies to prevent and treat PIPN.

Keywords: Paclitaxel, peripheral neuropathy, breast cancer, IL-20, QLQ-CIPN20

Introduction

Paclitaxel is a microtubule-stabilizing agent that has significant therapeutic utility for treating many cancers, including breast cancer. Paclitaxel-induced peripheral neuropathy (PIPN) is a dose-limiting side effect of paclitaxel that could require discontinuation of treatment, and the mechanism has not been fully explained. In clinical practice, PIPN can occur over a period of a few days to several months and mostly causes peripheral sensory neuropathy as well as motor and autonomic neuropathy (1,2). Although the cumulative dose of paclitaxel appears to be the most associated factor with neuropathy, factors such as concomitant medications, comorbidities, older age, and vitamin D levels are also important because PIPN can occur even after the first cycle (3,4).

Many animal studies have shown that the possible neuropathy mechanism induced by paclitaxel includes inflammation, oxidative stress, loss of epidermal nerve fibers, alterations of mitochondrial function, and excitability of neurons, which cause damage to peripheral neurons and the dorsal root ganglion (5-7). Immune upregulation (inducing overexpression of mRNA coding for cytokines such as tumor necrosis factor-alpha, interleukin 1beta (IL-1β), IL-6, CGRP, and substance P) after paclitaxel administration has been shown in previous studies to play an important role in the modulation of cell death (8-10). IL-20 is a proinflammatory and chemoattractant mediator involved in augmenting proinflammatory substances such as IL-6, IL-1, and macrophage inflammatory proteins-1 in astrocytes, monocytes, and epithelial cells (11,12). Previous studies have suggested that IL-20 may function as a proinflammatory mediator in the development of PIPN (13).

In this study, we investigated the relationship between serum IL-20 levels and paclitaxel-related neuropathy.

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Cite this article as: Karaboyun K, Çavdar E, İriağaç Y, Yılmaz A, Çelikkol A, Avcı O, Şeber ES. The Role of Interleukin-20 in Paclitaxel-Associated Peripheral Neuropathy in Non-Metastatic Breast Cancer Patients Receiving Chemotherapy. İstanbul Med J 2023; 24(4): 334-9.

Received: 27.09.2023
Accepted: 13.10.2023

Methods

Patients

In this prospective observational study, eligible patients were aged >18 years, with histologically proven breast cancer, and planned (adjuvant or neoadjuvant) to receive 4 cycles of epirubicin plus cyclophosphamide and then weekly paclitaxel (80 mg/m^2 x12 cycles). Patients with human epidermal growth receptor-2 (HER2) expression received HER2-directed therapy concurrently (trastuzumab, 17 cycles of neoadjuvant and/or adjuvant; if pertuzumab received, only 4 cycles in the NACT period). Patients with a prior history of peripheral neuropathy or diabetes mellitus and those with advanced -stage breast cancer were excluded from the study.

In this study, a total of 115 non-metastatic breast cancer patients receiving adjuvant or neoadjuvant chemotherapy between January 2022 and November 2022 were evaluated. Of the 115 patients, 15 patients with diabetes mellitus or preexisting peripheral neuropathy and 39 patients scheduled to receive docetaxel as a taxane were excluded from the study. Patients who had to discontinue treatment because of neuropathy were also excluded from the study. The study was eventually conducted with 59 eligible patients (Figure 1). The study was approved by the Namık Kemal University Local Ethical Committee under the Helsinki Declaration (approval number: 2021.264.11.08, date: 30.11.2021), and informed consent was obtained from all participants. This study was registered on clinicaltrials.gov under NCT05622617.

Questionnaire

Neuropathy symptoms were evaluated with the patients-reported EORTC chemotherapy-induced peripheral neuropathy questionnaire (QLQ-CIPN20) on the 7th day after the first paclitaxel administration and at the last administration of the treatment (Figure 1). QLQ-CIPN20 contains three types of neuropathy: sensory, motor, and autonomic, and consists of 20 questions scaled each 1 to 4 points (1, not at all; 4, very much). Each question is scored, and the sum of the scores ranges between 20 and 80. Because only female patients were recruited for the study, the question regarding autonomic dysfunction (erectile dysfunction) was omitted. Patients were divided into two groups: if patients rated any question as 2, 3 or 4 points, they were assumed to have neuropathy; if they rated all questions as 1 point, they were assumed to have no neuropathy. The Turkish Validation of QLQ-CIPN20 was used in this study.

Measuring Serum IL-20 Levels

Serum IL-20 levels were measured at three time points. Initial IL-20 measurement was performed before chemotherapy. The second IL-20 measurement time point was on the 7th day after the first paclitaxel treatment, and the third measurement time point was after the last paclitaxel treatment (Figure 1).

Serum IL-20 levels were measured by ELISA analysis method. Bio-Techne (R&D SYSTEM Inc., Bio-Techne Corporation Brands, Minneapolis, USA) commercial ELISA kit (catalog no: DL200) of 96 tests was used for this measurement. Blood samples of the subjects included in the study were collected in a red-capped gel tube. These blood tubes were centrifuged at 4000 rpm (revolutions per minute) for 10 min and, the separated serum samples were divided into microcentrifuge tubes and labeled. Collected samples were stored at -80 °C until the day of analysis.

Statistical Analysis

Data were analyzed using SPSS version 26. Descriptive statistics and frequency distributions were calculated for the clinicopathological characteristics of patients. Differences between neuropathy and laboratory, clinical, and pathologic characteristics of patients were evaluated using Independent sample t-tests, chi-square analyses, or Mann-Whitney U tests. Receiver operating characteristic analysis was used to calculate the ideal cut-off value for predicting neuropathy. Logistic regression models, including univariate and multivariate analyses, were established to identify predictors of PIPN. A P-value of ≤0.05 was considered statistically significant.

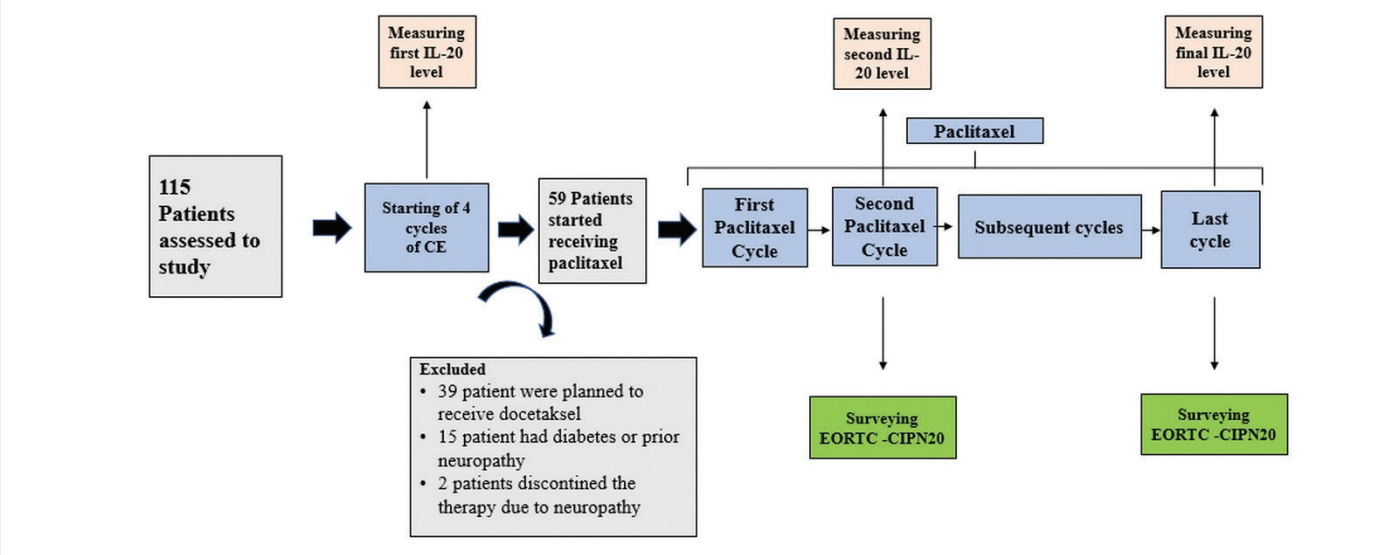

Figure 1. Study flow diagram

IL-20: Interleukin-20, EORTC: European Organization for Research and Treatment of Cancer, CIPN20: Chemotherapy-Induced Peripheral Neuropathy 20-item scale

Results

Fifty-nine female patients with a median age of 52.9 (33-78) years were included in this study. During the study, 47 patients (79.6%) reported any degree of neuropathy, whereas 12 patients (20.4%) had no neuropathy. On the 7th day after the first administration of paclitaxel, a rating score of 2, 3, or 4, which indicates the development of neuropathy, by patients for any of the questions in the QLQ-CIPN20 questionnaire was seen in 38.9% (n=23) patients (Table 1).

In the analysis of factors associated with neuropathy, serum IL-20 levels measured on day 7 (p=0.022), and last cycle serum IL-20 level (p=0.010) were statistically significant regarding the development of neuropathy. The serum IL-20 levels measured on day 7 and on the last cycle day were significantly higher in patients who developed neuropathy on day 7. There were no relationships between neuropathy and, chemotherapy type, estrogen receptor (ER) status, progesterone receptor (PR) status (p=0.670), HER2 expression, tumor size, first IL-20 level, and last serum IL-20 level (Table 1).

In the analysis of the relationship between the 7th-day serum IL-20 level and clinicopathological factors, a significant relationship was observed with the type of chemotherapy. The 7th-day serum IL-20 level was significantly higher in patients receiving adjuvant chemotherapy than in those receiving neoadjuvant settings (p=0.032). No significant difference was observed between the second serum IL-20 level and the following: age, body mass index (BMI), ER status, PR status, HER2 expression, Ki-67 level, and tumor size (Table 2).

Univariate and Multivariate Analyses

Univariate analysis to predict neuropathy measured on day 7 after first paclitaxel administration demonstrated that age [odds ratio (OR): 4.58,

Table 1. Relationship between patient' characteristics and neuropathy (n=59)

Variable	7th day survey after the first paclitaxel			During the entire study		
	Neuropathy, yes (n=23)	Neuropathy, no (n=36)	p	Neuropathy, yes (n=47)	Neuropathy, no (n=12)	p
Age	56.29±4.99*	52.46±11.51*	0.062	50.08±2.86*	53.63±1.64*	0.428
BMI	31.29±1.88*	27.99±0.77*	0.077	28.80±0.81*	26.75±1.55*	0.101
Chemotherapy types						
Adjuvant	2 (8.3%)	22 (91.7%)	0.689	19 (79.2%)	5 (20.8%)	0.594
Neoadjuvant	5 (14.3%)	30 (85.7%)		28 (80%)	7 (20%)	
Estrogen receptor						
Positive	4 (9.5%)	38 (90.5%)	0.399	35 (83.3%)	7 (16.7%)	0.299
Negative	3 (17.6%)	14 (82.4%)		12 (70.6%)	5 (29.4%)	
Progesteron receptor						
Positive	4 (10%)	36 (90%)	0.670	32 (80%)	8 (20%)	0.590
Negative	3 (15.8%)	16 (84.2%)		15 (78.9%)	4 (21.1%)	
HER2 status						
Positive	2 (9.5%)	19 (90.5%)	0.516	16 (76.2%)	5 (23.8%)	0.431
Negative	5 (13.2%)	33 (86.8)		31 (71.8%)	7 (18.2%)	
Ki67						
<18	1 (10%)	9 (90%)	0.662	8 (80%)	2 (20%)	0.673
≥18	43 (87.8)	6 (12.2%)		39 (79.6%)	10 (20.4%)	
Tumor size						
≤2 cm	4 (12.1%)	29 (87.9%)	0.635	26 (78.8%)	7 (21.2%)	0.851
>2 cm	3 (11.5%)	23 (88.5%)		21 (80.8%)	5 (19.2%)	
Labaratory paramaters						
White blood cell (10^3/uL)	6.69±2.01*	6.63±1.75*	0.851	6.67±0.27*	6.64±0.41*	0.814
Neutrophil (10^3/uL)	3.71±1.22*	4.07±1.56*	0.582	4.00±0.23*	4.22±0.37*	0.423
Lymphocyte (10^3/ uL)	2.31±0.78*	1.84±0.58*	0.056	1.93±0.08*	1.72±0.21*	0.292
Platelet count (10^3/uL)	259.4±92.9*	279.9±68.6*	0.512	279.1±10.8*	265.7±14.7*	0.553
Hemoglobin (g/dL)	12.31±0.79*	12.16±1.14*	0.618	12.15±0.16	12.33±0.38*	0.564
NLR	1.67±0.46*	2.31±1.23*	0.134	2.18±0.18	2.43±0.26*	0.69
Serum IL-20 levels						
Initial serum IL-20 level	116.62±33.19*	101.41±27.84*	0.289	103.90±4.11	100.90±10.32*	0.194
7th-day serum IL-20 level	134.78±43.97*	107.50±31.20*	0.022	109.95±5.04	114.82±10.64*	0.684
Last cycle serum IL-20 level	134.82±58.55*	104.70±39.09*	0.010	109.79±6.67	103.03±9.10*	0.969

*: Mean ± standart deviation, BMI: Body mass index, HER2: Human epidermal growth receptor-2, NLR: Neutrophil to lymphocyte ratio, IL-20: Interleukin-20

confidence interval (CI): 95%, 1.38-15.20, p=0.013], BMI (OR: 3.21, CI: 95%, 1.03-9.98, p=0.034), Lymphocyte count (OR: 8.33, CI: 95%, 1.43-48.54, p=0.018), 7th-day serum IL-20 level (OR: 10.42, CI: 95%, 1.17-93.20, p=0.036), and last cycle serum IL-20 level (OR: 4.58, CI: 95%, 1.38-15.20, p=0.013) were predictive for PIPN. In the multivariate regression model including predictive markers, age (OR: 3.45, CI: 95%, 0.93-12.80, p=0.064), lymphocyte count (OR: 4.16, CI: 95%, 1.10-15.74, p=0.036), and last cycle serum IL-20 level (OR: 4.79, CI: 95%, 1.24-18.46, p=0.023) were found to be independent predictors for PIPN (Table 3).

Discussion

In this study, we addressed PIPN, a dose-limiting side effect of paclitaxel chemotherapy that is a substantial component of breast cancer treatment management, which can jeopardize breast cancer treatment and quality of life of breast cancer patients. Univariate regression analysis revealed that PIPN detected on day 7 after the first paclitaxel cycle was associated with increased day 7 serum IL-20 levels and last cycle serum IL-20 levels as well as age, lymphocyte count, and BMI. A multivariate regression model investigating PIPN detected on day 7 showed age, lymphocyte count, and last cycle serum IL-20 levels as independent predictors of neuropathy.

The 2012 Early Breast Cancer Trialists' Collaborative Group meta-analysis showed that anthracycline plus taxane chemotherapy resulted in better progression-free survival and overall survival than CMF, which was the standard treatment at that time (14). Since then, taxanes have been an integral component of the management of early or locally advanced breast cancer. However, despite its strong survival effect, taxane-induced neuropathy is an important limiting factor. This may cause patients to discontinue chemotherapy, affect their quality of life, and lead to chronic neuropathic diseases. In our study, 47 patients (79.6%) reported any degree of neuropathy, and two patients who were receiving chemotherapy in neoadjuvant settings discontinued treatment because of peripheral neuropathy and were referred for surgery.

In a study that included female patients receiving paclitaxel as adjuvant therapy, neuropathy started within the first week of paclitaxel treatment, whereas PIPN according to CTCAE v3.0 was observed in 97% of patients during 57 months of long follow-up (15). In another prospective study evaluating patients receiving paclitaxel with QLQ-CIPN-20, neuropathy was observed in 76 of 85 patients (16). In our study, 79.6% of patients developed paclitaxel-associated neuropathy during follow-up, as measured by QLQ-CIPN20. In Chen et al. (13) study, serum IL-20 samples obtained in the first week serially from patients receiving paclitaxel for gynecological cancers showed a positive correlation with patients who developed neuropathy as assessed by QLQ-CIPN-20. They also reported that they regressed paclitaxel-associated neuropathy with IL-20-targeting antibodies in a mouse model (13). Another study in the

Table 2. Analysis of clinicopathologic factors related to 7th-day serum IL-20 levels

Variable	Mean ± SD	Range	p
Age			
≥53	110.67±33.30	60.84-231.90	0.531
<53	105.94±38.69	32.23-177.81	
BMI			
<25	112.38±35.00	68.15-177.81	0.862
≥25	107.09±36.01	32.23-231.90	
Chemotherapy types			
Adjuvant	121.22±43.06	32.23-231.90	**0.032**
Neoadjuvant	99.60±26.34	52.87-177.81	
Estrogen receptor			
Positive	110.11±39.52	32.23-231.90	0.896
Negative	104.47±22.71	74.97-150.49	
Progesteron receptor			
Positive	111.35±40.43	32.23-231.90	0.613
Negative	102.79±22.44	60.84-150.49	
HER2 status			
Positive	103.39±45.91	32.23-231.90	0.147
Negative	111.48±28.42	68.15-177.81	
Ki67			
≤18	121.88±30.34	74.97-170.30	0.143
>18	105.77±36.23	32.23-231.90	
Tumor size			
≤2 cm	108.45±41.52	32.23-231.90	0.626
>2 cm	108.67±26.58	60.84-177.81	

IL-20: Interleukin-20, SD: Standard deviation, BMI: Body mass index, HER2: Human epidermal growth receptor-2

Table 3. Univariate and multivariate analysis to predict neuropathy measured on day 7 after the first paclitaxel

		Univariate analysis		Multivariate analysis	
Variables	**Category**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p****
Age	<58.5 vs. >58.5*	4.58 (1.38-15.20)	**0.013**	3.45 (0.93-12.80)	**0.064**
BMI	<30 vs. >30*	3.21(1.03-9.98)	**0.034**		
Chemotherapy types	Adjuvant vs. neoadjuvant	1.83 (0.33-10.34)	0.492		
Estrogen receptor	Positive vs. negative	0.49 (0.98-2.48)	0.389		
Progesteron receptor	Positive vs. negative	0.59 (0.12-2.96)	0.524		
HER2	Positive vs. negative	0.70 (0.12-3.94)	0.681		
Ki67	Low vs. high	1.01 (0.98-1.05)	0.477		
Tumor size	≤2 cm vs. >2 cm	0.28 (0.04-1.73)	0.169		
Labaratory paramaters					
White blood cell (10^3/uL)	<6600 vs. >6600	1.20 (0.24-5.93)	0.823		
Neutrophil (10^3/uL)	<4050 vs. >4050	0.27 (0.03-2.38)	0.237		
Lymphocyte (10^3/uL)	>2.2 vs. <2.2*	8.33 (1.43-48.54)	**0.018**	4.16 (1.10-15.74)	**0.036**
Platelet count (10^3/uL)	>276 vs. <276	0.95 (0.19-4.66)	0.512		
Hemoglobin (g/dL)	>12 vs. <12	2.91 (0.33-26.17)	0.340		
NLR	>2.23 vs. <2.23	0.18 (0.02-1.60)	0.124		
Serum IL-20 levels					
Initial serum IL-20 level	>101.57 vs. <102.57	2.52 (0.51-12.50)	0.259		
7^{th}-day serum IL-20 level	>111.40 vs. <111.40*	10.42 (1.17-93.20)	**0.036**		
Last cycle serum IL-20 level	>126.44 vs. <126.44*	4.58 (1.38-15.20)	**0.013**	4.79 (1.24-18.46)	**0.023**

*The ideal cut-off value was calculated by the ROC curve, **Forward LR method was used, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, HER2: Human epidermal growth receptor-2, NLR: Neutrophil to lymphocyte ratio, IL-20: Interleukin-20

literature investigating paclitaxel neuropathy using the QLQ-CIPN-20 questionnaire showed that the highest neuropathy score was observed in the first 7 days after the first cycle of paclitaxel. Higher pain scores in the first chemotherapy cycle did not predict higher neuropathy scores in subsequent cycles (17). In accordance with the hypothesis of our study, IL-20 increases with paclitaxel administration and may contribute to the development of neuropathy by probably regulating chemoattractants. The fact that serum IL-20 measured before paclitaxel treatment was not associated with neuropathy and that IL-20 measured on day 7 after treatment and the last cycle of paclitaxel treatment was associated with neuropathy suggests that IL-20 may be one of the mediators contributing to the development of PIPN.

The association of PIPN with older age, lymphocyte count, and BMI in our study is consistent with the studies investigating PIPN in the literature. Ghoreishi et al. (18) showed that age, BMI, and PR positivity were predictive of PIPN in their study investigating PIPN in 56 breast cancer patients receiving paclitaxel. In another study exploring chemotherapy-associated neuropathy in patients who had received cisplatin or paclitaxel, older age was found to be predictive for chemotherapy-associated neuropathy (19). Mizrahi et al. (20) demonstrated that patients receiving paclitaxel or oxaliplatin, low hemoglobin before treatment, high body mass index, advanced age, and female gender were more likely to develop paclitaxel- or oxaliplatin-induced CIPN after treatment. It is very valuable for clinicians to identify markers that predict PIPN. In this study, we identified predictive markers in a well-selected (excluding diseases that may cause neuropathy) patient population with early-stage breast cancer. However, nevertheless, the key significance of this study is the insight into the relationship between IL-20 and PIPN, which can be an important marker in the future for the prevention or treatment of neuropathy.

Although the exact mechanism of paclitaxel-induced neuropathy is not clearly understood, treatments for possible causes have been investigated. Several studies have reported that approved therapies such as duloxetine, melatonin, minoxidil, N-acetylcysteine, or statins may diminish PIPN because of their anti-inflammatory, anti-oxidative, or neuroprotective effects (21-23). However, these studies appear to be experimental and mostly empirically applied treatments, and these treatments do not provide a standard treatment approach to prevent or treat PIPN. Moreover, studies with other and/or the same medications with similar mechanisms have shown that these agents do not prevent or reduce PIPN (24-26). These findings suggest that a lack of a clear understanding of the pathophysiology of paclitaxel-associated neuropathy makes an effective prevention or treatment option impossible. The association between neuropathy and IL-20 obtained from our study can be interpreted as the detection of an amplifier signal that triggers multiple mechanisms in the pathogenesis of the disease and may be the target of future therapies.

Study Limitations

This study is not without limitations. First, although the QLQ-CIPN-20 is a questionnaire with high sensitivity and specificity for neuropathy, it includes subjective assessment because it is self-administered. Second, the fact that IL-20 level measurement and neuropathy questionnaire could not be performed in every paclitaxel cycle is an important

limitation. In addition, the lack of long-term follow-up neuropathy results on the patients is another limitation. The lack of long-term follow-up neuropathy results in the patients and small population are other limitations. The strength of our study is its prospective design and the exclusion of patients with neuropathy and those with diseases that may affect neuropathy, such as diabetes.

Conclusion

In conclusion, with this study, we showed that age, BMI, and lymphocyte count may be predictors for the development of PIPN in patients receiving paclitaxel with curative intent for treating breast cancer. We also demonstrated the relationship between IL-20 and the pathophysiology of paclitaxel-associated neuropathy for treating breast cancer. Future studies targeting the significance of IL-20 in the development of neuropathy are needed to prevent and treat neuropathy in larger patient populations.

Ethics Committee Approval: The study was approved by the Namık Kemal University Local Ethical Committee under the Helsinki Declaration (approval number: 2021.264.11.08, date: 30.11.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - K.K., E.Ç., O.A.; Design - Y.İ., A.Y., A.Ç.; Data Collection or Processing - K.K., E.Ç.; Analysis or Interpretation - E.Ç., O.A.; Literature Search - E.Ç., O.A.; Writing - K.K., E.S.S.

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

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

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İstanbul Med J 2023; 24(4): 340-4
DOI: 10.4274/imj.galenos.2023.03604

Concordance between Patient and Physician Predictions of PCR Results and Predictive Capacity of Presenting Complaints in Suspected Infectious Diseases

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ABSTRACT

Introduction: The aim of this study was to investigate the concordance between patient and physician predictions of polymerase chain reaction (PCR) results in suspected infectious diseases and evaluate the predictive capacity of presenting complaints to enhance diagnostic decision-making.

Methods: A cross-sectional design was employed to recruit 1,369 participants with symptoms associated with coronavirus disease-2019 (COVID-19) infection. Data on demographics, medical history, presenting complaints, and PCR results were collected. Concordance between patient and physician predictions was assessed using kappa statistics, providing insights into the alignment of patient beliefs and physician expectations.

Results: The study revealed a lack of concordance between patient and physician predictions of PCR results. Loss of taste and smell emerged as the most sensitive symptoms associated with positive PCR results, whereas cough demonstrated higher specificity. However, relying solely on these symptoms may lead to missed cases, emphasizing the need for a comprehensive clinical evaluation. The suboptimal predictive accuracy of both patients and physicians highlights the importance of incorporating objective diagnostic tools such as PCR testing to enhance diagnostic decision-making.

Conclusion: Improved communication and shared decision making between patients and physicians are crucial for optimizing diagnostic strategies. Integrating objective diagnostic tools with clinical judgment is essential for improving accuracy. By identifying specific symptoms strongly associated with positive PCR results, this study contributes to enhancing the efficiency of diagnostic decision-making and the development of evidence-based guidelines in the realm of infectious diseases, ultimately improving patient care and healthcare delivery.

Keywords: Physcian-patient relations, infectious diseases medicine, emergency medicine, COVID-19

Introduction

Concordance between the Patient and Physician

In the era of infectious diseases, accurate and timely diagnosis is of paramount importance in guiding patient management and implementing appropriate public health measures (1,2). The availability of diagnostic tests, such as polymerase chain reaction (PCR), has revolutionized the detection of infectious agents (3). However, the decision to order a diagnostic test is not merely based on clinical suspicion but also relies on the predictive value of symptoms and the perceived likelihood of disease presence (4). Both patients and physicians play crucial roles in this decision-making process because their beliefs and expectations can significantly influence the pursuit of testing. The decision to order a diagnostic test is influenced by patient beliefs and physician expectations. Understanding the concordance between patient and physician predictions of test outcomes is crucial for optimizing diagnostic strategies (5).

One key aspect that affects the decision to undergo diagnostic testing is the patient's perception of their disease status. Patients who lack belief in their own likelihood of infection may be less inclined to consent to testing or seek medical attention altogether (6). Conversely, patients who perceive a high probability of infection are more likely to cooperate with testing procedures (7). Similarly, physicians consider the pretest probability of disease when determining the necessity of diagnostic tests. In cases where clinical suspicion is low, unless the test is deemed essential or has significant prognostic implications, physicians may be less inclined to order it (8). Understanding the factors influencing patient

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Cite this article as: Yurttaş TT, Dikme Ö, Akdağ B, Kızıldağ F, Dikme Ö. Concordance between Patient and Physician Predictions of PCR Results and Predictive Capacity of Presenting Complaints in Suspected Infectious Diseases. İstanbul Med J 2023; 24(4): 340-4.

Received: 04.08.2023
Accepted: 14.10.2023

and physician predictions of test outcomes is crucial for optimizing diagnostic strategies and promoting effective healthcare delivery.

The primary aim of this study was to investigate the concordance between patient and physician predictions of PCR results in the context of suspected infectious diseases. Furthermore, we sought to evaluate the predictive capacity of presenting complaints in relation to PCR test outcomes. Ultimately, these research endeavors to contribute to the development of evidence-based guidelines that optimize diagnostic practices and improve patient care in the realm of infectious diseases.

Methods

Study Design and Participants

This study employed a cross-sectional design to examine the concordance between patient and physician predictions of PCR results for the COVID-19 test and the predictive value of presenting complaints. A total of 1,369 participants were recruited from the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Emergency, representing diverse age ranges, medical conditions, and referral statuses. The inclusion criteria consisted of presenting to the emergency department with symptoms associated with COVID-19 infection and being ordered for a PCR test, while individuals with inconclusive data were excluded from the study.

Data Collection

Data collection involved a comprehensive approach to gather relevant information. Participants were invited to complete a detailed questionnaire that captured demographic data, medical history, and presenting complaints. The questionnaire was carefully designed to ensure comprehensive data collection. Clinical assessments were conducted by physicians, involving a thorough examination of each participant, including a review of medical records, physical examinations, and discussions with the patient. In addition, patient predictions of PCR results were obtained through direct questioning during the initial assessment, focusing on their beliefs regarding the likelihood of a positive test outcome.

PCR Testing

PCR testing was performed according to established protocols. Nasopharyngeal swabs were collected from each participant using sterile collection kits to ensure proper sample handling and preservation. The collected samples were processed in a designated laboratory by experienced technicians trained in PCR techniques. Quality control measures, including the use of internal controls and regular calibration of equipment, were implemented to ensure the accuracy and reliability of the PCR results.

Ethical Considerations

This study obtained ethical approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2833, date: 21.05.2021) to ensure participant protection and adherence to ethical guidelines. Informed consent was obtained from all participants before their participation in the study. Confidentiality of participant data was strictly maintained, and data were securely stored in compliance with data protection regulations. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical Analysis

Statistical Package for Social Sciences (SPSS, IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data analysis involved both quantitative and qualitative approaches. Descriptive statistics were used to summarize the demographic characteristics of the participants, presenting complaints, and PCR results. Measures of central tendency (e.g., means, medians) and dispersion (e.g., standard deviations, interquartile ranges) were calculated. The agreement between patient and physician predictions of the PCR results was evaluated using statistical measures such as kappa statistics or percentage agreement. The predictive capacity of presenting complaints was assessed by calculating the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and accuracy. Subgroup analyses may be conducted to explore variations in concordance and predictive capacities among different patient demographics or clinical characteristics.

Results

A total of 1,369 patients were enrolled in the study, with a median age of 33 years (interquartile range: 25-45). Among the participants, 49.5% (n=679) were female. The most prevalent chief complaint observed among the patients was sore throat, accounting for 34.9% (n=479) of the cases, followed by fatigue (34.1%, n=467) and cough (31.1%, n=427) as the second and third most frequently reported symptoms, respectively. In terms of the PCR test results, 17.6% of patients (n=241) tested positive. Interestingly, when specifically asked, 46.5% of the patients (n=637) expressed their belief that their test results would be positive. Remarkably, physicians themselves anticipated a positive outcome in 32.7% of cases (n=448) (Table 1).

Evaluation of the predictive accuracy of physicians in determining PCR results yielded several performance metrics. For all patients, physicians exhibited a sensitivity of 45.23% [95% confidence interval (CI): 38.83%-51.74%], specificity of 69.88% (95% CI: 67.71%-72.55%), positive likelihood ratio of 1.5 (95% CI: 1.27-1.77), negative likelihood ratio of 0.78 (95% CI: 0.69-0.88), and accuracy of 65.52% (95% CI: 62.93%-68.04%). In the subgroup of presenting patients, physicians achieved a sensitivity of 61.83% (95% CI: 55.37%-67.99%), specificity of 56.67% (95% CI: 53.73%-59.61%), positive likelihood ratio of 1.43 (95% CI: 1.27-1.61), negative likelihood ratio of 0.67 (95% CI: 0.57-0.79), and accuracy of 57.59% (95% CI: 54.92%-60.24%).

Notably, when examining the predictive power of presenting complaints, both physicians and patients demonstrated the highest sensitivity in identifying cases characterized by loss of taste and smell, with sensitivities of 78.38% (95% CI: 61.79%-90.17%) and 75.68% (95% CI: 58.88%-88.23%), respectively. In contrast, the highest specificity values were observed for patients presenting with a cough complaint, with specificity of 63.02% (95% CI: 57.63%-68.18%) and 52.96% (95% CI: 47.48%-58.38%) in the physician and patient groups, respectively. Remarkably, physicians demonstrated the highest accuracy in predicting

PCR results for patients with a history of contact with a suspected case (60.92%, 95% CI: 54.71%-60.24%), whereas patients exhibited the highest accuracy for those presenting with a cough complaint (55.97%, 95% CI: 51.12%-60.74%).

Assessing the agreement between physicians and patients in predicting PCR positivity, there was a noteworthy lack of concordance. The responses provided by both groups demonstrated weak agreement for all patients (kappa = 0.167, 95% CI: 0.116-0.218, p<0.001). Furthermore, subgroup analyses based on presenting complaints confirmed this finding, revealing weak concordance for patients with fever (kappa = 0.148, 95% CI: 0.023-0.273, p=0.023), cough (kappa = 0.175, 95% CI: 0.085-0.265, p<0.001), and a history of contact with a suspected case (kappa = 0.252, 95% CI: 0.140-0.364, p<0.001). Notably, for patients reporting a complaint of loss of taste and smell, no agreement was observed in PCR predictions between physicians and patients (kappa = 0.08, 95% CI: -0.124-0.284, p=0.431).

Table 1. Participant characteristics and PCR results

Variable	(n=1369)
Age	33 (25-45)
Sex (female)	679 (49.5%)
Complaint	
Fever	225 (16.4%)
Cough	427 (31.1%)
Shortness of breath	90 (6.6%)
Throatache	479 (34.9%)
Myalgia	348 (25.4%)
Nausea	92 (6.7%)
Diarrhea	80 (5.8%)
Loss of smell and taste	96 (7%)
Chest pain	58 (4.2%)
Malaise	467 (34.1%)
Dizziness	40 (2.9%)
Headache	299 (21.8%)
Contact with the infected	261 (19%)
Physician	448 (32.7%)
Patient	637 (46.5%)
PCR results	241 (17.6%)

PCR: Polymerase chain reaction

Discussion

The present study provides intriguing insights into several key aspects related to the prediction of PCR results, concordance between patients and physicians, and predictive value of presenting complaints. The most noteworthy finding of this investigation is the observed lack of concordance between patient and physician predictions of PCR results. This finding underscores the complex nature of diagnostic decision making and highlights the need for improved communication and shared decision making between patients and healthcare providers.

The lack of concordance between patient and physician predictions can be attributed to several factors. First, patient expectations and beliefs regarding their likelihood of infection may be influenced by various factors such as their knowledge of the disease, personal experiences, and media exposure (9,10). Patients may overestimate or underestimate their risk based on these subjective factors, leading to discordant predictions. Similarly, physicians' predictions may be influenced by their clinical experience, biases, and the prevailing prevalence of the disease in the population (11,12). It is crucial to bridge this gap in expectations to ensure effective patient provider communication and appropriate testing strategies.

Another intriguing finding of this study is the variation in the predictive capacity of presenting complaints. Loss of taste and smell emerged as the most sensitive symptoms associated with positive PCR results (Table 2). This aligns with the growing evidence highlighting the significance of these symptoms in COVID-19 diagnosis (13). However, relying solely on these symptoms may lead to missed cases because they are not specific to COVID-19. Cough, on the other hand, demonstrated higher specificity, suggesting its utility in ruling out COVID-19 in certain scenarios (Table 3). These findings emphasize the importance of considering multiple symptoms and clinical factors when making diagnostic decisions.

Furthermore, the suboptimal performance of both patients and physicians in predicting PCR results warrants attention. The relatively low sensitivity and specificity values observed in this study indicate that

Table 2. Predictive performance of presenting complaints for PCR results

	Complaint	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)	Accuracy (95% CI)
Pysician	Any	45.23 (38-83-51.74)	69.88 (67.71-72.55)	1.5 (1.27-1.77)	0.78 (0.69-0.88)	65.52 (62.93-68.04)
	Fever	51.43 (39.17-63.56)	58.28 (49.98-66.24)	1.23 (0.92-1.65)	0.83 (0.63-1.09)	56.11 (49.29-62.76)
	Loss of tastasis and smell	78.38 (61.79-90.17)	29.31 (18.09-42.73)	1.11 (0.88-1.41)	0.74 (0.36-1.54)	48.82 (38.04-58.9)
	Cough	52.81 (41.94-63.49)	63.02 (57.63-68.18)	1.43 (1.12-1.82)	0.75 (0.59-0.95)	60.89 (56.08-65.55)
	Contact with the infected	53.19 (38.08-67.89)	62.62 (55.76-69.12)	1.42 (1.03-1.95)	0.75 (0.54-1.03)	60.92 (54.71-66.88)
Patient	Any	61.83 (55.37-67.99)	56.68 (53.73-59.61)	1.43 (1.27-1.61)	0.67 (0.57-0.79)	57.59 (54.92-60.24)
	Fever	65.71 (53.4-76.65)	49.67 (41.44-57.91)	1.31 (1.04-1.65)	0.69 (0.48-0.99)	54.75 (47.94-61.44)
	Loss of taste and smell	75.68 (58.88-88.23)	37.93 (25.51-51.63)	1.22 (0.93-1.6)	0.64 (0.33-1.23)	52.63 (42.12-62.97)
	Cough	67.42 (56.66-76.98)	52.96 (47.48-58.38)	1.43 (1.19-1.72)	0.62 (0.45-0.85)	55.97 (51.12-60.74)
	Contact with the infected	72.34 (57.36-84.38)	50.47 (43.57-57.35)	1.46 (1.17-1.82)	0.55 (0.34-0.89)	54.41 (48.15-60.56)

+LR: Positive likelihood ratio, -LR: Negative likelihood ratio, CI: Confidence interval, PCR: Polymerase chain reaction

Table 3. Agreement (Kappa) between patient and physician predictions of PCR results

	Kappa	95% CI		p-value
Any	0.167	0.116	0.218	<0.001
Fever	0.148	0.023	0.273	0.023
Loss of taste and smell	0.08	-0.124	0.284	0.431
Cough	0.175	0.085	0.265	<0.001
Contact with the infected	0.252	0.140	0.364	<0.001

PCR: Polymerase chain reaction, CI: Confidence interval

relying solely on clinical judgment or patient beliefs may not be sufficient for accurate predictions (Table 2). This emphasizes the importance of incorporating objective diagnostic tools, such as PCR testing, to support clinical decision-making and enhance diagnostic accuracy.

The findings of this study have important implications for clinical practice and public health strategies. Enhancing patient education and awareness regarding disease risks and symptoms can help align patient expectations with clinical probabilities, facilitating more informed decision making (14). Improving physician knowledge and training on the predictive value of presenting complaints can aid in more accurate clinical assessments and appropriate testing strategies. Furthermore, considering the limitations of symptom-based predictions, the implementation of widespread and accessible diagnostic testing, such as PCR, remains crucial for timely and accurate disease detection (15).

In conclusion, this study sheds light on the discordance between patient and physician predictions of PCR results and highlights the importance of shared decision making and effective communication in diagnostic decision making. The varying predictive capacity of presenting complaints underscores the need for a comprehensive clinical evaluation that considers multiple factors. Moving forward, a multidimensional approach that integrates patient perspectives, clinical judgment, and objective diagnostic tools is essential for optimizing diagnostic strategies and improving patient outcomes.

Study Limitations

It is important to acknowledge the limitations of this study. The sample size and composition may limit the generalizability of the findings to broader populations. In addition, reliance on self-reported symptoms and predictions introduces the possibility of recall bias and subjectivity. The subjective nature of patient and physician predictions may also introduce variability and affect the concordance between predictions and actual PCR results. Furthermore, symptom-based predictions have inherent limitations because symptoms alone may not be specific to the target disease. Contextual factors, such as disease prevalence and variations in testing strategies, should also be considered. Finally, potential biases, including recall and selection bias, should be recognized. Future research with larger and more diverse samples, objective measures, and exploration of additional influencing factors is needed to address these limitations and strengthen the validity and generalizability of the findings.

Conclusion

This study highlights the importance of improved communication and shared decision-making between patients and physicians in diagnostic processes. The findings reveal a lack of agreement between patient and physician predictions. Enhancing patient education and physician training on the predictive value of presenting complaints is essential. Implementing accessible diagnostic testing methods, such as PCR, is crucial for timely disease detection. Future research should address limitations, including sample characteristics and reliance on self-reported data. Collaborative approaches that combine patient perspectives, clinical judgment, and objective tools are vital for optimizing diagnostics and improving patient care.

Ethics Committee Approval: This study obtained ethical approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2833, date: 21.05.2021) to ensure participant protection and adherence to ethical guidelines.

Informed Consent: Informed consent was obtained from all participants before their participation in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - Ö.D., Özl.D.; Design - T.T.Y., B.A., Özl.D.; Data Collection or Processing - Ö.D., B.A., F.K.; Analysis or Interpretation - Özl.D.; Literature Search - T.T.Y., Ö.D., B.A., F.K.; Writing - T.T.Y., Özl.D.

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

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

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İstanbul Med J 2023; 24(4): 345-51
DOI: 10.4274/imj.galenos.2023.19626

Relationship between Carotid Intima-Media Thickness and Fibroblast Growth Factor Binding Protein-3 in Patients with Metabolic Syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) causes arteriosclerosis (AS). Increased carotid intima-media thickness (CIMT) manifests as early vascular changes in AS. Fibroblast growth factor binding proteins (FGBP1, 2 and 3) are chaperones that are locally activated by binding paracrine FGFs from heparan sulfate stores in the extracellular matrix. Here we investigated whether FGFBP-3 affects AS by changing the glucose and fat metabolism of MetS. We propose that FGFBP-3 could be a new therapeutic agent to prevent AS by reversing MetS pathology.

Methods: Eighty-two 82 patients with MetS at University of Health Sicences Turkey, İstanbul Training and Research Hospital were prospectively included in the study. Serum FGFBP-3 levels of the patients were measured. For subclinical AS, CIMT was recorded with two right and left measurements using B-mode ultrasound.

Results: There was no significant correlation between FGFBP-3 and CIMT levels. A significant negative correlation was found between FGFBP-3 and systolic blood pressure (SBP) (p=0.048). The FGFBP-3 level was significantly lower in the diabetes mellitus (DM) group than in the non-diabetic group (p=0.049).

Conclusion: In our study, there was no relationship between serum FGFBP-3 levels and CIMT. However, there was a relationship between FGFBP-3 and high SBP and diabetes. We believe that FGFBP-3 can stabilize the bioactivity of endogenous FGF21 and therefore may have significant therapeutic benefits in metabolic diseases such as non-alcoholic fatty liver disease and type 2 DM.

Keywords: Metabolic syndrome, FGFBP-3, atherosclerosis

Introduction

Metabolic syndrome (MetS) is a complex of risk factors that cause cardiovascular disease (CVD) and type 2 diabetes mellitus (DM). These risk factors include increased blood pressure, high triglyceride (TG), dysglycemia, low high-density lipoprotein (HDL) cholesterol, and abdominal obesity (AO). Recent research has focused on the possible association of insulin resistance (IR) as a linking factor in establishing diagnostic criteria. With these risk factors, it has been conclusively shown that the syndrome is common with increasing obesity and sedentary lifestyle and has an increasing prevalence worldwide (1). According to the Heart Diseases and Risk Factors in Turkish Adults (TEKHARF) study, as of 2000, 9.2 million people aged 30 years and over in Turkey have MetS, and 53% of people with coronary artery disease have MetS. It is generally accepted that IR and AO are leading (2). A strong correlation has been shown between atherosclerosis and risk factors such as hypertension, body mass index, IR, high TG, and smoking (3,4). However, risk factors can also be observed in some people who are not clinically symptomatic, causing difficulties in the diagnosis of atherosclerosis and risk classification of atherosclerotic diseases (5).

Atherosclerosis starts with the aggregation of lipoprotein particles and leukocytes in the intima layer after endothelial dysfunction and first occurs in the form of fatty streaks with the accumulation of foam macrophage cells. During this process, smooth muscle cells in the media layer also begin to proliferate and form atheromatous plaques. Carotid intima-media thickness (CIMT) is increasingly used as a surrogate end point of vascular outcomes in clinical trials aimed at determining the success of interventions that lower risk factors for atherosclerosis and associated diseases (stroke, myocardial infarction and peripheral artery diseases). Atherosclerotic changes can be evaluated using ultrasonography and magnetic resonance imaging. However, B-mode ultrasonography is

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Cite this article as: Akdağ G, Altunoğlu EG. Relationship between Carotid Intima-Media Thickness and Fibroblast Growth Factor Binding Protein-3 in Patients with Metabolic Syndrome. İstanbul Med J 2023; 24(4): 345-51.

Received: 26.07.2023
Accepted: 15.10.2023

a cheap, reliable, and reproducible method for assessing changes in the arterial wall in the absence of atherosclerotic plaque (6,7).

Fibroblast growth factor binding proteins (FGBP1, 2, and 3) are chaperones that bind and activate paracrine FGFs from heparan sulfate (HS) stores in the extracellular matrix (8,9). Binding protein-1, the most characteristic member of this family, increases cellular FGF receptor signaling and interacts with paracrine FGFs such as FGF1, 2, 7, 10, and 22 to compensate for HS deficiency (10). However, the possible interactions of BPs with non-heparin-binding endocrine FGF19 family members are not fully understood. These endocrine FGFs, namely FGF19, FGF21, and FGF23, are released into the circulation and maintain the metabolic homeostasis of glucose, lipids, and phosphate (11,12). In a mouse study, exogenous BP3 expression in obese mice suppressed lipogenic gene expression in the liver and white adipose tissue, reducing weight, hyperglycemia, and normalized hepatic steatosis (13). In our study, we will investigate whether it affects atherosclerosis by changing metabolic homeostasis. We aimed to compare CIMT measurements with FGFBP-3 levels to determine the relationship.

Methods

Patients diagnosed with MetS in the internal medicine and diabetes polyclinics of University of Health Sciences Turkey, İstanbul Training and Research Hospital in 2019 were included in our prospective thesis study. Each patient participating in the study was informed, their consent was obtained, and they voluntarily participated in the study.

Definition of MetS according to the International Diabetes Federation-2006 diagnostic criteria;

Requirement AO (waist circuit measurement : ≥80 cm in women, ≥94 cm in men); hypertension [systolic blood pressure (SBP) >130 mmHg, diastolic blood pressure (DBP) >85 mmHg or those using antihypertensive drug], dyslipidemia (TG level >150 mg/dL or HDL level <40 mg/dL in men, <50 mg/dL in women), fasting blood glucose (FBG) >100 mg/dL, or having a diagnosis of type 2 DM defined by the presence of at least two.

In our study, to investigate whether there may be variability in patient groups as the number of existing criteria in MetS patients increases, those with three, four, or five criteria were divided into groups. The waist circumference of the patients was measured and recorded at the midpoint of the distance between the costar arch and anterior superior iliac spine. During the initial evaluation of the patients, systolic and DBP measurements were taken. Blood pressure measurements were made from both brachial arteries using a standard Erka brand (Germany) arm sphygmomanometer after the patient rested for at least 5 min in a sitting position before the examination.

While detecting the presence of IR, the Homeostasis Model Assessment (HOMA) formula was used, which was calculated as HOMA= fasting glucose (mg/dL) fasting insulin (uIU/mL)/ 405, and patients with a HOMA score of ≥2.7 were considered positive for IR. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate the glomerular filtration rate (14). In this formula, the sex, race, age, and creatinine parameters were calculated using.

CIMT of each case; B-mode ultrasonography and duplex Doppler was examined. All ultrasound examinations were performed by the same radiologist. Measurements were made from 3 different points 1 cm distal to the right and left anterior carotid arteries, and only the posterior 22 (distant) walls were evaluated. Both measurements were recorded as the right and left CIMT.

Biochemical and whole blood tests of all participants after 8 h of fasting [FPG, hemoglobin A1C (HbA1C), insulin, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), uric acid, urea, creatinine, total cholesterol, TG, low-density lipoprotein cholesterol (LDL) HDL, C-reactive protein (CRP), hemoglobin, and platelets] were recorded and FGFBP-3 levels were measured. An extra tube of venous blood was drawn into the chemistry tube at the same time. After the blood was centrifuged, it was stored in a -80 °C cabinet at the end of the study. Serum FGFBP-3 levels were studied from this blood using ELISA. For this, the "FGFBP-3 ELISA, USA" kit was used. The lower sensitivity limit of this kit is 0.015 ng/mL, and the detection range is 0.05-15 ng/mL.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics/Institutional Review Board University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1837, date: 24.05.2019).

Statistical Analysis

The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. Distribution was evaluated using the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. The chi-square test was used in the analysis of qualitative independent data, and the Fisher's exact test was used when the chi-square test condition was not met. The SPSS 22.0 program was used in the analysis.

Results

In our prospective study, 82 patients who had the MetS criteria, were included. 58.5% of the patient group were female (n=48), and the mean age was 59.6±10.6. Table 1 shows all demographic and laboratory data of the patients.

No significant relationship was observed between FGFBP-3 levels and CIMT right and CIMT left. Patients' FGFBP-3 levels between weight, waist circuit measurement, LDL, HDL, TG, ALT, AST, GGT, ALP, uric acid, urea, estimated glomerular filtration rate (e-GFR), insulin, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), CRP, HbA1C, hemoglobin, platelet count, age, and DBP levels were not significantly correlated. A significant positive correlation was found between FGFBP-3 levels and creatinine levels. FGFBP-3 levels were higher in patients with high creatinine values (p=0.012). A significant negative correlation was found between the FGFBP-3 level and SBP (p=0.048) (Table 2).

There was no difference between gender, smoking status, antihypertensive drug use, anti-hyperlipidemic drug use, MetS score

Table 1. Demographic and laboratory data of patients

		Minimum-Maximum	Median	Mean ± SD/(n, %)
Age		31.0-80.0	60.0	59.6±10.6
Gender	Female			48 (58.5%)
	Male			34 (41.5%)
Weight		57.0-116.0	80.0	80.4±11.7
Waist circumference		84.0-150.0	108.0	109.9±13.0
Smoker	(-)			51 (62.2%)
	(+)			31 (37.8%)
Diabetes mellitus	(-)			8 (9.8%)
	(+)			74 (90.2%)
Hyperlipidemia	(-)			41 (50.0%)
	(+)			41 (50.0%)
Hypertension	(-)			26 (31.7%)
	(+)			56 (68.3%)
Metabolic syndrome score	III			29 (35.8%)
	IV			30 (37.0%)
	V			22 (27.2%)
HDL		26.0-89.0	49.0	50.2±12.7
LDL		64.0-400.0	133.5	150.3±74.1
Triglyceride		55.0-651.0	159.5	203.6±130.9
AST		6.0-52.0	19.0	20.8±7.4
ALT		4.0-113.0	20.0	23.3±14.7
GGT		11.0-319.0	24.0	34.5±37.1
ALP		22.0-242.0	79.0	86.1±36.1
Uric acid		2.5-9.7	5.2	5.5±1.4
Urea		14.0-73.0	32.0	34.1±11.0
Creatinine		0.5-1.2	0.7	0.8±0.2
e-GFR		60.0-138.0	94.0	93.1±18.1
Fasting plasma glucose levels		16.0-419.0	140.0	156.8±65.8
Insulin		1.8-306.0	9.1	19.7±40.4
HOMA-IR		0.5-68.0	3.2	6.7±10.7
C-reactive protein		0.4-28.0	4.2	5.7±5.6
HbA1C		5.3-107.0	7.6	8.8±11.1
Hemoglobin		9.5-17.0	13.0	12.9±1.4
Platelet		150.0-514.0	257.5	265.7±68.2
CIMT right		0.5-1.3	0.8	0.8±0.2
CIMT left		0.5-1.2	0.8	0.8±0.2
Systolic blood pressure		110.0-145.0	120.0	123.2±8.5
Diastolic blood pressure		65.0-85.0	80.0	79.1±6.1
FGFBP-3		0.9-12.6	2.0	2.7±2.3

SD: Standard deviation, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase, e-GFR: Estimated glomerular filtration rate, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, HbA1C: Glycated hemoglobin, CIMT: Carotid intima-media thickness, FGFBP-3: Fibroblast binding protein-3

group, and FGFBP-3 level. FGFBP-3 level was significantly lower in the DM group than in the non-diabetic group (p=0.049) (Table 3, Figure 1).

Discussion

The risk of CVD is 3 times higher and that of DM is 5 times higher in individuals with MetS (15). However, no algorithm can predict risk on an individual basis (16). Effective management of this syndrome may be important for preventing the development of CVD and DM (17). MetS is a risk factor for early atherosclerosis (18). Although atherosclerosis is more common in individuals with DM (19), MetS significantly increases CVD risk and mortality in all individuals independent of diabetes (20). Therefore, an accurate diagnosis of MetS is important to predict

Table 2. Correlation of FGFBP-3 levels with medical parameters

		Age	Weight	Waist circumference	HDL	LDL
FGFBP-3	r	-0.013	0.048	0.061	-0.038	0.108
	p	0.906	0.671	0.589	0.732	0.334
		TG	**AST**	**ALT**	**GGT**	**ALP**
FGFBP-3	r	-0.057	-0.075	-0.074	0.017	-0.183
	p	0.608	0.504	0.508	0.881	0.100
		Uric acid	**Urea**	**Creatinine**	**e-GFR**	**FPG**
FGFBP-3	r	0.018	0.179	0.278	-0.057	-0.114
	p	0.871	0.109	**0.012**	0.614	0.310
		Insulin	**HOMA-IR**	**CRP**	**HbA1C**	**Hg**
FGFBP-3	r	-0.120	-0.134	-0.041	-0.171	0.169
	p	0.282	0.230	0.713	0.125	0.128
		PLT	**CIMT right**	**CIMT left**	**SBP**	**DBP**
FGFBP-3	r	-0.056	0.087	0.042	-0.219	-0.041
	p	0.620	0.439	0.707	**0.048**	0.713

Spearman correlation

FGFBP-3: Fibroblast growth factor binding protein-3, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein cholesterol, TG: Triglyceride, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase, e-GFR: Estimated-glomerular filtration rate, FPG: Fasting plasma glucose, HOMA-IR: Homeostasis Model Assessment of Insulin Resistance, CRP: C-reactive protein, HbA1C: Hemoglobin A1C, Hg: Hemoglobin, PLT: Platelet, CIMT: Carotid intima-media thickness, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 3. Comparison of FGFBP-3 levels and medical parameters

Minimum-Maximum		FGFBP-3 Median	FGFBP-3 Mean ± SD		p	
Gender	Female	1.22-9.57	1.88	2.45±1.91	0.178	[m]
	Male	0.87-12.59	2.11	3.12±2.80		
Smoker	(-)	0.87-11.83	1.87	2.57±2.21	0.105	[m]
	(+)	1.36-12.59	2.17	3.00±2.52		
Diabetes mellitus	(-)	1.79-9.17	2.52	3.21±2.44	**0.049**	[m]
	(+)	0.87-12.59	1.93	2.68±2.33		
Hyperlipidemia	(-)	0.87-9.17	1.87	2.37±1.74	0.250	[m]
	(+)	1.22-12.59	2.03	3.09±2.77		
Hypertension	(-)	0.96-8.96	1.74	2.50±2.12	0.093	[m]
	(+)	0.87-12.59	2.11	2.84±2.43		
Metabolic syndrome score	III	0.87-9.17	1.79	2.52±2.25	0.177	[K]
	IV	1.30-12.59	2.11	3.01±2.75		
	V	1.25-9.57	2.02	2.67±1.86		

[m]Mann-Whitney U test, [K]Kruskal-Wallis test, FGFBP3: Fibroblast growth factor binding protein-3, SD: Standard deviation

increased CVD risk (15). In our study, the mean of the right and left CIMT thicknesses of 82 patients with MetS were 0.8±0.2 mm. The median value was 0.8 mm. A result consistent with similar studies was obtained.

According to the literature, MetS is a principal risk factor for DM, and IR has an important place in the pathophysiology of both diseases. In our study, similar to the literature, the frequency of DM and the mean HOMA-IR levels were found to be high in patients with MetS. The HOMA-IR level of the patients in the study resulted in a minimum of 0.5, maximum of 68, median of 3.2, and mean of 6.7±10.7. The mean FPG levels in our patient group were 156.8±65.8. The results of our study were in agreement with the literature.

FGF signaling is key to many physiological processes, including tissue growth and development, tissue regeneration, and metabolism. FGF signals consist of twenty-two secreted factors that bind to four distinct membrane tyrosine kinase receptors. FGFs are divided into paracrine, endocrine, and intracellular factors. Paracrine FGFs are trapped in the extracellular matrix bound to HS, whereas endocrine FGFs have a low affinity for HS and circulate freely in the bloodstream to act on distant target organs (21). Members of the endocrine FGF family are central to various metabolic processes. In the liver, FGF15/19 stimulates protein and glycogen synthesis and acts as a regulator of bile acid synthesis by suppressing 7α-hydroxylase, the rate-limiting enzyme of bile acid

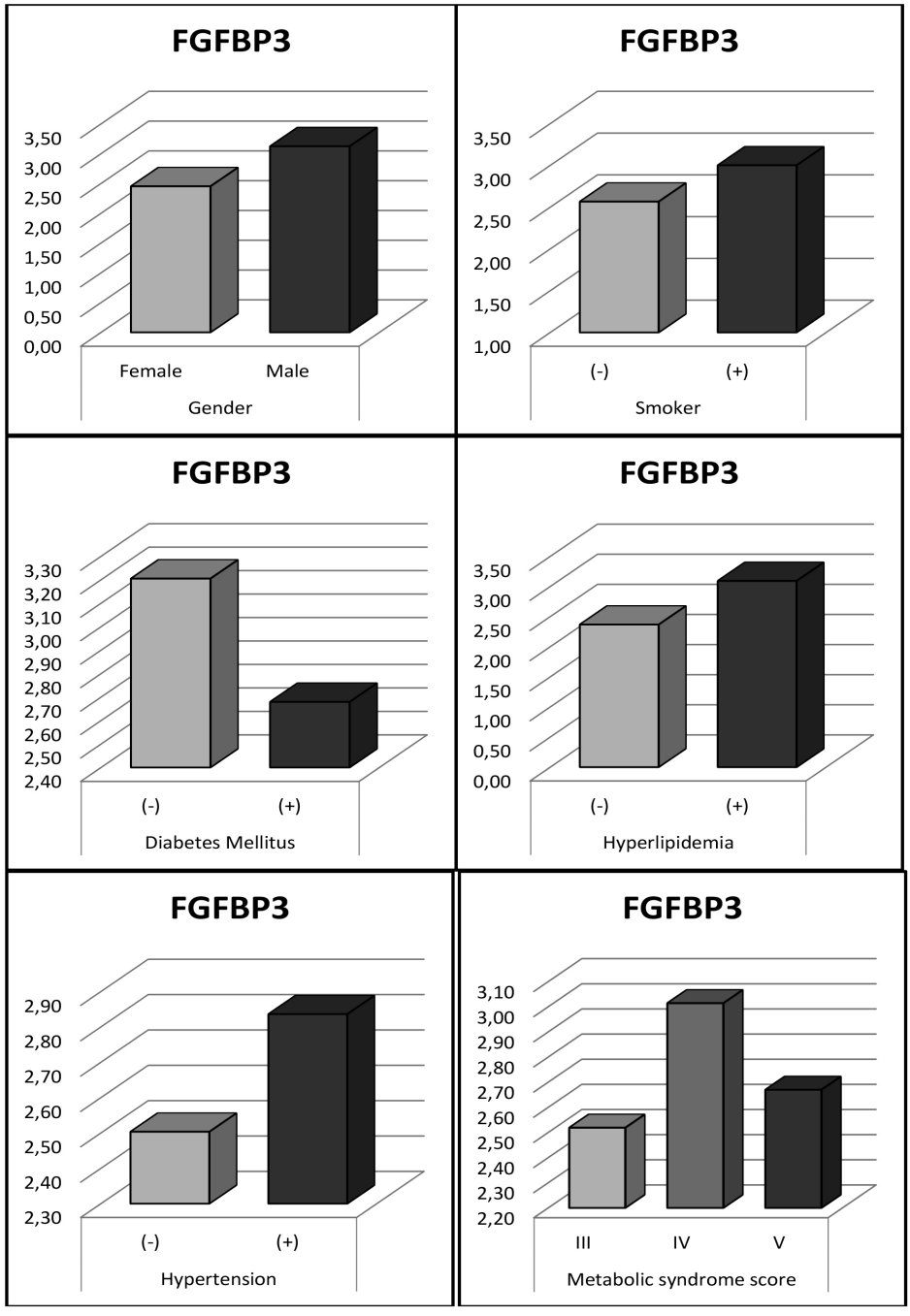

Figure 1. Relationship between FGFBP-3 levels and medical parameters
FGFBP3: Fibroblast growth factor binding protein-3

synthesis. FGF21 is involved in carbohydrate and lipid metabolism in multiple organs, including the liver, skeletal muscle, pancreatic beta cells, adipose tissue, and brain, through various mechanisms (22). Furthermore, FGF21 is protective against NALFD. Many studies have shown that obesity, type 2 DM, and NAFLD are associated with abnormal plasma FGF19 and FGF21 levels (23-25). In our study, however, no significant relationship was found between FGFBP-3 levels and weight. However, the FGFBP-3 level in the DM group was significantly lower (p=0.049) than that in the nondiabetic patients.

FGFBP-3 serves as a chaperone protein for paracrine FGFs and shares some biological effects with FGFBP-1, such as decreased FGF2 binding to HS and increased paracrine FGF signaling (9). Based on the current understanding that FGFBP-3 enhances FGF binding and activation of FGF receptors and FGF21 regulatory effects on serum blood glucose and liver fat content homeostasis, it has been hypothesized that FGFBP-3 acts on the liver to improve glucose intolerance, IR, and hepatosteatosis. However, in our study, no significant relationship was found between FGFBP-3 and fasting insulin, FBG, and HOMA-IR.

In a 2017 study by Tassi et al. (26), the relationship between FGFs and blood pressure was examined. It participates in organ development and tissue maintenance alongside the control of vascular function. A genetic polymorphism in the human *FGFBP-1* gene was associated with higher gene expression and an increased risk of familial hypertension (26). In our study, a significant (p=0.048) negative correlation was observed between the FGFBP-3 level and the systolic pressure level. FGFBP-3 was found to be lower in patients with high SBP.

Study Limitations

Our study has several limitations. First, the absence of healthy control group patients, except for those with MetS, prevented us from performing subgroup analysis. The sample size collected was small, which could be improved in future studies by adding patients in later years. Further studies are required to confirm the current results.

Conclusion

In our study, patients with high SBP and diabetes had lower FGFBP-3 levels, which were statistically significant. These results show that FGFBP-3 contributes to glucose homeostasis and has a significant effect on blood pressure. Collectively, these studies suggest a possible cooperation between FGFBP-3 and FGF21 to regulate homeostasis of blood glucose and liver fat content. We believe that FGFBP-3 may have significant therapeutic benefits in metabolic diseases such as non-alcoholic fatty liver disease and type 2 DM.

Ethics Committee Approval: Approval was granted by the Ethics/Institutional Review Board University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1837, date: 24.05.2019).

Informed Consent: Each patient participating in the study was informed, their consent was obtained, and they voluntarily participated in the study.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 352-6
DOI: 10.4274/imj.galenos.2023.32798

Evaluation of the Systemic Immune-Inflammation Index and Systemic Inflammatory Response Index in Ankylosing Spondylitis Patients

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ABSTRACT

Introduction: The aim of this study was to investigate the relationship between the Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI) and disease activity in patients with ankylosing spondylitis (AS).

Methods: In our study, 104 AS and 51 healthy controls (HC) were analyzed. The SII and SIRI differences between AS and HC were investigated. Those with BASDAI <4 were defined as remission (BASDAI-r) and those with BASDAI >4 as active (BASDAI-a). SII, SIRI, and other parameters were compared between the groups. As a second classification, patients were divided into two groups according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) scores. Those with ASDAS <2.1 were defined as low-grade disease activity (ASDAS-l) and those with ASDAS >2.1 were defined as high-grade disease activity (ASDAS-h). SII, SIRI, and other parameters were compared between the groups.

Results: The median SIRI value was significantly higher in the patient group than in the HC group. The mean SIRI value was significantly higher in the BASDAI-a group than in the BASDAI-r group and in the ASDAS-h group than in the ASDAS-l group, but the median SIRI levels did not differ significantly between the groups. The optimal cut-off value of SIRI for identifying active patients was 1.12.

Conclusion: These results suggest that SIRI may be considered in the evaluation of patients with AS and may be a new biomarker to identify patients with active disease activity.

Keywords: Ankylosing spondylitis, SIRI, SII

Introduction

Ankylosing spondylitis (AS) is a progressive, persistent, and systemic inflammatory disorder. The common clinical findings of AS include restriction of mobility of the spine and inflammatory low back pain (1). Although its etiology has not yet been fully elucidated, it has a strong relationship with human leukocyte antigen (HLA) B27. HLAB27 positivity is observed in approximately 90% of patients with AS (2).

Although AS is a slowly progressing disease, it can cause mobility problems. For this purpose, reliable methods are needed to monitor disease activity. Some scales have been developed to evaluate disease activity. Evaluating the level of disease activity and assessing the effectiveness of treatment in AS is a multifaceted and challenging undertaking. Laboratory biomarkers, particularly C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are consistently used to assess disease activity. However, it cannot completely distinguish between infection and disease activity and has low sensitivity and specificity (3-6). Therefore, new parameters have been studied in recent years to determine disease activity [Systemic Immune-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI)].

SII has been demonstrated to be related to activity as well as prognosis in Behcet's disease, rheumatoid arthritis (RA), and AS (7-9). SIRI has been used in cardiovascular diseases and malignancies; the determination of its association with disease activity and prognosis has been established (10,11). SIRI was investigated in patients with RA and was not associated with disease activity (9). However, SIRI did not conduct a previous study on AS patients. This study examined the association between SII and SIRI, two novel markers of inflammatory conditions, and disease activity in patients with AS.

Methods

This retrospective study included AS patients who were followed up in University of Health Sciences Turkey, İstanbul Training and Research

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Cite this article as: Dede BT, Bulut B, Oğuz M, Bağcıer F, Aytekin E. Evaluation of the Systemic Immune-Inflammation Index and Systemic Inflammatory Response Index in Ankylosing Spondylitis Patients. İstanbul Med J 2023; 24(4): 352-6.

Received: 08.09.2023
Accepted: 17.10.2023

Hospital between June and July 2023. Approval of the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 262, date: 19.08.2022). This study was registered on clinicaltrials.gov under NCT05914532.

Participants

The study included a sample of 104 individuals diagnosed with AS, ranging in age from 18 to 65 years old. The diagnosis was established using the classification criteria of the Assessment of SpondyloArthritis International Society (ASAS) in 2009. In addition, a group of 51 healthy individuals was included as a control for comparison. Patients with infections, coronary artery disease, kidney and liver dysfunction, cancer diagnosis, surgery in the last three months, hypertension, and diabetes mellitus were not included. Age, gender, disease duration, and complete blood counts (ESH, CRP, and HLAB27) were recorded. SIRI and SII were calculated from complete blood counts. To calculate the SII, multiply the platelet count by the neutrophil count and divide by the lymphocyte count. SIRI is computed by dividing neutrophil and monocyte counts by lymphocyte counts.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) were employed to assess disease activity. The BASDAI questionnaire comprises a total of six questions. Higher than 4 points are defined as active disease. The ASDAS consists of five questions. We preferred ASDAS-CRP in our study. The ASDAS is categorized into four distinct groups based on disease activity levels. These groups are defined as follows: "low disease activity" for ASDAS values below 1.3, "moderate disease activity" for ASDAS values between 1.3 and 2.1, "high disease activity" for ASDAS values between 2.1 and 3.5, and "very high disease activity" for ASDAS values exceeding 3.5. The functional status of the participants was assessed using the Bath Ankylosing Spondylitis Functional Index, a 10-item measurement tool. The Ankylosing Spondylitis Metrology Index (BASMI), which consists of 5 items, was used in our study. The Maastricht Ankylosing Spondylitis Enthesitis Score was determined by assessing the occurrence of enthesitis susceptibility in 13 anatomical sites (6).

Initially, the patients were categorized into two distinct groups based on their BASDAI scores: individuals in a state of remission and those with active disease. Those with a BASDAI score below 4 are in remission (BASDAI-r); those with a BASDAI score above 4 are considered active (BASDAI-a). As a second classification, patients were divided into two groups based on their ASDAS-CRP scores. Those with an ASDAS-CRP score below 2.1 were considered low grade (ASDAS-l), and those above 2.1 were considered high grade (ASDAS-h). Comparisons of SIRI and SII were made between the groups. In addition, the relationship between SIRI and SII and disease activity was investigated. The optimal cut-off values of the parameters evaluated to differentiate AS patients from healthy controls and to differentiate active AS patients from remission AS patients were investigated.

Sample Size

NCSS, LLC.'s Power Analysis, and Sample Size Software 15 (2017) (Kaysville, UT, USA; www.ncss.com/software/pass) was used to determine the sample size. To calculate the sample size in our study, a power analysis was performed with 95% power according to the SIRI in a previous retrospective study (9).

Statistical Analysis

For statistical analysis, IBM SPSS 22.0 was used. The Kolmogorov-Smirnov/Shapiro-Wilk test was used to check for normal distribution. While descriptive analyses are presented, the mean and standard deviation or median and 1. quartile/3. quartile values are given for quantitative variables. Mann-Whitney U or Student's t-test was used when comparing data. While presenting the categorical variables, we performed the chi-square test. Correlation analyses were performed using the Spearman or Pearson test. Researchers examined receiver operating characteristic (ROC) curves to determine the best cut-off values. It was determined that $p<0.05$ was statistically significant.

Results

This study included 104 patients and 51-HCs. The mean age of the patients was 41.27±10.46 years and 35 of them were female. The mean age of HCs was 41.9±9.0 years and 14 of the HCs were female. There was no statistically significant difference between patients and HC in terms of gender or age (p=0.61; p=0.441, respectively). The mean disease duration of the patients was 9.23±7.52. 46 (44.2%) of the patients were receiving biological treatment, whereas 58 (55.8%) were receiving non-biological treatment or no medical treatment (Table 1).

Median SIRI was significantly higher in AS than in HC (p=0.001). The median SIRI was not significantly different between AS and HC (p=0.472). The median SIRI was significantly higher in BASDAI-a than in BASDA-r (p=0.005). Although the median SII was higher in BASDAI-a than in BASDA-r, there was no significant difference (p=0.256). The median SIRI was significantly higher in ASDAS-h than in ASDAS-l (p=0.015). Although the median SIRI was higher in ASDAS-h than in ASDAS-l, there was no statistically significant difference (p=0.113).

There was a positive linear correlation between SIRI and ASDAS-CRP (r=0.379; p=0.001), BASDAI (r=0.314; p=0.001), CRP (r=0.421; p=0.001), BASMI (r=0.296; p=0.002) in AS patients. In patients with AS, there was a positive linear correlation between SII and ASDAS-CRP (r=0.226; p=0.021) and CRP (r=0.293; p=0.003). The relationship among SIRI, SII, and other variables is shown in Table 2.

ROC curve analysis was performed to determine the optimal cut-off values of SIRI, CRP, and ESR to differentiate AS patients from HC; the optimal cut-off values of SIRI and CRP to differentiate BASDAI-a from BASDAI-r; and the optimal cut-off values of SIRI to differentiate ASDAS-h from ASDAS-l. SIRI is more sensitive and specific than other parameters for assessing disease activity. The optimal cut-off value of SIRI to differentiate BASDAI-a from BASDAI-r is 1.12. The optimal cut-off value of SIRI to differentiate ASDAS-h from ASDAS-l is 1.07. The area under the curve (AUC), sensitivity, specificity, and cut-off values are shown in Table 3.

Table 1. Comparisons between the groups			
Comparison of SIRI and SII between the patient and healthy control (HC)			
	Patient, (n=104)	**HC, (n=51)**	**p**
SIRI Median (1Q-3Q)	1.13 (0.76-1.51)	0.69 (0.54-0.92)	**0.001**
SII Median (1Q-3Q)	468.2 (315.44-595.2)	435.5 (352.5-573.5)	0.472
CRP (mg/L) Median (1Q-3Q)	4.83 (1.9-9.1)	0.92 (0.45-1.70)	**0.001**
ESR (mm/h) Median (1Q-3Q)	9 (5-20)	7 (3-12)	**0.021**
Comparison between the BASDAI-r and BASDAI-a groups			
	BASDAI-r, (n=49)	**BASDAI-a, (n=55)**	**p**
SIRI Mean ± SD	1.01±0.46	1.26±0.46	**0.005**
SII Median (1Q-3Q)	427.8 (304.4-592.0)	492.2 (365.2-601.4)	0.256
CRP (mg/L) Median (1Q-3Q)	4.36 (1.46-7.45)	5.56 (2.37-14.93)	**0.045**
ESR (mm/h) Median (1Q-3Q)	8 (4.5-7)	9 (5-25)	0.606
Comparison between ASDAS-r and ASDAS-a			
	ASDAS-r, (n=32)	**ASDAS-a, (n=72)**	**p**
SIRI Mean ± SD	0.98±0.52	1.22±0.43	**0.015**
SII Median (1Q-3Q)	420.1 (301.1-547.2)	485.7 (341.4-614.0)	0.113
CRP (mg/L) Median (1Q-3Q)	0.88 (2.18-4.80)	6.47 (2.62-14.25)	**0.001**
ESR (mm/h) Median (1Q-3Q)	9 (4-14,7)	5 (9-24)	0.131

SIRI: Systemic Inflammatory Response Index, SII: Systemic Immune Inflammation Index, HC: Healthy control, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

Table 2. Correlation analysis of SIRI and SII with the scales and laboratory findings									
	ASDAS-CRP	**BASDAI**	**CRP**	**ESR**	**BASFI**	**MASES**	**BASMI**	**VAS**	**DD**
SIRI									
r	**0.379***	**0.314***	**0.421***	0.101	0.182	-0.006	**0.296***	**0.248***	0.118
SII									
r	**0.226***	0.101	**0.293***	0.132	-0.031	0.038	0.137	0.188	0.007

*p<0.05 was considered significant. SIRI: Systemic Inflammatory Response Index, SII: Systemic Immune Inflammation Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ESR: Erythrocyte sedimentation rate, BASFI: Bath Ankylosing Spondylitis Functional Index, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, BASMI: Bath Ankylosing Spondylitis Metrology Index, VAS: Visual analog scale, DD: Disease duration

Discussion

Biological therapies are widely used to suppress disease activity for treating AS. Therefore, there is a need for early diagnosis and new parameters with higher sensitivity and specificity to prevent deformities and loss of functionality in patients with AS. ASAS recommends the use of acute-phase reactants as a tool to assess the level of disease activity and monitor the efficacy of therapeutic interventions (12). However, according to available reports, CRP and ESR have low sensitivity and specificity in AS patients (13). Therefore, normal CRP and ESR levels do not exclude the presence of inflammation.

A complete blood count is an inexpensive, rapid, and easily accessible test used to obtain information about the immune system. Previous studies have shown that neutrophils, monocytes, lymphocytes, and platelets assessed from a complete blood count play an important role in inflammatory events during AS development. Increased transcription and protein expression of inflammation-related genes in monocytes are effective in abnormal responses in monocytes of patients with AS (14). Neutrophils play an important role in the immune response by acting as the first protection against inflammatory stimulation caused by external pathogens. In many previous studies, cytokines and chemokines,

Table 3. ROC curve analysis

To differentiate patients from controls					
	AUC	**Cut-off**	**p**	**Sensitivity, (%)**	**Specificity, (%)**
CRP	0.848	1.77	0.000	76.0	76.5
ESR	0.614	8.5	0.021	52.9	52.9
SIRI	0.734	0.87	0.000	69.2	68.6
Differentiating BASDAI-a from BASDAI-r					
	AUC	**Cut-off**	**p**	**Sensitivity, (%)**	**Specificity, (%)**
CRP	0.614	4.83	0.045	54.5	55.1
SIRI	0.659	1.12	0.005	65.5	65.3
Differentiating ASDAS-h from ASDAS-l					
	AUC	**Cut-off**	**p**	**Sensitivity, (%)**	**Specificity, (%)**
SIRI	0.660	1.07	0.010	62.5	62.5

ROC: Receiver operating characteristic, AUC: Area under the curve, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SIRI: Systemic inflammatory response index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score

including interleukin-8 (IL-8), IL-17, interferon-gamma, and GM-CSF, have been shown to be effective in promoting the activation and viability of neutrophils. In another study, it was reported that the expression of genes such as ANXA3 and SORL1 differed significantly in AS patients compared with the control group. A significant positive correlation between these genes and neutrophil count was also found (15). Lymphocytes are also an important part of the immune system. Abnormal lymphocyte function is effective in the development of autoimmune diseases. An increase in the number of neutrophils in systemic inflammation corresponds to a decrease in the number of lymphocytes in immune system dysfunction (16,17).

Taha et al. (3) found the SII value to be significantly higher in AS patients than in HC patients. However, they used only ASDAS instead of BASDAI to assess disease activity. In addition, they divided AS patients into 3 groups according to their ASDAS scores: inactive, low activity, and high activity. They found that the SII value was significantly higher in the highly active disease group than in the inactive disease group. However, they did not find a significant difference between the other groups. Wu et al. (8) found the SII value to be significantly higher in AS patients than in the control group, unlike our study. In addition, they found the SII value to be significantly higher in active AS than in remission AS. Taha et al. (3) found SII to be positively correlated with CRP, ESR, and ASDAS in patients with AS, and Wu et al. (8) found SII to be positively correlated with CRP, ESR, and BASDAI in patients with AS. Similar to these studies, we found SII to be correlated with ASDAS and CRP levels. However, in this study, we did not find the SII value to be significantly different in AS patients than in healthy controls and in active AS patients than in remission AS patients. This may be because of the difference in the number of patients receiving biological therapy in the patient group. It has been previously reported that the use of TNF-alpha inhibitors may cause changes in cell counts (18). Another reason may be the difference in the cut-off values of the disease activity scales used. While Taha et al. (3) analysed 3 groups according to ASDAS in their study, we analysed in 2 groups according to ASDAS in this study. In our study, we also evaluated SIRI, unlike these studies. In our study, we also found SIRI to be correlated with ASDAS, BASDAI, CRP, BASMI, and VAS.

Satis (9) found that SII was significantly higher in RA than in HC. They also found that SII was significantly higher in patients with active disease than in those in remission. However, no significant difference was found between the disease groups in terms of SIRI. In contrast to this study, Xu et al. (19) reported that SIRI may help in the diagnosis of RA and that SIRI is associated with disease activity. In the same study, the author stated that SIRI could be used to predict tumor development and RA-related interstitial lung disease. In another study, Jin et al. (20) found that SIRI levels in patients with RA were much higher than those in patients with HC. They also found a strong correlation between SIRI and disease activity. In this study, they emphasized that high SIRI levels should be closely monitored for ischaemic stroke in RA.

In our study, we suggest that SIRI can be used to assess disease activity in RA. According to the ROC curve analysis, SIRI may be a more reliable parameter than CRP in determining disease activity by calculating the AUC. Its sensitivity and specificity in predicting disease activity were higher than those of CRP. In addition, the positive correlation of SIRI with scales assessing disease activity and mobilization in AS patients, such as BASDAI, ASDAS, and BASMI, emphasized that our findings should be considered.

Study Limitations

The limitations of our study are that it was retrospective and the number of patients was small and in a single center. Second, we could not evaluate the use of tobacco products by the patients, and the importance of this is that it has been previously reported that the neutrophil-to-lymphocyte ratio was associated with smoking, whereas the platelet-to-lymphocyte ratio was not affected by smoking (21). It would be appropriate to conduct additional studies to confirm the findings and evaluate the effect of SIRI and SIRI on the treatment responses of patients.

Conclusion

There is no doubt that new parameters are required to manage the difficulties in assessing disease activity in AS. These results show that SIRI can be taken into account when evaluating AS, and maybe a novel biomarker has been identified for evaluating disease activity.

Ethics Committee Approval: Approval of the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 262, date: 19.08.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - B.T.D., B.B.; Concept - B.T.D., M.O., F.B.; Design - B.T.D., B.B., M.O., E.A.; Data Collection or Processing - B.T.D., M.O., F.B.; Analysis or Interpretation - B.T.D., B.B., M.O., E.A.; Literature Search - B.T.D., E.A.; Writing - B.T.D., B.B., F.B.

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

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

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İstanbul Med J 2023; 24(4): 357-63
DOI: 10.4274/imj.galenos.2023.42949

Risk of the Development of Fibrosis in Metabolic Dysfunction-Associated Fatty Liver Disease in Patients with Rheumatoid Arthritis

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ABSTRACT

Introduction: Individuals diagnosed with rheumatoid arthritis (RA) face a heightened risk of developing metabolic dysfunction-associated fatty liver disease (MAFLD). The primary objective of this study was to examine the progression of hepatic fibrosis through non-invasive tests in patients with MAFLD, both those with RA and those without RA.

Methods: In our retrospective study, a total of 120 MAFLD patients aged between 18 and 65 years, excluding those with juvenile RA, were included. Patients were divided into two main groups as patients with (n=60) and without (control group, n=60) RA. Fibrosis-4 (FIB-4) and NAFLD Fibrosis Score (NFS) (NAFLD/MAFLD fibrosis) scores were used to determine the risk of hepatic fibrosis in patients with MAFLD. These scores were compared between the two groups. The relationship between FIB-4 and NFS scores and other parameters was evaluated. SPSS 25.0 software was used for statistical analysis, and significance was accepted as $p<0.05$.

Results: The RA group exhibited a higher NFS value than the control group ($p<0.05$). Receiver operating characteristic analysis indicated that NFS, although relatively weak, could be considered a viable variable for diagnosis ($p<0.05$). Notably, a statistically significant correlation was identified between the FIB-4 score and several other factors, including age, estimated-glomerular filtration rate, platelet (PLT) count, and aspartate aminotransferase values ($p<0.001$; $r=0.860$). Similarly, a statistically significant correlation was found between the NFS score and factors such as age ($p<0.001$), albumin ($p<0.001$), PLT count ($p<0.001$), and alanine aminotransferase values ($p<0.05$) ($r=0.956$).

Conclusion: Our study highlights that patients with both MAFLD and RA face a heightened risk of fibrosis progression compared with those without RA. While existing literature acknowledges MAFLD's association with liver fibrosis, there is a scarcity of research on RA's influence in this context. Our findings emphasize RA as an additional risk factor for liver fibrosis, particularly among patients with MAFLD. Consequently, liver fibrosis is more prevalent in patients with MAFLD and RA.

Keywords: Fibrosis, MAFLD, rheumatoid arthritis

Introduction

Persistent inflammation and excessive buildup of collagen in the extracellular matrix, primarily driven by chronic inflammation and damage to hepatocytes, play a pivotal role in the development of chronic liver disease. Over time, this fibrosis can progress to cirrhosis, portal hypertension, and liver failure. The etiological factors contributing to this condition include obesity, viral infections, systemic diseases, alcohol consumption, and metabolic-associated fatty liver disease (MAFLD). Despite liver biopsy being considered the gold standard for diagnosis, its invasiveness and limitations in fibrosis assessment have spurred interest in non-invasive alternatives. Notably, patients with rheumatoid arthritis (RA) are at an increased risk of developing MAFLD and subsequent liver fibrosis. Early detection of hepatic fibrosis in patients with RA is paramount for preventing complications, improving their quality of life, and mitigating healthcare costs. Unfortunately, there is a dearth of research investigating the influence of RA on fibrosis in individuals with MAFLD.

Although liver biopsy is regarded as the "gold standard" for diagnosis, it comes with limitations in evaluating fibrosis, potentially leading to heterogeneity within the liver parenchyma. Furthermore, it is an invasive procedure that may not be practical for frequent follow-up and monitoring. Consequently, there is a growing trend toward non-invasive tests that can serve as viable alternatives to biopsy. Patients with RA are susceptible to MAFLD and, consequently, liver fibrosis. Timely detection of hepatic fibrosis in patients with RA plays a pivotal role in averting fibrosis-related complications, enhancing their quality of life,

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Cite this article as: Aydın M, Aksakal B, Basat S. Risk of the Development of Fibrosis in Metabolic Dysfunction-Associated Fatty Liver Disease in Patients with Rheumatoid Arthritis. İstanbul Med J 2023; 24(4): 357-63.

Received: 14.08.2023
Accepted: 18.10.2023

and reducing overall healthcare expenses. Remarkably, no study has investigated the influence of RA on fibrosis in individuals with MAFLD.

The definition of MAFLD was validated using data from the "Third National Health and Nutrition Examination Surveys" (1988-1994) database, leading to the conclusion that MAFLD offers a more practical and precise framework for identifying patients compared with NAFLD/NASH (1).

MAFLD affects approximately one-quarter of the global adult population, imposing a significant healthcare and economic burden on societies worldwide. It is anticipated that the affected population will increase by up to 56% over the next decade (2). A recent meta-analysis reported the global prevalence of MAFLD at 25.2%. MAFLD exhibits higher prevalence rates in the Middle East (32%) and South America (31%), whereas Africa demonstrates a lower prevalence at 14%. Prevalence is 27% in Asia, 24% in North America, and 23% in Europe (3). Assessing liver damage is an important step in the management of individuals with chronic liver disease. Although liver biopsy is considered the gold standard for evaluating necrosis, inflammation, and fibrosis, its invasiveness and difficulty in repetition have led to the development of several non-invasive methods as alternatives to liver biopsy. Some non-invasive tests used for assessing hepatic fibrosis include fibrosis-4 (FIB-4), NAFLD Fibrosis Score (NFS), the AST to Platelet Ratio Index (APRI), and AST/ALT Ratio and Diabetes (BARD) (4).

Recent studies on the incidence and prevalence of RA have revealed significant variations in disease occurrence across different populations (5). The prevalence of RA varies from 0.5% to 1.0% in many populations, with higher rates observed in specific groups such as Pima Indians (5.3%) and Chippewa Indians (6.8%), while lower prevalence is noted in Chinese and Japanese populations (6).

RA is a progressive and chronic inflammatory disease characterized by uncontrolled proliferation of synovial tissue and the development of multisystemic comorbidities. Its pathogenesis results from a combination of genetic and environmental factors, with a higher incidence in women than in men. Without proper treatment, 20% to 30% of patients may experience permanent disability within 2 to 3 years after diagnosis (7). Extra-articular manifestations of RA can manifest at any age following its onset, affecting various organs such as the skin, eyes, heart, lungs, kidneys, nerves, and gastrointestinal system (8). Gastrointestinal and hepatological complications in RA are primarily iatrogenic and often stem from medication use (9). The most common non-iatrogenic gastrointestinal and hepatological comorbidity involves liver dysfunction, which is characterized by elevated liver function test results in 18% to 50% of patients. Other associated findings include intrahepatic bleeding, hepatosplenomegaly, cirrhosis, and necrotic pancreatitis (10).

Methods

This retrospective study was conducted at the Clinic of Internal Medicine and Rheumatology, University of Health Sciences Turkey, Ümraniye Training and Research Hospital from February 2020 to February 2022. The study included a total of 120 patients aged 18 to 65 who had been diagnosed with MAFLD. Ethical approval was obtained from University of Health Sciences Turkey, Ümraniye Training and Research Hospital Ethics Committee (approval number: B.10.1TKH.4.34.H.GP.0.01/41, date: 10.02.2022), and all participants provided informed consent. The patients were categorized into two primary groups: those with a diagnosis of RA and those without RA (the control group).

Both groups comprised patients with similar age and gender characteristics. In the RA group, special attention was paid to confirm the presence of abdominal imaging performed within the last year in patients who were not in the active phase of their disease and to assess the consistent use of antirheumatic drugs. Exclusion criteria for the study included patients with a history of cancer within the past 5 years, individuals with obesity, diabetes, hypertension, those undergoing chronic renal replacement therapy (such as hemodialysis, peritoneal dialysis, or renal transplantation), pregnant patients, as well as those with a history of chronic viral hepatitis or HIV infection.

In this study, individuals diagnosed with abnormal fat accumulation in liver cells, known as hepatic steatosis, were included in the non-RA MAFLD group. The diagnosis was based on findings from imaging, biomarkers, or histological assessments. To be eligible for inclusion, these patients needed to meet at least two of the following criteria: being overweight or obese or having metabolic dysfunction. These criteria included waist circumference measurements of ≥102 cm for men and ≥88 cm for women, blood pressure readings ≥135/85 mmHg or receiving treatment for hypertension, plasma triglyceride levels ≥150 mg/dL, high-density lipoprotein cholesterol levels <40/50 mg/dL for men/women, prediabetes, a Homeostatic Model Assessment for Insulin Resistance score ≥2.5, and plasma high-sensitivity C-reactive protein levels exceeding 2 mg/dL.

In contrast, the RA group consisted of patients diagnosed with RA.

FIB-4 score= [age x aspartate aminotransferase (AST)]/platelet (PLT) value x [alanine aminotransferase (ALT)] 1/2 was calculated using the formula. NFS= (-1.675 + 0.037 x age (yr) + 0.094 x body mass index (BMI) (kg/m^2) + 1.13 x impaired fasting glycaemia/diabetes (yes= 1, no= 0) + 0.99 x AST/ALT ratio - 0.013 x PLT count ($x10^9/L$) - 0.66 x albumin [g/dL)] was calculated using the formula.

To assess the risk of hepatic fibrosis in patients diagnosed with MAFLD, non-invasive tests were employed, including FIB-4 and NFS. FIB-4 was evaluated based on age, AST, ALT, and PLT values, with low risk indicated if <1.45 (F0-1), intermediate risk if 1.45/3.25 (F2-3), and high risk if >3.25 (F4-6). NFS, on the other hand, was assessed using age, BMI, diabetes mellitus, AST, ALT, ALB, and PLT values, categorizing individuals as low risk if <-1.455, intermediate risk if -1.455/0.675, and high risk if >0.675 for hepatic fibrosis.

Furthermore, the patients' BMI was calculated, and various laboratory tests were conducted during their diagnostic and treatment visits, encompassing fasting glucose, hemoglobin A1C (HbA1C), urea, creatinine, AST, ALT, glomerular filtration rate (GFR), lipid profile, complete blood count, and albumin levels. In addition, the results of liver imaging, including ultrasound, computed tomography, and magnetic resonance imaging, were verified and recorded through the hospital system.

Statistical Analysis

The data were analyzed using the SPSS 25.0 software package. To assess the data distribution, the Kolmogorov-Smirnov test was applied. Descriptive statistical techniques, including measures such as mean, standard deviation, median, interquartile range, frequency, and ratio, were employed to evaluate the study dataset.

To compare the two groups exhibiting a parametric distribution, the independent t-test was used. In cases where two groups demonstrated a non-parametric distribution, the Mann-Whitney U test was employed.

For the purpose of elucidating the variation in dependent variables, linear regression analysis was conducted. In addition, receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of FIB-4 and NFS values. In all analyses, statistical significance was considered $p<0.05$.

Results

The study enrolled a total of 120 participants, evenly divided into two groups: 60 patients diagnosed with RA, comprising 30 females and 30 males, and 60 patients diagnosed with non-RA, with an equal gender distribution. The patients' average age was 53.34±9.46 years, and their mean BMI was 25.73±1.15 kg/m2.

Descriptive statistics, encompassing measures such as mean, standard deviation, median, minimum, and maximum values, were computed for the laboratory parameters, FIB-4, and NFS scores, along with an assessment of liver fibrosis risk based on FIB-4 and NFS scores, as presented in Table 1.

To determine disparities in demographic and laboratory parameters between the groups, the independent t-test and Mann-Whitney U test were employed. The results, outlined in Table 2, revealed a statistically significant contrast in the median values of HbA1C and albumin ($p<0.05$). Specifically, the RA group exhibited higher HbA1C levels, whereas the non-RA group demonstrated elevated albumin levels.

Table 3 displays the outcomes of the Mann-Whitney U test, which investigated potential differences in FIB-4 and NFS scores between the groups. The findings indicated a statistically significant variance in NFS scores ($p<0.05$), signifying that NFS values diverged between the

Table 1. Descriptive statistics of patients' demographic and laboratory measurements

	Average ± SD	**Median (minimum-maximum)**
Age	53.34±9.46	54 (28-65)
Height (cm)	166.56±7.61	167 (152-192)
Weight (kg)	71.6±7.19	70.5 (56-100)
BMI (kg/m^2)	25.73±1.15	25.9 (22.2-27.4)
Glucose	94.23±7.18	94 (74-107)
HbA1C (%)	5.29±0.3	5.4 (4.6-6)
BUN	26.27±5.73	26 (15-45)
Creatinine	0.74±0.15	0.7 (0.4-1.1)
GFR	98.25±14.3	99 (63-135)
AST	22.02±10.82	19 (10-82)
ALT	23.75±15.48	19 (5-88)
PLT	270.24±79.56	262.5 (108-535)
Albumin	4.37±0.41	4.4 (2.6-5)
Total cholesterol	187.82±39.01	191 (102-299)
HDL cholesterol	46.18±11.57	44 (19-83)
LDL cholesterol	115.27±31.75	116 (46-211)
Triglyceride	133.05±66.16	114 (41-353)
FIB-4	1.02±0.62	0.88 (0.2-4.52)
NFS	-2.65±1.30	-2.54 (-6.62-0.74)
	n	**%**
FIB-4		
Low risk	100	83.3
Medium risk	18	15.0
High risk	2	1.7
NFS		
Low risk	101	84.2%
Medium risk	18	15.0%
High risk	1	0.8%

SD: Standard deviation, BMI: Body mass index, HbA1C: Hemoglobin A1C, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase platelet, ALT: Alanine aminotransferase, PLT: Platelet, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FIB-4: Fibrosis-4, NFS: NAFLD Fibrosis Score

groups. In contrast, the FIB-4 scores displayed no statistically significant disparity. Notably, NFS measurements were notably higher in the RA group.

Regression Analysis of the Effects of Risk Factors on FIB-4 Measurements in Patients with RA

The regression analysis outcomes revealed significant impacts of age, GFR, and PLT parameters on the model. Age emerged as the most influential factor, followed by PLT and GFR. Notably, the effects of age were statistically significant at $p<0.05$, while both PLT and GFR exhibited significant effects at the more stringent $p<0.001$ level within the model.

Regression Analysis of the Effects of Risk Factors on NFS Measurements in Patients with RA

In the univariate analysis of key variables such as age, BMI, and identified risk factors, which encompassed HbA1C, creatinine, GFR, ALT, PLT, albumin, and triglyceride levels, each of them demonstrated noteworthy individual impacts on NFS. To assess their combined effects, a linear regression (backward) analysis was conducted.

The results of the regression analysis indicated that all these parameters exerted significant influences on the model. Albumin emerged as the most influential, closely followed by age and PLT values. Notably, the effects of albumin, age, and PLT were deemed statistically significant at the $p<0.001$ level in the model.

Regression Analysis of the Effects of Risk Factors on FIB-4 Measurements in Non-RA Patients

In the univariate analysis of characteristic variables such as age, BMI, and identified risk factors including glucose, HbA1C, creatinine, AST, GFR, and PLT values, it was observed that they individually had significant effects on FIB-4. To demonstrate their multivariate effects, a linear regression (backward) analysis was conducted.

Regression Analysis of the Effects of Risk Factors on NFS Measurements in Non-RA Patients

The results of the regression analysis indicated that, with the exception of ALT, the other parameters did not have a significant impact on the model. However, the effect of ALT was deemed statistically significant at the $p<0.05$ level within the model.

In Table 4 and Figure 1, the ROC analysis outcomes revealed an area under the curve (AUC) of 59.0% for the FIB-4 variable, suggesting that FIB-4 is not statistically appropriate for diagnosis ($p>0.05$). Conversely,

Table 2. Comparison of demographic data and laboratory measurements between the groups

	RA		Non-RA			
	Median	IQR	Median	IQR	Z/t	p
Age	55.7	11.5	54.8	12.5	-0.762	0.415**
Height (cm)	166.0	10.0	167.0	12.0	-0.527	0.598**
Weight (kg)	70.0	9.0	72.0	11.0	-0.860	0.390**
BMI	26.0	1.6	25.9	2.0	-0.313	0.755**
Glucose	93.0	12.0	96.0	10.0	-1.934	0.053**
HbA1C	5.4	0.5	5.2	0.5	-2.192	**0.028****
BUN	26.0	4.0	26.0	10.0	0.063	0.950**
Creatinine	0.7	0.2	0.8	0.3	-1.194	0.232**
GFR	97.0	15.0	102.0	23.0	-1.345	0.181*
AST	18.0	9.0	20.0	11.0	-0.691	0.489**
ALT	19.0	13.0	22.0	17.0	-1.072	0.284**
PLT	255.0	103.0	270.0	89.0	-0.052	0.958**
Albumin	4.2	0.6	4.5	0.4	-4.058	**0.001****
Total cholesterol	193.0	49.0	190.0	49.0	-0.273	0.785*
HDL cholesterol	46.0	17.0	44.0	10.0	-10.69	0.285**
LDL cholesterol	112.0	36.0	119.0	42.0	-0.524	0.602*
Triglyceride	104.0	84.0	119.0	82.0	-0.258	0.796**

*Independent t-test, **Mann-Whitney U test, RA: Rheumatoid arthritis, IQR: Interquartile range, BMI: Body mass index, HbA1C: Hemoglobin A1C, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase platelet, ALT: Alanine aminotransferase, PLT: Platelet, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

Table 3. Comparison of demographic data and laboratory measurements between the groups

	RA		Non-RA			
	Median	IQR	Median	IQR	Z	p
FIB-4	0.91	0.58	0.81	0.64	-1.709	0.087**
NFS	-2.32	1.8	-2.87	1.76	-2.357	**0.018****

**Mann-Whitney U test, RA: Rheumatoid arthritis, IQR: Interquartile range, FIB-4: Fibrosis-4, NFS: NAFLD Fibrosis Score

Table 4. ROC analysis was conducted for the FIB-4 and NFS values

	AUC (95%)	Cut-off	Standard error	p	Sensitivity (%)	Specifity (%)
FIB-4	0.590 (0.488-0.693)	0.910	0.052	0.088	0.550	0.550
NFS	0.625 (0.525-0.724)	-2.505	0.051	**0.018**	0.567	0.583

*ROC curve, ROC: Receiver operating characteristic, FIB-4: Fibrosis-4, NFS: NAFLD Fibrosis Score, AUC: Area under the curve

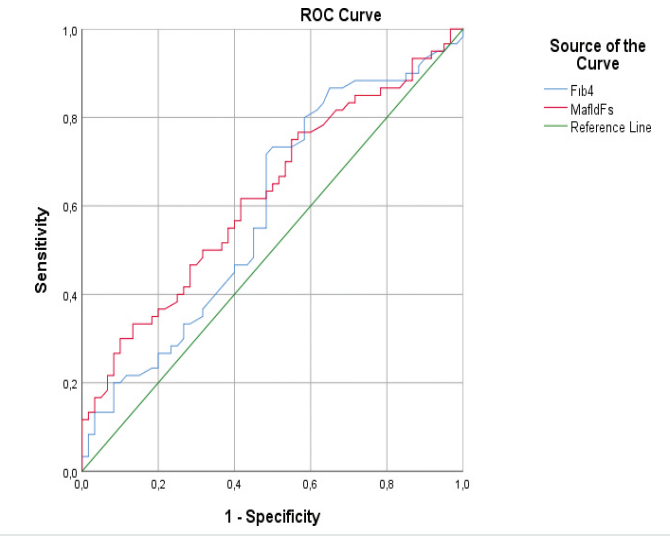

Figure 1. ROC curve for the FIB-4 and NFS values

ROC: Receiver operating characteristic, FIB-4: Fibrosis-4, NFS: NAFLD Fibrosis Score

the ROC analysis of the NFS variable yielded an AUC of 62.5%. The NFS value could be considered statistically suitable for diagnosis, although it demonstrates a relatively weak diagnostic capability ($p<0.05$).

Discussion

In this study, we demonstrated that RA increases the risk of liver fibrosis in individuals diagnosed with MAFLD. The uniqueness of MAFLD as a novel definition and the scarcity of research exploring its impact on liver fibrosis in patients with RA using non-invasive tests contribute to the value of our study.

Given the limitations associated with the gold standard method of liver biopsy for diagnosing liver fibrosis, various non-invasive methods have been developed. Primary among these methods are FIB-4, NFS, APRI, and BARD (11). A study conducted by Lee et al. (12) on non-invasive tests found significant AUC values for predicting liver-related events for NFS, FIB-4, and APRI. In another study by Roh et al. (13), FIB-4 was identified as having low sensitivity but high specificity in the diagnosis of liver fibrosis. In line with the existing literature, our study also found NFS to be a useful albeit weak diagnostic tool, while the same cannot be said for FIB-4.

A study by Yun Hao Xun et al., involving 152 NAFLD patients to assess the effectiveness of non-invasive tests in detecting fibrosis, reported FIB-4 and NFS scores similar to our study involving 120 patients. In Yun Hao Xun's study, FIB-4 exhibited low sensitivity but high specificity, and NFS also displayed low sensitivity but high specificity. Considering the body of literature, both tests can be considered specific in diagnosing liver fibrosis although they may have lower sensitivity. Correspondingly, in a study by McPherson et al. (14) in 2010, which included 145 patients with fatty liver, the effectiveness of non-invasive tests was evaluated. The results demonstrated that non-invasive tests could be safely employed in patients without advanced fibrosis. Our study similarly identified patients without advanced-stage fibrosis on the basis of their FIB-4 and NFS scores, further enhancing the meaningfulness of the findings.

Methotrexate (MTX) is a commonly prescribed medication for the treatment of specific malignancies, psoriasis, and rheumatoid diseases. Although hepatotoxicity is not a leading cause of death in RA patients undergoing MTX treatment, it represents the most frequently encountered side effect. Research has indicated that approximately 50% of Japanese patients with RA exhibit elevated serum AST and ALT levels. Typically, these elevations are mild and either self-correct or can be managed with additional folate supplementation. However, even when transaminase levels remain within the normal range, prolonged MTX use can lead to liver conditions such as steatosis, steatohepatitis, and fibrosis, which can ultimately progress to cirrhosis (15-17).

A study by Miyata et al. (18) examined the relationship between cumulative MTX dosage and FIB-4 scores in patients with RA using MTX. Notably, the average age of their study group was significantly higher compared to the average age of the patients in our study. Their exclusion criteria encompassed factors such as alcoholism, viral hepatitis, and autoimmune hepatitis. Interestingly, the control group in their study exhibited higher FIB-4 scores compared with our study (18).

In our study, we had a smaller number of patients with RA, all of whom were using MTX, and the average age of the RA group was lower. Our exclusion criteria covered a wide range of secondary causes of liver damage, including alcoholism, viral hepatitis, autoimmune hepatitis, advanced age, pregnancy, diabetes, obesity, hypertension, malignancy, and chronic renal replacement therapy. In our study, the FIB-4 score for patients with RA was low. Although the limited number of patients in our study should be acknowledged, the lower FIB-4 score can be attributed to the younger average age of our patients and the lower prevalence of comorbidities.

In our research, we discovered that age, GFR, and PLT count had significant effects on the FIB-4 score. While the effects of age and PLT were expected because they are already part of the scoring system, the influence of GFR was an unexpected finding, and this effect was not present in the non-RA group. This finding suggests that renal function may contribute to the progression of liver fibrosis in patients with RA. A study by Mima (19) involving 179 patients diagnosed with NAFLD and chronic kidney disease also found a significant effect of GFR on the FIB-4 score. Another study by Ishiba et al. (20) with patients diagnosed with NAFLD demonstrated that the FIB-4 score increased with age. Our study's findings align with the literature, showing a correlation between the FIB-4 score, age, and GFR.

NFS, another non-invasive test designed as an alternative to liver biopsy, evaluates age, BMI, insulin resistance/diabetes, AST, ALT, PLT, and albumin levels. According to a study by Wai-Sun et al. (21) in the Chinese population, implementing NFS would have rendered approximately four-fifths of liver biopsies unnecessary. Hsieh et al. (22) also established a relationship between NFS, age, and ALT in their study. Similarly, Gisondi et al. (23) identified a connection between NFS, age, and BMI. In accordance with the existing literature, our study also revealed correlations between age, ALT, and NFS. Furthermore, in our study, unlike the literature, we observed associations between PLT, albumin, and NFS in the RA group. These associations may be attributed to RA itself and the anti-rheumatic drugs employed. In contrast to the literature, we did not find a correlation between BMI and NFS scores in our study. This discrepancy could be attributed to the relatively similar BMI values among the patients included in our study, who were non-obese and non-cachectic.

While debates persist concerning the classification of liver damage as an extra-articular manifestation of RA, it is widely acknowledged that liver injury occurs in a range of 6-74% of RA patients. The primary factors contributing to liver damage in patients with RA include autoimmunity, infections, metabolic factors, alcohol consumption, and the adverse effects of medications (24). An autopsy study discovered abnormal liver histology in 92% of patients with RA, with clinical studies reporting similar abnormalities in 65% of cases. Predominant histological findings included periportal fibrosis, fatty liver, obstruction, and portal system inflammation (25). Patients with RA are susceptible to developing fatty liver disease because of their unfavorable metabolic profiles, adverse cardiovascular profiles, systemic inflammation, and chronic exposure to teratogenic drugs such as glucocorticoids and MTX (26). Research conducted by Ogdie et al. (27) revealed a higher prevalence and incidence of various liver diseases, including fatty liver and cirrhosis risk, in patients with RA compared with a control group. In our study, in line with the existing literature, both FIB-4 and NFS scores, which serve as predictors of liver damage, were elevated in the RA group. However, the disparity between the two groups was only statistically significant for NFS scores, likely because NFS evaluates a broader range of parameters. Additionally, our study's ROC analysis indicated that NFS is a more valuable tool than the FIB-4 score for diagnosing liver damage.

Indeed, the precise cause of liver damage in RA remains unclear, whether it results from the disease itself, medication use, or a combination of both factors. In our study, we tried to include patients with RA who were taking similar medications for comparable durations. However, concerns persist regarding the consistent and timely use of these medications by patients and whether they were exposed to additional hepatotoxic drugs (similar concerns apply to the control group as well).

Study Limitations

Several limitations characterize our study, including its single-center and retrospective nature. Assessments aimed at identifying liver hepatosteatosis were operator-dependent and qualitative. Furthermore, we employed only two tests to assess liver fibrosis, and there may be a relatively limited body of literature related to MAFLD because of its recent emergence as a diagnostic entity. These limitations are crucial to acknowledge when interpreting our study findings.

Conclusion

Our study employed two non-invasive tests for diagnosing liver fibrosis, with ROC analysis highlighting the utility of NFS as a diagnostic variable, despite its relative weakness. In line with the existing literature, our study revealed that age and GFR impacted the FIB-4 score, whereas age and ALT influenced the NFS score. In addition, we identified AST and PLT values as significant contributors to the FIB-4 score, and albumin and PLT values as significant determinants of the NFS score. Nevertheless, we believe that further comprehensive studies in this domain will offer valuable insights.

MAFLD is a recently adopted and more encompassing term for fatty liver disease linked to metabolic dysfunction. In our study, we observed higher NFS values in the RA group, implying that patients with RA diagnosed with MAFLD face an elevated risk of developing liver fibrosis.

Ethics Committee Approval: Ethical approval was obtained from University of Health Sciences Turkey, Ümraniye Training and Research Hospital Ethics Committee (approval number: B.10.1 TKH.4.34.H.GP.0.01/41, date: 10.02.2022).

Informed Consent: All participants provided informed consent.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 364-9
DOI: 10.4274/imj.galenos.2023.73483

Can Biomarkers be used for Prognosis Prediction in Patients with Acute Mesenteric Ischemia?

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ABSTRACT

Introduction: Acute mesenteric ischemia (AMI) is a severe clinical condition that leads to intestinal ischemia and necrosis due to acute blockage of the mesenteric arteries. The mortality rate of AMI is still high, and early diagnosis and treatment are lifesaving. This study provides an overview of the biochemical parameters used to determine the prognosis of AMI patients.

Methods: This was an observational and single-center study. Demographic data, vital signs, comorbidities, laboratory tests, operative status, length of hospital stay, and outcome information of patients diagnosed with AMI were recorded.

Results: Twenty-eight (41.2%) female and 40 (58.8%) male patients were included in the study. Of the patients diagnosed with AMI, 45 (66.2%) underwent surgery. Twenty-six patients (38.2%) had a fatal outcome. The area under the curve (AUC) values for blood urea nitrogen (BUN)/albumin [0.850 (0.743-0.925)] and lactate/albumin [0.753 (0.633-0.849)] were statistically significant ($p<0.001$) for the outcome. The AUC analysis for C-reactive protein/albumin [0.654 (0.529-0.765)] indicated a significant relationship for surgical settings ($p<0.05$). In the intensive care unit setting, all ratios were statistically significant.

Conclusion: This study shows that the BUN/albumin ratio is a robust prognostic indicator of patients with AMI and guides clinicians' decision-making. However, further studies are required to confirm these data.

Keywords: Acute mesenteric ischemia, early prediction, BUN, albumin

Introduction

Acute mesenteric ischemia (AMI) is a pathological disease characterized by intestinal ischemia and necrosis due to sudden occlusion of the mesenteric arteries. The mortality rate associated with acute myocardial infarction remains considerable, underscoring the critical need for timely identification and intervention to preserve lives (1). Several biochemical indicators are employed to assess the clinical prognosis of patients with acute myocardial infarction. Numerous blood tests, including blood urea nitrogen (BUN), have demonstrated associations with illness severity and prognosis. Measurement of BUN provides valuable insights into the functioning of the liver and kidneys. In addition, it is a useful tool in assessing the prognosis of patients with acute myocardial infarction (2,3).

Albumin is a biomarker that is closely linked to the severity of illnesses and can provide valuable insights into the prognosis of many medical conditions. Patients diagnosed with acute myocardial infarction who exhibit low albumin levels are more prone to have a worse prognosis. This trend is also observed in other pathological conditions (4,5). Lactate is a noteworthy indicator of cellular hypoxia and exhibits elevated levels in individuals with impaired tissue perfusion. Elevated lactate levels in patients with acute myocardial infarction have been correlated with a worse prognosis, as indicated by previous studies (6,7). C-reactive protein (CRP) serves as a biomarker for inflammation. Elevated levels of CRP are correlated with the severity of illness and prognosis in individuals with acute myocardial infarction (8). Historically, biochemical ratios, including BUN/albumin, lactate/albumin, and CRP/albumin ratios, have been used to assess the prognosis of patients with acute myocardial infarction. The predictive values of these ratios are greater than those of individual biochemical tests, as reported in previous studies (5).

This study comprehensively examines the biochemical measures employed for prognostic evaluation in patients with acute myocardial infarction. Therefore, it is possible to enhance comprehension regarding the timely identification and suitable management of patients with acute myocardial infarction.

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Cite this article as: Çınaroğlu OS, Bora ES, Efgan MG, Çınaroğlu D, Payza U. Can Biomarkers be used for Prognosis Prediction in Patients with Acute Mesenteric Ischemia?. İstanbul Med J 2023; 24(4): 364-9.

Received: 10.09.2023
Accepted: 23.10.2023

Methods

Study Design

This observational, single-center study was conducted in the emergency department of a tertiary care hospital. Ethical approval was obtained from the İzmir Katip Çelebi University Local Committee before the study (approval number: 0095, date: 24.02.2022). Demographic data, vital signs, comorbidities, laboratory tests, operative status, length of hospital stay, and outcome information of patients who presented to the emergency department and were diagnosed with AMI between March 2017 and May 2022 were recorded in a data form. BUN/albumin, lactate/albumin, and CRP/albumin ratios were calculated using the obtained data. All data were used for statistical analysis.

Patients and the Setting

The study included 104 patients aged 18 years who presented to the emergency department with an AMI diagnosis. Thirty-six patients whose laboratory test results or outcome information could not be accessed were excluded from the study. Information about 68 patients was retrieved from the hospital's electronic records. Patients under 18 years of age, those with end-stage renal failure, those previously diagnosed with AMI, and those with end-stage malignancy were excluded from the study.

Outcomes

The primary outcome of this study was to determine the predictive power of the BUN/Alb ratio on mortality and morbidity in AMI, and the secondary outcome was to investigate the superiority of the BUN/Alb ratio over the lactate/albumin and CRP/Alb ratios.

Data Collection

Data of the included patients were collected from the hospital information system, and their vital parameters, demographic data, and laboratory test results were recorded on patient forms created for statistical analysis. Information regarding admission to the service and intensive care unit (ICU) for AMI treatment, including mortality and discharge, was noted. The effects of the calculated BUN/albumin, lactate/albumin, and CRP/albumin ratios on hospital discharge and outcome were compared.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA). The descriptive statistics comprised the mean ($\bar{x}$), standard deviation, median, and interquartile range. The "Levene" test was used to evaluate variance homogeneity, a prerequisite for parametric testing. The normality assumption was tested using the Shapiro-Wilk test. If the data had a normal distribution, the "Independent two-sample t-test" was used to compare the groups. If data did not fit a normal distribution, the "Mann- Whitney U test" was used. Two or more diagnostic or laboratory tests were compared using the "receiver operating characteristic (ROC) curve" analytic method. Because the data did not meet the usual distribution standards, Spearman's rho coefficient was used to examine the relationship between the two quantitative variables. The chi-square test analyzed categorical data. P-values below 0.05 were considered significant.

Results

Twenty-eight (41.2%) female and 40 (58.8%) male patients were included in the study. Of the patients diagnosed with AMI, 45 (66.2%) underwent surgery, whereas 23 patients did not undergo surgery because of the lack of surgical indication. Twenty-six patients (38.2%) had fatal outcomes. Forty-two patients were discharged after the completion of their treatments. The average length of hospital stay for the patients was 7.98±9.41 days. Mean laboratory values were calculated on the basis of the obtained data. The mean BUN value was 29.82±19.84 mg/dL, creatinine value was 1.57±1.33 mg/dL, CRP value was 94.15±260.22 mg/L, albumin value was 31.92±8.58 g/dL, and lactate value was 3.42±3.61 U/L. The calculated BUN/albumin, lactate/albumin, and

Table 1. Laboratory values of the patients

Variables	Detailed statistics	
BUN (mmol/L)	$\bar{x}$± SD Median (min.-max.)	29.82±19.84 23 (7-87)
Creatinine (mg/dL)	$\bar{x}$ ± SD Median (min.-max.)	1.57±1.33 1.21 (0.49-8.64)
CRP (g/dL)	$\bar{x}$ ± SD Median (min.-max.)	94.15±260.22 20.08 (0.10-1528.0)
Albumin (g/dL)	$\bar{x}$ ± SD Median (min.-max.)	31.92±8.58 33 (10-48)
Lactate (mmol/L)	$\bar{x}$ ± SD Median (min.-max.)	3.42±3.61 2.20 (0.60-23.0)
BUN/albumin	$\bar{x}$ ± SD Median (min.-max.)	1.04±0.80 0.83 (0.19-4.35)
Lactate/albumin	$\bar{x}$ ± SD Median (min.-max.)	0.12±0.17 0.07 (0.02-1.10)
CRP/albumin	$\bar{x}$ ± SD Median (min.-max.)	1.91±3.29 0.53 (0-15)

$\bar{x}$: Mean, SD: Standard deviation, BUN: Blood urea nitrogen, CRP: C-reactive protein, min.: Minimum, max.: Maximum

CRP/albumin ratios were 1.04±0.80, 0.12±0.17, and 1.91±3.29, respectively (Table 1).

For outcome, the area under the curve (AUC) value for BUN/albumin [0.850 (0.743-0.925)] was statistically significant (p<0.05). A diagnostic value for BUN/Alb was considered to be above 0.7. The AUC analysis for BUN/albumin indicated a statistically significant diagnostic marker for the outcome. In addition, a value above 0.7 was an essential indicator in patient selection. The AUC value for lactate/albumin [0.753 (0.633-0.849)] was statistically significant (p<0.001). The diagnostic value for lactate/albumin was above 0.09. The AUC analysis confirmed that lactate/albumin is a statistically significant diagnostic marker for the outcome. Furthermore, a value above 0.09 was an essential indicator of patient selection. The ROC (AUC) analysis for CRP/albumin did not show statistical significance (p=0.342) (Table 2).

In the ICU setting, the AUC value for BUN/albumin [0.832 (0.722-0.912)] was statistically significant (p<0.05). The diagnostic value for BUN/Alb was considered to be above 1.04. The AUC analysis confirmed that BUN/albumin is a statistically significant diagnostic marker for the outcome. Additionally, a value above 1.04 was an essential indicator of patient selection. The AUC value for lactate/albumin [0.663 (0.539-0.774)] was statistically significant (p<0.05). The diagnostic value for lactate/albumin was above 0.09. The AUC analysis confirmed that lactate/albumin is a statistically significant diagnostic marker for the outcome. Furthermore, a value above 0.09 was an essential indicator of patient selection. The AUC value for CRP/albumin [0.657 (0.532-0.768)] was statistically significant (p<0.05). The diagnostic value for CRP/albumin was above 0.14. The AUC analysis confirmed that CRP/albumin is a statistically significant diagnostic marker for the outcome. Additionally, a value above 0.14 was a significant indicator of patient selection.

The AUC value for BUN/albumin in the surgical setting was insignificant (p=0.690). The AUC value for lactate/albumin was not statistically significant (p=0.311). The AUC analysis for CRP/albumin [0.654 (0.529-0.765)] indicated that the AUC was statistically significant (p<0.05). The diagnostic value for CRP/albumin was above 0.17. The AUC analysis confirmed that CRP/albumin was a statistically significant diagnostic marker for the outcome. Furthermore, a value above 0.17 was an important indicator of patient selection.

Patients admitted to the ICU with a high BUN/albumin ratio showed a 7.5 times higher risk than those receiving outpatient treatment (1,434-39,246). We observed a 4.56 (1,773-12,048) times higher BUN/albumin ratio in patients with fatal outcomes than in discharged patients (p=0.002). Among comorbidities, the mortality risk in patients with congestive heart failure was 5.23 (1,050-12,048) times higher than that in discharged patients (p=0.043). However, determining the lactate/albumin and CRP/albumin ratios was not statistically significant for distinguishing mortality (p>0.05).

While 65.5% of patients with a BUN/albumin ratio ≤0.7 were in the ward follow-up (p<0.001), this ratio was >0.7 in 85% of patients in the ICU (p<0.001). Among the surviving patients, 29 (69.0%) had a BUN/albumin value ≤0.7, which was statistically higher than that in patients with a BUN/albumin value >0.7. All patients with fatal outcomes (n=26) had a BUN/albumin value >0.7.

The BUN/albumin ratio was ≤1.04 in 90.9% of outpatients (p<0.001). This ratio was ≤1.04 in 86.2% of patients in the ward follow-up (p<0.001). On the other hand, the BUN/albumin ratio was >1.04 in 67.9% of ICU patients (p<0.001).

In the comparison of endpoint analysis, the number of patients with a BUN/albumin value ≤1.04 with a fatal outcome was 35 (83.3%), which was statistically higher than that of the patient group with a BUN/albumin ratio >1.04. The results supported the ROC analysis (Figure 1, Table 3).

Discussion

In this study, 68 patients with AMI were evaluated. Of the patients, 58.8% were male, 41.2% were female, and the mean hospitalization duration was 7.98±9.41 days. Similarly, Kougias et al. (9) reported that male patients were at higher risk, and the mean hospitalization period was 9.1 days. The treatment and outcomes of patients with AMI may show different outcomes in different studies. In our study, 66.2% of the patients underwent surgery.

In contrast, several studies noted different rates of operated patients. For instance, Reintam Blaser et al. (10) reported that only 31.8% of the patients underwent surgery; however, Yıldırım et al. (11) showed that 77.8% of the patients underwent surgery. It is known that patients

Table 2. ROC analysis for the outcome

		Area under the curve	Standard mistake	p	Area under the curve 95% confidence bounds		Sensitivity	Specificity	Limits
					Lower bound	Upper bound			
ROC analysis for the outcome	BUN/Alb	0.850	0.047	**<0.001**	0.743	0.925	69.05	100.0	>0.7
	Lactate/Alb	0.753	0.064	**<0.001**	0.633	0.849	69.23	80.95	>0.09
	CRP/Alb	0.570	0.073	0.342	0.444	0.690	76.92	45.24	-
ROC analysis for intensive care	BUN/Alb	0.832	0.050	**<0.001**	0.722	0.912	67.86	87.50	>1.04
	Lactate/Alb	0.663	0.069	**0.019**	0.539	0.774	57.14	75.0	>0.09
	CRP/Alb	0.657	0.067	**0.020**	0.532	0.768	85.71	42.50	>0.14
ROC analysis for surgery	BUN/Alb	0.629	0.070	0.690	0.503	0.743	85.0	46.43	-
	Lactate/Alb	0.571	0.070	0.311	0.445	0.690	37.50	78.57	-
	CRP/Alb	0.654	0.067	**0.023**	0.529	0.765	77.50	50.0	>0.17

ROC: Receiver operating characteristic, BUN: Blood urea nitrogen, CRP: C-reactive protein

diagnosed in the emergency department with AMI have a high mortality risk. In this study, 38.2% of the patients showed mortality. This rate was similar to that reported by Yıldırım et al. (11) in 2017. They showed that 31.2% of patients with AMI had a fatal outcome. Delayed diagnosis may be the main reason for higher mortality rates.

ROC analyses revealed that BUN/albumin, lactate/albumin, and CRP/albumin ratios are important prognostic indicators in patients with AMI. The AUC value for all three ratios (BUN/albumin especially) was statistically significant. These results are consistent with those of other studies in the literature. For instance, the BUN/albumin ratio is an important indicator in determining the mortality risks of patients with acute kidney injury during the ICU period (12-14). Similarly, the lactate/albumin ratio has been detected as a prognostic indicator of mortality in patients with severe sepsis (15). The CRP/albumin ratio has also been reported to be used as a prognostic tool in inflammation-related diseases (16). Although all ratios have a significant relationship, our results showed that the BUN/albumin ratio was the best predictor tool for determining mortality risk. Decreased effective circulating volume secondary to the body's defense mechanism caused by stress and indirectly high BUN level and/or meeting the energy need from protein (albumin) due to stress may be one of the reasons that increase this rate.

Numerous studies documented in the existing literature have demonstrated the potential use of the CRP/albumin ratio as a predictive tool for postoperative problems. Xu et al. (13) demonstrated that the CRP/albumin ratio serves as a reliable biomarker in the prediction of postoperative problems following colorectal cancer surgery. In a similar vein, Kougias et al. (9) found that the CRP/albumin ratio demonstrated a notable level of sensitivity and specificity when used as a predictive

Table 3. Reference value table for the BUN/albumin ratio

Prognosis boundary of the BUN/Alb ratio	**Groups**		**χ^2 value**	**p-value**
	≤0.7 n, (%)	**>0.7 n, (%)**		
Outpatient	6 (54.5)[a]	5 (45.5)[a]	16,046	**<0.001**
Ward	19 (65.5)[a]	10 (34.5)[b]		
Intensive care	4 (14.3)[a]	24 (85.7)[b]		
Outcome				
Survivor	29 (69.0)[a]	13 (31.0)[b]	31,302	**<0.001**
Ex	0 (0.0)[a]	26 (100.0)[b]		
to the limit value of BUN/albumin ratio (ICU and others)	Groups		**χ^2 value**	**p-value**
	≤1,04 n, (%)	>1.04 n, (%)		
Outpatient	10 (90.9)[a]	1 (9.1)[b]	22,178	**<0.001**
Ward	25 (86.2)[a]	4 (13.8)[b]		
Intensive care	9 (32.1)[a]	19 (67.9)[b]		
Outcome				
Survivor	9 (34.6)	17 (65.4)	16,690	**<0.001**
Ex	35 (83.3)	7 (16.7)		

χ^2: Chi-square test, %: Percentage of rows, BUN: Blood urea nitrogen, ICU: Intensive care unit

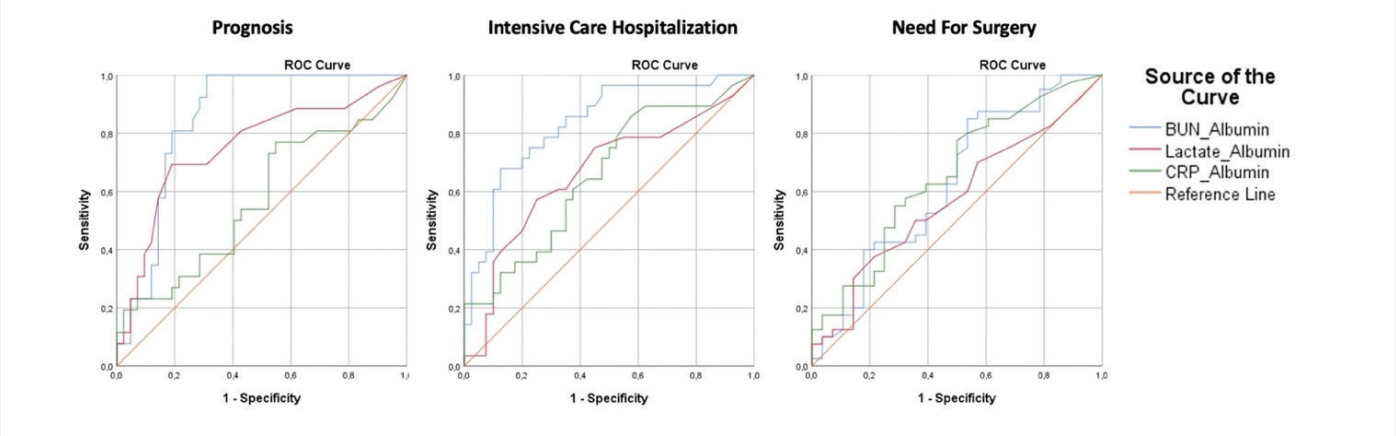

Figure 1. Diagram of the ROC analysis
ROC: Receiver operating characteristic, BUN: Blood urea nitrogen, CRP: C-reactive protein

measure for post-gastrectomy problems. Furthermore, several studies have demonstrated that the CRP/albumin ratio can serve as an effective tool for assessing inflammatory conditions. Zhang et al. (12) conducted a study that found that the CRP/albumin ratio was useful in predicting the outcomes of individuals afflicted with coronavirus disease-19. The findings of our study indicate that a CRP/albumin ratio of ≥0.17 may serve as a reliable predictor of postoperative problems. The observation that CRP exhibits positive acute phase reactivity, whereas albumin demonstrates negative acute phase reactivity, suggests that AMI, a significant stressor affecting several physiological systems, have the potential to enhance this phenomenon.

Another critical issue is anticipating the need for ICU in patients with AMI. Our results indicated that the BUN/albumin ratio was the best predictor of determining this requirement. In addition, lactate/albumin and CRP/albumin values were also effective parameters for predicting patients. These findings were consistent with those of other studies. Caluwaerts et al. (17) demonstrated that patients exhibiting an elevated BUN/albumin ratio have a heightened need for ICU services.

Furthermore, these patients experience elevated rates of death. In a similar vein, it was shown that a greater lactate/albumin ratio exhibited a positive correlation with a heightened need for ICU admission and an elevated risk of mortality (18). Moreover, this association was noted in patients with an elevated CRP/albumin ratio (19,20). This study examined the BUN/albumin ratio as a prognostic indicator in critical care unit hospitalizations, revealing its significant predictive capacity. In comparison with the other ratios discussed, it was determined that the BUN/albumin number is the most practical measure.

In a study by Efgan et al. (21), they found that the BUN/albumin ratio is as effective as the BISAP scores in determining high-risk acute pancreatitis. It also has powerful predictive power in pancreatitis, an inflammatory process like AMI.

Study Limitations

The most important limitations of this study are that it was retrospective and included only patients diagnosed with acute mesenteric artery ischaemia and not all patients presenting to the emergency department. The study was conducted using patient records. The onset and duration of symptoms and the time until diagnosis and treatment are important determinants of morbidity and mortality in patients with AMI; however, because, this study was designed as a retrospective study, appropriate data could not be accessed due to archiving deficiencies. another limitation is that the study could not be detailed in terms of imaging (affected vessel, affected bowel section, etc.).

Conclusion

This study shows that the BUN/albumin ratio is a robust prognostic indicator of patients with AMI and guides clinicians' decision-making. However, further studies are required to confirm these data.

Ethics Committee Approval: Ethics committee approval was obtained for the study from the İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee to which the hospital is affiliated (approval number: 0095, date: 24.02.2022).

Informed consent: Retrospective study.

Peer review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - O.S.Ç., E.S.B., M.G.E., D.Ç.; Design - O.S.Ç., U.P.; Data Collection or Processing - M.G.E., D.Ç.; Analysis or Interpretation - E.S.B., U.P.; Literature Search - O.S.Ç.; Writing - D.Ç.

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

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

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İstanbul Med J 2023; 24(4): 370-4
DOI: 10.4274/imj.galenos.2023.03704

Gastrointestinal Malignant Melanoma: A Single Center Experience

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ABSTRACT

Introduction: Malignant melanoma (MM) is a tumor that develops from skin-derived melanocytes and has a poor prognosis. Extracutaneous involvement of MM is also known, and one of these localizations is in the gastrointestinal tract. The study investigated gastrointestinal MM cases diagnosed as primary or metastatic in terms of their clinicopathological findings and survival rates.

Methods: Patients diagnosed with gastrointestinal MM in our clinic between August 2013 and December 2022 were retrospectively evaluated. Data including demographics, physical examination, laboratory and imaging findings, surgical procedures, oncological treatment status, presence of metastasis, histopathological features, and mortality were recorded and analyzed.

Results: The study group consisted of 9 patients: 4 (44.5%) women and 5 (55.5%) men with a mean age of 57.8±13.5 (median: 61, range: 40-75). Surgery could not be performed in four patients because of locally advanced or metastatic disease. Radical surgical interventions were performed in 4 (44.4%) patients who were operable. A second surgical intervention was performed in one patient. The mean duration of hospital stay of surgically treated patients was 6.4±4.3 (median: 5, range: 2-13) days. The mean overall survival in these patients was 40.0±25.7 (median: 40, range: 12-74) months. Three (33.3%) patients who underwent surgery are still being followed up.

Conclusion: In operable cases of histopathologically proven primary or metastatic MM disease, surgical treatment has an important impact on terms of providing local control and improving survival.

Keywords: Melanoma, gastrointestinal tract, neoplasm metastasis, general surgery

Introduction

Malignant melanoma (MM) is a skin-derived malignant tumor that has increased in frequency in recent years and has an aggressive course. MM is the rarest but most deadly type of skin cancer and is most likely to metastasize (1). MM can develop primarily in many organs other than the skin, albeit at a low rate. It may occur in the eye, oropharynx, nasopharynx, anal canal, rectum, small intestine, esophagus, or urinary system (2). The main presenting symptom of patients with primary gastrointestinal MM is bleeding. The diagnosis can usually be made by endoscopic visualization of the lesion. In the gastrointestinal tract, MM can also occur metastatically. Metastatic lesions may present with organ-specific symptoms. Radical surgical treatment of patients diagnosed histopathologically is effective for elimination of the disease and survival. Oncological treatment is also part of the treatment. Surgical treatment is the primary option for patients who develop gastrointestinal metastases.

Methods

All patients who were histopathologically diagnosed with primary or metastatic gastrointestinal MM between August 2013 and December 2022 in the department of general surgery were included. The study was conducted after the approval of the Local Ethics Committee of University of Health Sciences Turkey, Medeniyet University, Göztepe Training and Research Hospital (approval number: 2023/0199, date: 29.03.2023).

The patients' historical records, including demographics, physical examination, laboratory and imaging findings, surgical procedures, presence of metastases, histopathological features, and mortality, were prospectively recorded and retrospectively analyzed. Lesions located in the anorectum were diagnosed endoscopically or via excisional biopsy, whereas lesions located in the liver were diagnosed using

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Cite this article as: Özsoy MS, Eren T, Erol CI, Seneldir H, Baysal H, Büyüker F, Ekinci Ö, Alimoğlu O. Gastrointestinal Malignant Melanoma: A Single Center Experience. İstanbul Med J 2023; 24(4): 370-4.

Received: 10.08.2023
Accepted: 27.10.2023

Table 1. Patient characteristics

		n	%
Gender	Women	4	44.5
	Male	5	55.5
Diagnostic method	Endoscopic biopsy	6	66.7
	Excisional biopsy	1	11.1
	Tru-cut biopsy	2	22.2
Surgical procedure	No	5	55.5
	Yes	4	44.5
Surgical method	Right hemicolectomy, non-anatomical hepatectomy (segment 6), and duodenal wedge resection	1	25
	Abdominoperineal resection	1	25
	Segmentary liver resection	1	25
	Total transanal excision and non-anatomical hepatectomy (segments 4B and 5)	1	25

n: Number of patients

ultrasound- guided percutaneous tru-cut biopsy (Table 1). Magnetic resonance imaging (MRI) and 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) were used as cross-sectional imaging methods for detecting metastatic lesions.

Postsurgical and oncological follow-ups were conducted via office visits in the surgical outpatient clinic. Survival rates were determined at the end of the long-term follow-up period.

Statistical Analysis

Statistical analysis was performed using standard descriptive statistical methods (mean, median, percentage, minimum, maximum).

Results

The total study group of 9 patients consisted of 4 (44.5%) women and 5 (55.5%) men. The mean age of the patients was calculated to be 57.8±13.5 (median: 61, range: 40-75) years. 4 (44.4%) patients were considered inoperable because of locally advanced or metastatic disease. One patient (11.1%) who was lost to follow-up had to be excluded from the study mandatorily. Chemotherapy was initiated in 4 (44.4%) patients who were considered inoperable (Table 2). Among patients who were candidates for surgical treatment, primary lesions within the gastrointestinal tract were detected endoscopically, as in three patients (33.3%), the lesion was located in the anorectum. In one (11.1%) patient, imaging studies showed that the lesion was metastatically located in the liver, whose primary tumor site was known to be the uvea because she had a history of left eye enucleation 30 years ago.

The diagnosis of MM was confirmed histopathologically in all patients. Histopathological examinations revealed that the melanoma marker antibody (HMB-45) and pan cytokeratin (pan CK) were positive in all (100%) patients. Melanosomal protein (Melan-A) was positive in 5 (55.5%) patients, whereas 7 (77.8%) patients were positive for S100 protein, and the mean Ki-67 value was determined to be 71.7±17.2 (median: 80, range: 50-90) %.

Table 2. Non-operative malignant melanoma cases

Patient#	Age	Gender	Primary tumor location	Metastasis site	The type of biopsy	Surgical procedure	Recurrence/ metastasis	CD45	HMB45	S100	Melan-A	Pan CK	Ki67 (%)	Adjuvant therapy	Survival/ period
1	50	M	Anal canal	Liver	Excisional	No	+	0	+	+	0	-	80	+	Exitus/5 months
2	75	M	Rectum	Liver, lung	Endoscopic	No	+	0	+	+	+	-	80	+	Exitus/3 months
3	61	F	Skin	Liver	Tru-cut	No	+	0	+	+	0	-	-	+	Exitus/7 months
4	53	M	Skin	Liver, bone marrow	Tru-cut	No	+	0	+	-	+	0	50	+	Exitus/2 months

Table 3. Operative malignant melanoma cases

Patient#	Age	Gender	Primary tumor location	Metastasis site	The type of biopsy	Surgical procedure	TNM	HMB45	S100	Melan-A	Pan CK	Ki67 (%)	Adjuvant therapy	Distant metastasis	Survival/ period
1	40	F	Anal canal	None	Endoscopic	1. Total transanal excision (2016) 2. Right hemicolectomy non-anatomical hepatectomy (segment 6) And duodenal wedge resection (2020)	T4NxMx	+	+	No	-	80	+	+	Alive/74 months
2	64	F	Rectum	None	Endoscopic	Abdominoperineal resection	T2bN1bMx	+	+	+	-	-	+	+	Exitus/12 months
3	65	F	Uvea	Liver	Tru-cut	Non-anatomical hepatectomy (segments 4B and 5)	-	+	+	+	-	-	+	-	Alive/40 months
4	74	M	Anal canal	None	Endoscopic	Rectal polypectomy	-	+	+	+	-	50	+	+	Alive/34 months

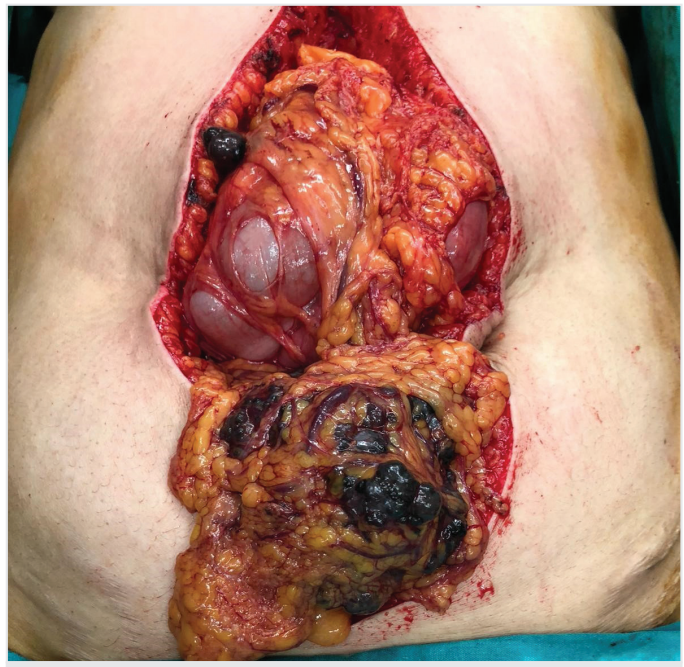

Figure 1. Right hemicolectomy, nonanatomical hepatectomy, and duodenal wedge resection were performed in this patient, and she is still being followed up with no new findings of recurrence or metastasis. Written informed consent was taken from the patient

Radical surgical procedures were performed for the lesion in 4 (44.4%) patients who were determined to be operable after their initial clinical and radiological evaluations (Table 3). Interventions performed on patients with primary gastrointestinal MM included rectal polypectomy, abdominoperineal resection, and total transanal excision. The patient with liver metastasis underwent non-anatomical hepatectomy. The mean duration of hospital stay in the early postoperative period was 6.4±4.3 (median: 5, range: 2-13) days.

In the patient who was treated with endoscopic polypectomy, local recurrence at the previous polypectomy site was encountered at control colonoscopy in the 4th year which also was confirmed via imaging studies. Right hemicolectomy, nonanatomical hepatectomy, and duodenal wedge resection were performed in this patient, and she is still being followed up with no new findings of recurrence or metastasis (Figure 1).

In the patient who underwent abdominoperineal resection as a radical surgical procedure, liver metastasis developed in the postoperative 3rd month and she died at the 12th month during her adjuvant treatment period.

All (100%) patients who were treated non-operatively died during their long-term follow-ups. Three (33.3%) surgically treated patients are still being followed up. At the end of the long-term follow-up period of the surgically treated patients, the overall survival was found to be 40.0±25.7 (median: 40, range: 12-74) months.

Discussion

MM is characterized by various molecular subtypes and different types of clinical presentations. It is the rarest but most deadly groups of skin cancers with the highest probability of metastasis (1). Although MM is a

primary skin tumor, the lesions are located extracutaneously in 4-5% of cases. It may develop in uveal, ocular, mucosal, anorectal, urinary, or vulvovaginal localizations other than the skin (3). The idea that primary gastrointestinal MM arises from anywhere in the gastrointestinal tract where melanocytes are present is common. However, lesions are predominantly detected in the anorectum (4).

Anorectal MMs detected in the gastrointestinal tract constitute approximately 0.4-1.1% of all MM cases (5). Anorectal MMs may originate from melanocytes located in the anoderm, which is the non-keratinized stratified squamous epithelium below the dentate line, as well as in the transitional zone neighboring the dentate line. In our study, the primary tumor sites within the gastrointestinal tract were detected to be the anorectum in 5 (55.5%) patients. The extraintestinal primary tumor sites were the skin in 2 (22.2%) patients and the uvea in one (11.1%) patient, as these cases had presented with liver metastasis.

Gastrointestinal MMs can be seen at any age, but it is reported that they are usually seen in the age of 50-60 yr (6). In our study, the mean age of the patients was calculated to be 57.8±13.5 (median: 61, range: 40-75) years. With the understanding of the disease and its molecular and immunological aspects, more effective treatment modalities have emerged recently (3).

The endoscopic appearance is not the same for every patient and may vary. Gastrointestinal metastatic lesions may also be misleading. Polypoid or excavated lesions may be observed, and although the color may be helpful in recognizing the lesion, some lesions may be amelanotic, and biopsy should be performed from suspicious lesions (7). Patients with gastrointestinal metastatic MM may present with nonspecific symptoms, such as abdominal pain or constipation, primarily depending on the affected location. Tumor-related gastrointestinal obstruction and active bleeding cases due to MM have also been reported (8). Bleeding is the most typical symptom in primary anorectal MM and should be considered in the differential diagnosis of hemorrhoids because of its localization and appearance. Endoscopic or excisional biopsies of the lesions observed on anorectal examination also contribute to the diagnosis. Gastrointestinal system MMs are mostly detected by the detection of cavitary, infiltrating, or polypoid lesions in endoscopic examinations performed to investigate gastrointestinal bleeding confirmed by the histopathological examination of the specimens of these lesions (9). In our study, all gastrointestinal primary lesions were histopathologically confirmed to be MMs according to their endoscopic biopsies.

Immunohistochemical positivity of HMB-45 facilitates the diagnosis of the disease (10). The presence of another immunohistochemical marker, S-100, is also important for definitive diagnosis, which is positive in most cases (11). In the present study, HMB-45 and pan CK were positive in all (100%) patients, whereas 7 (77.8%) patients were positive for S100 protein.

MM can metastasize to many organs and are among the most common carcinomas that metastasize to the gastrointestinal tract. However, it has also been reported that these tumors have a specific affinity for the small intestine, especially the jejunum and ileum (12). The clinical diagnosis of primary or metastatic MM disease may not be easy in the presence of non-specific or mild complaints. The interval between the surgical procedure for the primary lesion of MM and the metastatic disease may also be a confounding factor in the diagnosis. Distant metastases of MMs are mostly diagnosed within the first 3 years, but some cases report metastatic disease 15 years after initial treatment (13). Metastatic disease can be detected at the time of admission in approximately 4% of patients diagnosed with primary skin-related MM (7). MMs can also occur in the gastrointestinal tract, typically with liver metastases (4). Multifocal gastrointestinal mucosal melanomas are also usually of metastatic origin (14). In our study, most metastatic cases presented with liver metastases followed by lung and bone marrow metastases, as the primary tumor sites were primarily the gastrointestinal tract, especially the anorectum, followed by the skin and uvea. All 4 (44.4%) patients who were decided to be inoperable consisted of metastatic cases. Among surgically treated cases, only one (11.1%) patient presented with liver metastasis, which was considered operable according to pre-operative clinical evaluations.

In primary or metastatic gastrointestinal MM cases, imaging such as MRI, CT, or 18-FDG-PET/CT may be useful in identifying possible lesions or metastatic melanoma sites and can also be used during follow-up, especially in advanced disease (12). In lesions located in the anorectal region, pelvic MRI is important to determine the depth of the tumor and to have an idea about lymphatic involvement, therefore, to evaluate operability and determine the treatment method.

Radical surgery plays an important role in treating primary or metastatic MM of the gastrointestinal tract. Surgical intervention not only provides local control of the disease but also contributes to the elimination of possible bleeding or obstruction focus. In operable cases, there is an increase in the quality of life and survival of patients whose lesions can be resected by radical surgery (15). Before deciding on radical surgery for the disease, the comorbidities, age, general condition, and disease burden of the patients should also be considered. In this study, all (100%) patients who were treated non-operatively died during their long-term follow-ups. On the other hand, among surgically treated cases, one (11.1%) mortality occurred and three (33.3%) patients are still being followed up, revealing the survival benefit of surgical treatment as the median overall survival of these patients was found to 40 (range: 12-74) months.

Study Limitations

The limitations of our study can be considered as being a single-center study including a limited number of cases. However, given that primary or metastatic gastrointestinal MM is a rare presentation of this particular disease, we believe that the results of our series may shed light on the treatment outcomes of this entity.

Conclusion

The possibility of MM in primary or metastatic lesions detected in gastrointestinal system evaluations should be kept in mind, and should be considered in the differential diagnosis in histopathological examination. For treating histopathologically proven primary or

metastatic MM disease, surgical treatment plays an important role in providing local control of the disease in operable cases. There is an increase in patient survival with radical surgical procedures. Oncological treatment also maintains its place as a part of the multidisciplinary management of MM cases.

Ethics Committee Approval: The study was conducted after the approval of the Local Ethics Committee of University of Health Sciences Turkey, Medeniyet University, Göztepe Training and Research Hospital (approval number: 2023/0199, date: 29.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 375-8
DOI: 10.4274/imj.galenos.2023.25589

Impact of COVID-19 Lockdown on Glycemic Control in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: The coronavirus disease-2019 (COVID-19) pandemic resulted in social distancing measures. In this study, we investigated the impact of these measures on glycemic control in patients with type 2 diabetes mellitus.

Methods: This retrospective observational study was conducted at our hospital's obesity and diabetes clinic, involving patients who were regularly followed up. Data from two time points were retrieved from patient files: visit 1, which occurred within the three months before the lockdown, and visit 2, which occurred within the first two months following the lockdown. Exclusion criteria included pregnancy or breastfeeding, malignancy, start of medications influencing weight and body fat distribution, and non-compliance with regular follow-up appointments after lockdown. Anthropometric measurements and blood tests, including fasting glucose, lipid profile, and hemoglobin A1C (HbA1C) values, were compared between visits 1 and 2. The values of variables at visits 1 and 2 were compared using the Wilcoxon test.

Results: The study included 200 patients, with a mean age of 55.2±10 years, and a mean body mass index of 35.3±6.2 kg/m^2, with a female predominance (77.5%). Before the lockdown, the patients had a mean body weight of 91.4±16.0 kg, which increased to 93.1±16.3 kg after the lockdown ($p<0.001$). Blood examinations revealed a significant increase in mean fasting blood glucose levels, from 136±43.1 mg/dL to 148.0±53.6 mg/dL ($p=0.003$), as well as an increase in mean HbA1C levels from 7.2±1.4 to 7.9±1.7 ($p<0.001$).

Conclusion: During the lockdown period, patients with diabetes experienced weight gain and deterioration in diabetes regulation.

Keywords: Social distancing, lifestyle changes, glycemic control

Introduction

The coronavirus disease-2019 (COVID-19) pandemic, which is caused by the severe acute respiratory syndrome-coronavirus-2, originated in late 2019 in the People's Republic of China (1). Within a matter of weeks, COVID-19 swiftly spread to nearly all nations, prompting the World Health Organization to classify it as a pandemic. Diabetes mellitus (DM), another global pandemic, is an important public health problem worldwide, with its increasing prevalence at the beginning of the 21st-century. The data in our country show that the number of patients with diabetes has doubled in ten years, and the prevalence of diabetes in adults reached a critical level of 13.4% in 2010 (2). The coexistence of these two pandemics results in a poor prognosis in these patients (3).

One of the measures taken worldwide during the pandemic is social distancing, which includes maintaining a safe distance from others, avoiding large gatherings, and limiting physical contact. This has resulted in the interruption of the daily routines of the populace. In a prospective cohort study involving 1,565 Dutch patients with cardiovascular disease, a significant decrease in the amount of time spent exercising was observed, whereas sedentary time increased during the lockdown period (4). According to a recent study conducted by Elliot et al. (5), the percentage of people meeting the recommended levels of physical activity decreased during the lockdown period, dropping from 43% to 33%. In a cross-sectional study conducted in the adult population of Israel during COVID-19 measures, it was found that 70% of Israelis reduced their training compared with their usual routine (6).

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Cite this article as: Bahçacı Doğan F, Takır M, Doğan Ö, Torun C. Impact of COVID-19 Lockdown on Glycemic Control in Patients with Type 2 Diabetes Mellitus. İstanbul Med J 2023; 24(4): 375-8.

Received: 12.09.2023
Accepted: 30.10.2023

In our nation, from March 2020 until June 2021, a series of social distancing measures, including lockdowns, were implemented to mitigate the transmission of COVID-19. The objective of this study was to assess the effect of the lockdown period on the management of glycemic control in patients with type 2 DM.

Methods

Study Population

This retrospective, cross-sectional study was conducted at a single center in accordance with the principles of the Declaration of Helsinki. Approval for the study was obtained from the İstanbul Medeniyet University, Göztepe Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021/0374, date: 30.06.2021).

The records of patients with type 2 DM who were under regular follow-up at our hospital's obesity and diabetes outpatient clinic and who visited the clinic within the three months before the onset of the lockdown (visit 1) and within the two months following the beginning of the return to normalcy (visit 2) were retrospectively reviewed. The inclusion criteria comprised individuals who were 18 years of age or older and possessed comprehensive records of antidiabetic medication usage, anthropometric measurements, blood glucose levels, and HbA1C levels at both visits 1 and 2. Exclusion criteria included pregnancy or breastfeeding, diagnosis of malignancy, initiation of drugs affecting weight and body fat distribution (such as glucocorticoids), presence of critical illness that may impact nutritional status, and failure to attend regular follow-up after the lockdown. Eligible patients were consecutively included in the study.

Clinical Assessment

Patient data, including age, gender, height, body weight, treatment status, and results of full blood count and biochemical tests, were collected from the medical records of the obesity and diabetes clinic and the hospital's electronic information system (Nucleus®).

Height and weight measurements were obtained using an height scale and automatic weight machine, and the body mass index (BMI) was calculated.

Laboratory examinations were conducted after an overnight fast of 8-12 hours, including fasting plasma glucose, HbA1C, triglycerides, and high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Complete blood counts were performed using venous blood samples on a Mindray BC-6800 (Mindray BioMedical Electronics Co., Ltd., Shenzhen, China) device. Thyroid function tests were performed using the Roche Cobas e801 (Roche Diagnostics, Basel, Switzerland) module.

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated using the following equation: glucose (mg/dL) x insulin (mU/L)/405.

Statistical Analysis

Descriptive statistics, including mean, standard deviation, number, and percentage frequencies, were used to summarize the characteristics of the study participants. The normality of the continuous variables was assessed using the Kolmogorov-Smirnov test.

For the assessment of differences between dependent variables, the Wilcoxon signed-rank test was used. Statistical analysis was conducted using IBM SPSS Statistics 18 software. The significance level was set at 0.05 for all analyses.

Results

Of the 200 patients included in the study, 45 (22.5%) were male and 155 (77.5%) were female. The mean age of the patients was 55.2±10 years. The mean height of the patients was 161.1±8.3 cm, mean weight was 91.4±16.0 kg, and mean BMI was 35.3±6.2. Table 1 presents the demographic data and clinical characteristics of the patients. Among the participants, 78 (39%) had a history of hypertension, 57 (28.5%) had hyperlipidemia, 25 (12.5%) had hypothyroidism, and 4 (2%) had coronary artery disease.

During the lockdown (between visit 1 and 2), laboratory examinations indicated a significant increase in the mean fasting glucose levels from 136±43.1 mg/dL to 148.0±53.6 mg/dL (p=0.003). The HbA1C levels of the patients also showed a significant increase from 7.2±1.3 to 7.9±1.7 (p<0.001). Other parameters associated with metabolic syndrome were examined, revealing that the mean triglyceride level increased from 176±153 mg/dL to 190±133 mg/dL (p=0.001). No significant changes were observed in HOMA-IR and HDL cholesterol levels (p=0.171 and 0.889, respectively). Additional laboratory findings are presented in Table 2. The mean weight of the patients increased from 91.4±16.0 kg to 93.1±16.3 kg (p<0.001), leading to a significant increase in the mean BMI (p<0.001). Table 2 presents a comparison of patients' anthropometric measurements between visits 1 and 2.

Table 1. Demographic data and clinical characteristics of patients during visit 1

Age, year (mean ± SD)	55±10
Gender, n (%)	
Female	155 (77.5)
Male	45 (22.5)
Height, cm (mean ± SD)	161.1±8.3
Weight, kg (mean ± SD)	91.4±16.0
BMI, kg/m^2 (mean ± SD)	35.3±6.2
Body mass index group, kg/m^2, n (%)	
20-24.9	8 (4.0)
25-29.9	35 (17.5)
30-34.9	54 (27.0)
35-44.9	87 (43.5)
45-49.9	12 (6.0)
50 and above	4 (2.0)
Hypertension, n (%)	78 (39)
Hyperlipidemia, n (%)	57 (28.5)
Hypotiroid, n (%)	25 (12.5)
Coronery artery disease, n (%)	4 (2.0)

SD: Standart deviation, BMI: Body mass index

Table 2. Changes in laboratory and anthropometric values of patients between visit 1 and visit 2

	Visit 1, (mean ± SD)	Visit 2, (mean ± SD)	p-value
Glucose (mg/dL)	136.3±43.1	148.0±53.6	0.003
HbA1C (mmol/mol)	7.2±1.3	7.9±1.7	<0.001
Insulin (mU/L)	16.1±18.6	12.5±10.2	0.043
HOMA-IR	5.5±7	4.6±3.9	0.171
Creatinine (mg/dL)	0.8±0.2	0.8±0.2	<0.001
ALT (U/L)	24±18	23±18	0.184
AST (U/L)	20±10	20±10	0.606
Total cholesterol (mg/dL)	198±46	188±43	0.002
Triglyceride (mg/dL)	176±153	190±133	0.001
LDL cholesterol (mg/dL)	114±37	101±35	<0.001
HDL cholesterol (mg/dL)	50±13	50±13	0.889
TSH (mIU/L)	2±2.08	2.4±2.2	<0.001
T4 (ng/dL)	1.0±0.2	1.2±0.2	<0.001
Hemoglobin (g/dL)	13.3±1.5	13.4±1.6	0.596
Weight (kg)	91.4±16.0	93.1±16.3	<0.001
BMI (kg/m^2)	35.3±6.2	38.5±6.3	<0.001

SD: Standart deviation, HbA1C: Hemoglobin A1C, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid-stimulating hormone, BMI: Body mass index

Discussion

Our study revealed significant increases in patients' body weight, fasting blood glucose, HbA1C, and triglyceride levels during the post-lockdown examination compared with the pre-lockdown findings.

To mitigate the transmission of the COVID-19 infection, social distancing measures were implemented in our country and worldwide during the pandemic. Previous studies have investigated the influence of these measures, including lockdown, on changes in weight, which are of significant importance for cardiometabolic diseases. A population-based study involving 3,473 American adults revealed that 48% of participants reported weight gain one year after the pandemic, with a higher tendency for weight gain among those who were already overweight before the pandemic (7). Our study aligns with these findings because, we observed a significant increase in weight during the lockdown period. A recent meta-analysis, which evaluated data from 36 studies, also revealed a prevailing tendency for weight gain during lockdown (8).

Studies investigating changes in metabolic parameters and anthropometric measurements during the pandemic period suggest that the increase in body weight during this period is associated with sudden lifestyle changes. A study conducted in Spain demonstrated that type 2 diabetes patients experienced physical inactivity during house arrest (9). According to a survey study on house arrest during the pandemic period, daily sitting time increased from 5 to 8 h and eating quality worsened (10). Although our study did not specifically examine patients' lifestyle changes, we excluded other factors such as medications and inflammatory processes that could contribute to weight change.

In our study, we found significant increases in patients' fasting blood glucose, triglyceride, and HbA1C levels. Numerous studies investigating the course of diabetes during the pandemic have also reported impaired metabolic parameters. In a study, Karataş et al. (11) evaluated the impact of COVID-19 on patients with diabetes and healthy individuals. They found weight gain in both groups, impaired glucose metabolism, and increased triglyceride levels in patients with diabetes (11). The recently conducted meta-analysis demonstrated a significant increase ($p<0.05$) in HbA1C levels, fasting glucose, and BMI among patients with type 2 diabetes during the COVID-19 lockdown, which is consistent with our findings. Interestingly, they also found that total cholesterol, triglyceride, and LDL cholesterol levels were lower than those in the pre-lockdown period. Similarly, in our study, we observed a significant decrease in LDL cholesterol and total cholesterol, which could be attributed to improved adherence to statin medication during the pandemic period (12).

The management of chronic illnesses was interrupted during the pandemic period (13,14). In their study, Khader et al. (15) demonstrated that the disruption in diabetes care during the lockdown has contributed to the decline in glycemic control among patients with diabetes. However, in our country, the fact that medications could be obtained from pharmacies without the need for a prescription during the lockdown period and the examination of post-lockdown medical records revealed no decrease in medication adherence among patients, challenges the assumption that healthcare access difficulties are the primary cause. In a study with type 2 diabetes, significant improvement in medication adherence was observed during the lockdown period (16). A review by Eberle et al. (17), which investigated the effect of COVID-19 quarantine on glycemic control in patients with diabetes, observed significant improvement in glycemic values among individuals with type 1 diabetes during the quarantine period, attributed to compliance with insulin treatment and scheduled meals. Taking into account these combined findings, we are inclined to believe that the decline in glycemic control during this period is primarily a result of sudden lifestyle changes.

Study Limitations

The strength of our study lies in the detailed examination and exclusion of other factors that could contribute to weight changes and deterioration of glycemic control, apart from lifestyle changes. However, there are some limitations to our study. First, since it was conducted in a single diabetes center with a homogeneous population, the findings may not be applicable to different populations. Second, we did not have information regarding whether patients continued their active work life during the lockdown, engaged in exercise, or had any dietary habits. Therefore, our study did not specifically investigate which lifestyle changes were more closely associated with a deterioration in glycemic control, such as alterations in diet quality, adherence to dietary recommendations, meal timings, frequency of snacking, consumption of ready-made meals, frequency of ordering food from external sources, fruit consumption, alcohol consumption, exercise duration and frequency, and the duration of time spent at home. Finally, upon reviewing the patient files during post-lockdown visits, although all patients indicated that they obtained their medications from the pharmacy during the lockdown period, we do not have any data to confirm whether they consistently used their medications.

Conclusion

Our findings indicate that during the lockdown period implemented because of the COVID-19 pandemic, there was a tendency for diabetes patients to gain weight and experience deterioration in glycemic control. The reason behind this is the sudden lifestyle changes resulting from the restrictions, and these results confirm the role of lifestyle recommendations in disease management for patients with diabetes.

Ethics Committee Approval: Approval for the study was obtained from the İstanbul Medeniyet University, Göztepe Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021/0374, date: 30.06.2021).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - F.B.D., M.T., Ö.D.; Concept - F.B.D., M.T., C.T.; Design - F.B.D., M.T., Ö.D.; Data Collection or Processing - F.B.D., M.T., Ö.D., C.T.; Analysis or Interpretation - F.B.D., M.T., Ö.D., C.T.; Literature Search - F.B.D., M.T., Ö.D., C.T.; Writing - F.B.D., C.T.

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

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

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İstanbul Med J 2023; 24(4): 379-83
DOI: 10.4274/imj.galenos.2023.01057

Comparison of Conservative and Closed Reduction Percutaneous Pinning Methods for the Treatment of 5th Metacarpal Neck Fractures

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ABSTRACT

Introduction: This study aimed to evaluate the clinical and radiological outcomes of conservative treatment and closed reduction with anterograde pinning for the treatment of 5th metacarpal (MC) neck fractures.

Methods: Data of patients who underwent surgery for 5th MC neck fractures between January 2017 and December 2020 were retrospectively analyzed. Two groups were formed: those treated with closed reduction and anterograde intramedullary Kirschner wire fixation and those treated with closed reduction and casting. The groups were statistically compared in terms of pre- and post-treatment radiological angulation, functional outcomes, and return to work times. Quick-Disability of Arm, Shoulder and Hand Outcome Measure and visual analog scale (VAS) were used for functional scoring.

Results: The study included 33 patients (6 male, 27 female) treated conservatively and 32 patients (4 male, 28 female) treated with closed reduction and anterograde percutaneous pinning. In the closed reduction and casting group, the post-treatment angulation was measured as 19 degrees (10-30). In the anterograde pinning group, the post-treatment angulation was 15 degrees (9-20). At the end of the first year, 5th MC joint flexion was measured as 75 degrees (30-100) in group 1 and 75 degrees (50-100) in group 2. The DASH score was 0 (0-25) in group 1 and 0 (0-40) in group 2. The VAS score was 96 (18-100) in group 1 and 100 (30-100) in group 2.

Conclusion: The results of this study suggest that intramedullary Kirschner wire fixation is a safe option for treating 5th MC neck fractures. In addition, an increase in angulation was observed after closed reduction even in cases where acceptable limits of angulation were maintained. While emphasizing the need for more comprehensive research, this study also suggests that surgical treatment could be effective in different angulations.

Keywords: 5th metacarpal neck fracture, percutaneous pinning, conservative treatment, closed reduction

Introduction

Fractures of the hand can lead to significant issues affecting daily life activities, making the treatment of such fractures of paramount importance. In particular, the 5th metacarpal (MC) bone fracture is a commonly encountered type of hand fracture in adults, often affecting males and displaying a tendency to occur in the dominant hand (1). The incidence of such fractures generally peaks within the age group of 10 to 29 years (2). Conservative and surgical approaches are used to treat MC fractures. Treatment options maintain hand mobility and restore grip strength. The decision to perform surgical intervention is based on factors such as the presence of clinical abnormalities or radiological evaluations. Specifically, factors such as clinical abnormalities in the frontal or horizontal axis (malrotation) or radiological palmar tilt determine surgical indications. The palmar tilt limit varies between 30° and 45° in adults (3). Studies indicate that with a palmar tilt of 30° at the distal end of the MC, there is an 8% loss of grip strength in the 5th digit and a 22% loss of MCP joint mobility (4,5). Additionally, due to displacement during flexion, a 2-10 mm shortening of the MC can result in an 8% to 55% reduction in interosseous muscle strength (6). Surgical treatment options include external fixation, percutaneous K-wire fixation, and internal fixation with a plate. Among minimally invasive percutaneous methods, anterograde intramedullary pinning and cross-pinning between the fourth and 5th rays are also employed (7-10). We preferred the anterograde intramedullary pinning technique because it provides less soft tissue damage and a more stable fixation than the cross-pinning technique. This study aimed to evaluate the clinical and

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Cite this article as: Karıksız M, Erol MF. Comparison of Conservative and Closed Reduction Percutaneous Pinning Methods for the Treatment of 5th Metacarpal Neck Fractures. İstanbul Med J 2023; 24(4): 379-83.

Received: 02.09.2023
Accepted: 05.11.2023

radiological outcomes of conservative treatment and closed reduction with anterograde pinning in treating neck fractures of the 5th MC bone. This study was conducted to understand which method is more effective for treating 5th MC fractures and to shed light on clinical practices.

Methods

This study was based on a retrospective analysis of data from patients who underwent surgery for fractures of the 5th MC neck between January 2017 and December 2020. In accordance with the ethical considerations of our study, necessary permissions were obtained from the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Local Ethics Committee (approval number: 490, date: 12.06.2020). Patients 18 years of age, those with open or comminuted fractures, or those treated with a different method were excluded from the study.

The patients included in the study were divided into two treatment method groups: patients treated with closed reduction and anterograde intramedullary Kirschner wire fixation method and patients treated with closed reduction and casting method. Written informed consent forms were obtained from all patients planned to be included in the study.

These two groups were extensively evaluated regarding radiological angulation values, functional outcomes, and return-to-work durations during pre- and post-treatment periods. Quick-Disability of Arm, Shoulder and Hand Outcome Measure score and visual analog scale (VAS) were used to measure functional outcomes (11).

The main objective of this study was to compare the effects of different treatment methods on the clinical outcomes of patients with fractures of the 5th MC neck. The collected data were statistically analyzed, and the results were reported in detail.

Closed Reduction and Cast Fixation Method

Application of the Method

The patients were placed in a supine position in the outpatient clinic. Traction was applied to the fracture area, and reduction was performed closed using the Jahss maneuver. In this method, the metacarpophalangeal (MP) joint and proximal interphalangeal joints were flexed to 90 degrees, and reduction was completed by pushing the MC distal fragment of the proximal phalanx dorsally (12). Subsequently, an ulnar gutter splint was applied with the wrist in 30 degrees of extension and the MP joint in 70 degrees of flexion (13) (Figure 1). The splint was shaped by applying slight pressure to the distal volar and proximal dorsal sides to prevent malalignment in the fracture area. The following splint application, confirmation of proper alignment was obtained using control plain radiographs.

Post-Treatment Period

All patients were invited for weekly follow-up appointments. For patients with confirmed alignment during the first two weeks of follow-up, removal of the cast was planned for the 5th week of treatment. The cast was removed, and wrist and hand exercises were recommended after detecting sufficient signs of bone union in direct radiographs taken at the end of the 5th week. When adequate joint range of motion and muscle strength were restored at follow-up appointments two weeks later, patients were granted permission to return to work. Cases with insufficient rehabilitation progress were included in a physical therapy and rehabilitation program.

Closed Reduction and Antegrade Intramedullary Kirschner Wire Fixation Method

Surgical Technique

In cases with an angulation of 30 degrees or more at the fracture site, a surgical treatment approach was chosen. All surgeries were performed under regional block anesthesia applied to the dorsal and volar branches of the ulnar nerve at the proximal level of the 5th MC. Suitable diameter Kirschner wires were selected and shaped for operation (Figure 2). A percutaneous entry site was prepared under fluoroscopic control, twice the width of the chosen Kirschner wire from the ulnar side, at the proximal dorsal aspect of the 5th MC. The wires were placed with rotational manipulations into the MC medulla under fluoroscopic guidance. Once the fracture line was reached, appropriate alignment was achieved using the Jahss technique. Subsequently, after confirming that the tip of the first wire was within the distal fragment, it was rotated dorsally to secure the fracture alignment. The second wire was advanced into the distal fragment through similar manipulations under fluoroscopic control to achieve compression. The procedure was concluded by dressing the wire tips.

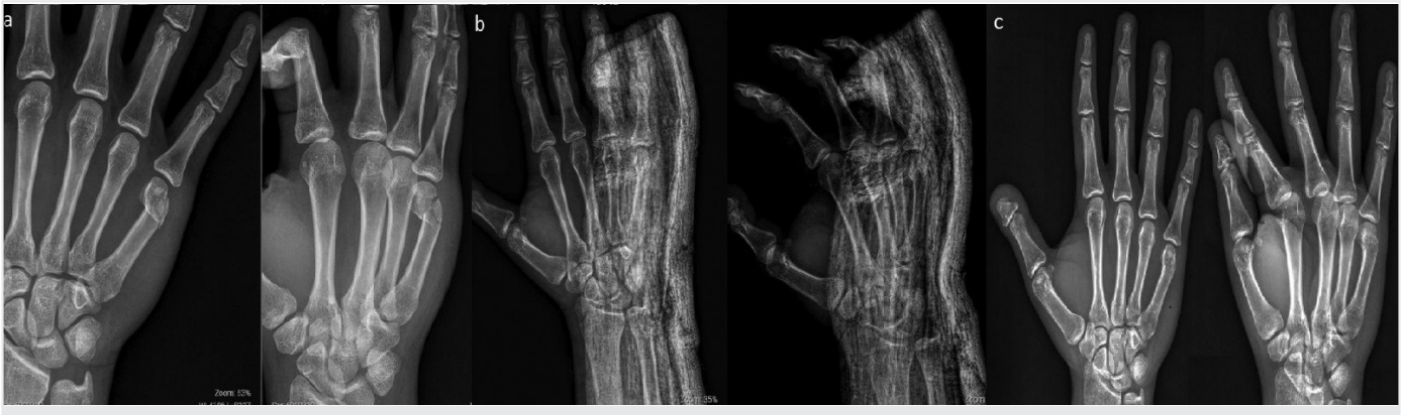

Figure 1. (a) Two-way X-ray (5th metacarp neck fracture), (b) two X-rays (after conservative treatment), (c) two X-rays (after bone healing)

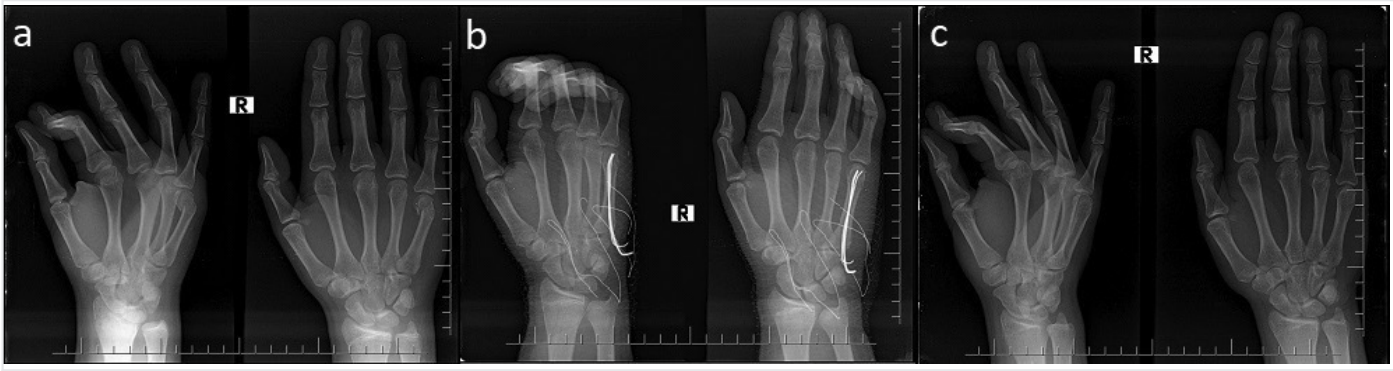

Figure 2. (a) Two-way X-ray (5th metacarp neck fracture), (b) Two X-rays (after surgical operation), (c) Two X-rays (after bone healing)

Post-Treatment Period

All patients were discharged on the day of surgery. Starting from the first day after the operation, wrist and hand exercises were recommended to the patients. Patients engaged in jobs that did not require heavy lifting were granted immediate permission to return to work. Patients were evaluated on the 10th day after the operation to assess joint range of motion. A physical therapy and rehabilitation program was planned for patients who did not reach the rehabilitation level. Radiographic assessment of bone union was performed during the 5th week of follow-up. When sufficient signs of bone union were observed, the wires were extracted under outpatient conditions. The following wire removal, no rehabilitation program was implemented.

Statistical Analysis

SPSS 16.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis. Measurement values are expressed as mean and standard deviation.

Results

In the first group, 6 patients were female and 27 were male. In the second group, there were 4 female and 28 male patients. The mean ages of the groups were determined as 29 (18-65) and 25 (18-67), respectively. The average time to intervention was 2 (1-7) days in the first group and 4 (1-10) days in the second group. The pre-intervention palmar angulation value was measured as an average of 41 (30-60) degrees in the first group and 43 (30-62) degrees in the second group (Table 1). In the group treated with closed reduction and casting, the post-treatment angulation values were measured as an average of 19 (10-30) degrees. The angulation values in patients treated with percutaneous pinning were an average of 15 (9-20) degrees. In evaluations based on the date of fracture occurrence, the average time to return to work was 63 days in the first group and 35 days in the second group. At the end of the first year, MP joint flexions were measured at an average of 75 (30-100) degrees in the first group and 75 (50-100) degrees in the second group. The DASH score used for functional scoring was an average of 0 (0-25) in the first group and 0 (0-40) in the second group. The VAS score was measured as an average of 96 (18-100) in the first group and 100 (30-100) in the second group (Table 2). In the first group, 6 patients experienced displacement at the fracture site during follow-up and received reapplication of a cast. In the second group, no displacement at the fracture site was observed during follow-up. Complications such as damage to the dorsal branch of the ulnar nerve, extensor tendon injury, and avascular necrosis of the MC head did not occur in the first group. Surgical cases did not experience pin tract infection. Three patients experienced pin tract pain; however, no treatment other than anti-inflammatory therapy was required. The average duration of surgery in these patients was recorded as 15 (10-25) minutes. The mean frequency of fluoroscopy usage was 18 (12-30).

Table 1. Main values

	Group 1	Group 2
Sex		
Female	6	4
Male	27	28
Age (year)	29 (18-65)	25 (18-67)
Time elapsed between trauma and intervention (days)	2 (1-7)	4 (1-10)
Palmar angulation value (degrees)	41 (30-60)	43 (30-62)

The data are presented as mean and total values

Table 2. Control values at the end of the first year

	Group 1	Group 2
Palmar angulation value (degrees)	19 (10-30)	15 (9-20)
Active flexion of the MP joint (degrees)	75 (30-100)	75 (50-100)
Average return to work (days)	63	35
QuickDASH (0-100, 0 being best)	0 (0-25)	0 (0-40)
VAS (0-100, 100 being best)	96 (18-100)	15 (9-20)

Data are presented as mean and total values. MP: Metacarpophalangeal. QuickDASH: Quick-Disability of Arm, Shoulder, and Hand Outcome Measure, VAS: Visual analogue scale

Discussion

Boxer's fractures, also known as 5th MC neck fractures, constitute a significant portion of hand injuries and are the most common type of MC bone fractures (1,14,15). Especially in cases where displacement is within acceptable limits at the fracture site, casting remains a preferred method (3). In cases where the amount of displacement exceeds acceptable limits, closed reduction and casting may be preferred. The fact that this treatment can be easily applied in outpatient clinics

without the need for any anesthesia method is a major reason for its preference. Additionally, the wide acceptable range of functional alignment limits for 5th MC neck fractures makes this option stand out in terms of preference, as it allows achieving acceptable functional outcomes without the risks of surgery.

However, even in cases where the initial alignment is appropriate, poor consolidation can occur because of the inadequacy of casting during treatment, leading to malalignment during the treatment process (2). In our series, closed reduction and recasting were performed in 6 patients because of displacement observed during follow-up. In the group treated with closed reduction and antegrade pinning, there were displacement cases requiring re-operation. Although functional losses seen in cases where consolidation is completed without proper alignment might be tolerated within acceptable limits, these losses can be problematic, especially for individuals engaged in tasks requiring delicate hand skills. In cases treated with casting, patients may not be able to return to work until consolidation is achieved, particularly in injuries affecting the dominant hand. Moreover, after casting is removed, a period of exercise is necessary to compensate for limited joint mobility and muscle strength in the wrist and hand joints. In some cases, the recommended exercise programs may not be sufficient, and physical therapy and rehabilitation sessions may be required. All these processes can significantly prolong the time from fracture occurrence to return to work.

Several surgical treatment options have been developed to preserve bone alignment in boxer's fractures. Among these options, anterograde intramedullary Kirschner wire fixation is the preferred method because of its less invasive nature, adequate stability, and shorter application time (7). The most significant advantage of this method is its ability to achieve proper fracture alignment under fluoroscopy and provide stable fixation with minimal damage. The literature show that these practices are often performed under general anesthesia or axillary block anesthesia (7-9). This implies that this method includes all the risks of general anesthesia or axillary block anesthesia applications as well as the associated time losses. In addition, routine follow-up casting performed at intervals of 2 to 3 weeks after this procedure poses a risk of causing functional losses. Evaluating this entire process, it can theoretically be anticipated that this method will be more successful than casting in terms of preserving alignment, but it might not offer a significant advantage in terms of anesthesia method, rehabilitation, and return to work periods compared with casting treatment.

Regarding the functional outcomes, the DASH score was 0 (0-25) in group 1 and 0 (0-40) in group 2 at the end of the first year. The VAS score was 96 (18-100) in group 1 and 100 (30-100) in group 2. No significant difference was found between the two groups.

When comparing the plaster casting and antegrade pinning techniques that form the basis of our study, it can be observed that the antegrade pinning method is statistically significantly superior to the plaster casting method in terms of post-treatment angulation values and return to work periods.

Treatment of a displaced 5th MC neck fracture by antegrade intramedullary pinning yielded a better improvement in active ROM and QuickDASH in the first 3 months than percutaneous retrograde crossed-pinning, and both groups had similar DASH scores in the final follow-up (16). We preferred the anterior intramedullary pinning technique to start early movement of the joint and ensure an early return to work.

In today's world, the economic importance of the return to work period is increasing. In our study, to utilize the advantages of the intramedullary fixation method, mitigate its risks, and minimize the return to work period, we found it appropriate to make some modifications to this method. We aimed to eliminate the risks associated with general anesthesia by performing operations using regional anesthesia at the proximal region of the 5th MC. Subsequently, by preparing the percutaneous entry site and applying previously shaped Kirschner wires percutaneously, we avoided the risks associated with incisions. Leaving the proximal ends of the wires outside the skin, although it brings the risk of pin tract infection, allowed us to remove the pins without anesthesia in outpatient conditions after consolidation was completed. Not applying additional casting treatment in any of the patients and starting exercise programs on the first day following surgery aimed to minimize problems such as joint movement limitation or muscle strength loss in the wrist and hand region. This also helped us achieve the intended shortening of the return to work period.

Study Limitations

There is no doubt that our study has several limitations. One of the most significant limitations is the number of cases. Studies with larger sample sizes and multicenter designs can provide higher-quality evidence. Another limitation of our study is that we included only two treatment options for MC bone fractures. Comparative studies that encompass other treatment methods mentioned in the literature could provide clinicians with more enlightening data. Another limitation is that a single surgeon performed the surgical interventions in our study. Investigating operations performed by different surgeons could be more valuable for evaluating the reproducibility of the study method.

Conclusion

At the end of our study, we can infer that treating intramedullary Kirschner wires may be a safe option for managing of 5th MC neck fractures. The observation of increased angulation even in cases where fracture displacement is within acceptable limits at the end of casting treatment suggests that surgical treatment can be considered not only for cases with angulation greater than 30 degrees but also for cases with lower angulation. However, it should be noted that more comprehensive studies are needed to obtain more reliable results.

Ethics Committee Approval: In accordance with the ethical considerations of our study, necessary permissions were obtained from the University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital Local Ethics Committee (approval number: 490, date: 12.06.2020).

Informed Consent: Written informed consent forms were obtained from all patients planned to be included in the study.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 384-9
DOI: 10.4274/imj.galenos.2023.36786

Effect of Priming Dose Rocuronium Use on Intubation Quality and Duration

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ABSTRACT

Introduction: This study aimed to investigate the effects of priming dose application with rocuronium, considering ideal body weight (IBW), on intubation quality and duration during the use of rocuronium and vecuronium as neuromuscular blockers.

Methods: Our study was conducted at University of Health Sciences Turkey, Haseki Training and Research Hospital on 60 patients who were in the American Society of Anesthesiology I-II group, aged between 20-70, Mallampati I-II-III, body mass index between 20-35, and planned for medium-term elective surgical intervention. The patients were randomly divided into four groups. Group I was administered a priming dose of rocuronium 0.06 mg/kg and rocuronium 0.54 mg/kg following anesthesia induction, and group II was administered a priming dose of saline and 0.1 mg/kg vecuronium following anesthesia induction, and group III was administered a priming dose of rocuronium 0.06 mg/kg and vecuronium 0.1 mg/kg following anesthesia induction, and group IV was administered a saline priming dose and rocuronium 0.6 mg/kg following anesthesia induction. Priming and intubation doses of neuromuscular blockers were calculated according to the IBW of the patients. In addition to routine monitoring, the TOF-Guard device was used for neuromonitoring, and the T95 onset time [the time from the end of the muscle relaxant injection until maximum neuromuscular block (95%) was achieved] was recorded. The same person intubated the patients when the TOF value decreased to 5% or below. The quality of endotracheal intubation was assessed using the Clarke and Mirakhur scale. Statistical analyses were performed using SPSS 18.0 software.

Results: The effect onset time of group 1, in which rocuronium was used as a neuromuscular blocker and priming application, was significantly shorter than that of group 4, in which bolus dose rocuronium was used. Although the effect onset time of vecuronium in group 3, primed with rocuronium, was shorter than that in group 2, where the bolus dose of vecuronium was used, the difference was not observed to be significant.

Conclusion: As a result, it was concluded that priming dose application with rocuronium accelerates the neuromuscular block created by rocuronium, has no significant effect on the rate of neuromuscular block created by vecuronium, and provides excellent intubation conditions. It provides fast, high quality, and safe intubation in rapid induction required cases.

Keywords: Priming dose application, intubation quality, rocuronium

Introduction

Endotracheal intubation is one of the most critical periods in anesthesia applications in terms of hypoxia and pulmonary aspiration, and it must be completed as soon as possible to ensure airway patency (1-3). Neuromuscular blocker drugs have become an indispensable part of anesthesia practices today, allowing surgical intervention to be performed more safely, comfortably, and in a shorter time by creating a suitable working environment in addition to rapid and atraumatic endotracheal intubation. An ideal neuromuscular blocker should be potent, rapid, and short-acting, should not be accumulative, should not have cardiovascular side effects, should disappear completely in a short time, should not release histamine, should be antagonized by anticholinesterases, should be broken down into pharmacologically inactive metabolites, and should have a non-depolarizing mechanism of action (4). Non-depolarizing blockers can provide reliable intubation in only 2-3 min (5). In cases where rapid intubation is required, succinylcholine, a depolarizing blocker, is used because it acts within 10-30 seconds. However, it has serious side effects such as triggering hyperkalemia, bradycardia, ventricular arrhythmia, and malignant hyperthermia, as well as muscle pain due to fasciculations caused by succinylcholine (6). Its routine use is controversial because of reported cases of serious arrhythmia and cardiac arrest (7). In recent studies, different methods have been tried using nondepolarizing blockers in endotracheal intubations and to shorten this time (8-11).

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Cite this article as: Ateşal Ö, Tünay A, Uzman S. Effect of Priming Dose Rocuronium Use on Intubation Quality and Duration. İstanbul Med J 2023; 24(4): 384-9.

Received: 19.10.2023
Accepted: 06.11.2023

The "priming principle", which has become widely used in recent years, is a method that aims to provide a faster effect when the actual drug dose is applied by reducing the sensitivity of acetylcholine receptors by administering non-depolarizing blockers in subparalytic doses (12). In this technique, a small portion of the intubation dose of the neuromuscular blocking drug is administered before the induction of anesthesia, and the remaining main intubation dose is administered after a certain time interval. This initial dose applied was called "priming dose" by Foldes (13). This application accelerates the effect onset time of neuromuscular drugs (14,15). Two theories have been proposed to explain this acceleration mechanism. The first one states that the priming dose retains some of the postsynaptic nicotinic receptors; and thus, when the actual intubation dose is applied, the number of receptors required for clinical paralysis is reached much faster. On the other and, the second theory states that the priming dose blocks the presynaptic nicotinic receptors, reducing the release of acetylcholine. As a result, the intubation dose causes paralysis much faster (12). If the nondepolarizing agent applied as the first dose is different from the basic nondepolarizing drug, the effect onset time of the drug main and the dose requirement may vary depending on the interaction between the two drugs (16). Excessive fat stores theoretically increase the volume of distribution of fat-soluble drugs, thus requiring a larger loading dose to maintain the same plasma concentration. This is the basic logic of adjusting some drug doses according to the actual body weight of obese patients. Maintenance doses should also be given less frequently because a larger volume of distribution is expected to further slow clearance. On the contrary, ideal body weight (IBW) should be considered when adjusting the dose of water-soluble drugs such as neuromuscular blocking drugs because they have more limited distribution volumes that are not affected by fat stores (17).

Our study aimed to investigate the effects of priming dose application with rocuronium, taking into account IBW, and the use of rocuronium and vecuronium as neuromuscular blockers on intubation quality and duration.

Methods

Obtained permission from University of Health Sciences Turkey, Haseki Training and Research Hospital Ethics Committee (approval number: 43-2023, date: 09.08.2023). Our study was carried out at University of Health Sciences Turkey, Haseki Training and Research Hospital on 60 patients who were in group I-II according to the American Society of Anesthesiology classification, aged between 20-70 Mallampati I-II-III, BMI between 20-35, and planned for medium-term elective surgical intervention.

Patients with neuromuscular, cardiovascular, renal, and hepatic diseases or those using medications that could affect neuromuscular function (polypeptide antibiotics, anticonvulsants, magnesium sulfate, etc.), those with malnutrition, those who received radiotherapy-chemotherapy, and those who were alcohol dependent were excluded from the study.

In the prospective, randomized, double-blind research, 60 patients included in the study were randomly divided into 4 groups of 15 patients. Vascular access was established on the patients who were taken to the operation room, and fluid infusion was started. Heart rate (HR), diastolic arterial pressure, systolic arterial pressure, mean arterial pressure (MAP), oxygen saturation (SpO_2), and end-tidal carbon dioxide (ETCO2) values were recorded. Acceleromyographic monitoring of the patient was provided noninvasively with a TOF watch device placed on the other arm (TOF watch-Organon Teknika).

For this purpose, the acceleromyography probe of the TOF watch was fixed to the pulp of the thumb with a patch. The negative electrode of the nerve stimulator was placed 2-3 cm proximal to the skin fold formed when the wrist was flexed on the ulnar nerve trace, and the positive electrode was placed 2-3 cm proximal to the negative electrode. The stimulator receiver was fixed to the pulp of the thumb, and the thermoreceiver was placed in the thenar region. The hand is fixed with the palm facing up and the thumb moving freely, but the other four fingers remain motionless. Single twitch T1 and TOF stimulation was chosen as neuromuscular stimulation.

The four patient groups areas follows:

Group I: Priming dose with 0.06 mg/kg rocuronium bromide and 0.54 mg/kg rocuronium bromide following anesthesia induction.

Group II: Priming dose with physiological saline and 0.1 mg/kg vecuronium following anesthesia induction.

Group III: Priming dose with 0.06 mg/kg rocuronium bromide and 0.1 mg/kg vecuronium followed by induction of anesthesia.

Group IV: Priming dose with physiological saline, and 0.6 mg/kg rocuronium bromide following anesthesia induction.

After premedication of 1-2 mcg/kg fentanyl and 0.03 mg/kg midazolam were administered to the patient, TOF was calibrated at 100% and stimulation was paused until muscle relaxants were administered. Primings and intubation doses of the neuromuscular blocker to be administered were calculated according to the patients' IBW.

IBWs were calculated according to Devine's formula (18):

IBW_MAN = 1.0× [Height(cm) – 100 + 0.25× [Height(cm) – 150]],

IBW_WOMEN = 0.9× [Height(cm) – 100 + 0.25× [Height(cm) – 150]].

Anesthesia induction was achieved with 4-6 mg/kg of thiopental sodium given three minutes after the priming dose. After the remaining part of the intubation dose of neuromuscular blockers was administered, the T95 onset of action time [the time from the end of the muscle relaxant injection until maximum neuromuscular block (95%) was achieved] was recorded with neuromuscular monitoring. When the TOF value dropped to 5% or below, the same person intubated the patients. The quality of endotracheal intubation was assessed using the Clarke and Mirakhur scale (Table 1).

Anesthesia maintenance of the patients was provided with 40% O_2/air and 2% sevoflurane. To maintain an end-tidal CO_2 pressure of 30-35 mmHg, mechanical ventilation was used. T95, T25 (time from the end of muscle relaxant injection to recovery of neuromuscular transmission to 25% of the initial value), recovery index (T25-75) and responses to a series of four stimuli at 15-second intervals were monitored and

recorded. MAP, HR, SpO_2, ETCO2 were recorded before induction, after induction, before intubation, after intubation, and on the 1st, 3rd, 5th and 10th minute of the operation. At the end of the operation, the inhalation agents were discontinued, and the patients were extubated and transferred to their services after being observed for half an hour.

Statistical Analysis

SPSS 18.0 program was used for statistical analysis. Descriptive statistics are given as numbers and percentages for categorical variables and as mean and standard deviation for numerical variables. When comparing groups, the chi-square and Fisher's exact test were used for categorical variables. Comparisons of numerical variables between the two groups were made with Student's t-test, provided that the normal distribution condition was met. The paired sample test was used to compare the same variables at different times within the group. More than two group comparisons were made with the Kruskal-Wallis test. In cases where statistical significance was found using the Kruskal-Wallis test, the Mann-Whitney U test was used as a post-hoc multiple comparison method. In evaluation, $p<0.05$ was accepted as the significance level.

Results

Demographic data of 60 patients in this study are given in Table 2. Between the groups, no statistically significant difference was detected in terms of age, height, weight, IBW, BMI, operation time, and gender ($p>0.05$) (Table 2).

With regard to Mallampati scoring, no statistically significant difference was detected between the groups ($p>0.05$) (Table 3).

The MAP between the groups were compared. While a statistically significant difference was detected in post-induction MAP between group 4 and group 2 ($p<0.05$), MAP at other times did not show a statistically significant difference ($p>0.05$).

The MAPs were compared according to the pre-induction values within the groups. Values in group 1, after intubation, 1st minute and 10th minute, in group 2, after intubation and 1st minute, in group 3, after intubation and 1st minute, and in group 4 in the pre-intubation, post-intubation, 1st minute and 5th minute showed a statistically significant difference ($p<0.05$), while no statistically significant difference was detected in the other values ($p>0.05$).

The HRs between the groups were compared, and a statistically significant difference was detected between 1st minute HR values of group 1 and group 2 ($p<0.05$). No statistically significant difference was detected between the groups for HR at other times ($p>0.05$).

No statistically significant difference was observed between the groups ($p>0.05$) when the O_2 saturation between the groups was compared at all times.

Table 1. Clarke and Mirakhur rating scale

Score	Jaw opening	Vocal cords	Reaction to intubation
0	Impossible	Closed	Severe coughing or straining
1	Difficult	Half closed	Moderate straining
2	Medium	Moving	Slight diaphragmatic movement
3	Easy	Open	No reaction

Scoring: 9-8: Excellent, 7-6: Is good, 5-3: Medium, 2-0: Bad

Table 2. Demographic data of the study group

	Group 1	Group 2	Group 3	Group 4	p
Age	47.27±13.64	50.4±15.22	52.53±13.22	47.4±14.15	0.71
Height	164.47±6.61	165.47±8.5	161.07±9.8	163.8±6.6	0.19
Weight	79.4±11.3	77.47±13.46	75.8±9.4	81.6±10.97	0.51
BMI	28.83±2.88	27.86±4.54	28.93±3.65	29.8±3.68	0.58
IBW	56.53±6.93	57.69±8.45	53.45±8.94	55.65±6.69	0.18
Operation duration	67.53±21.35	77.33±27.66	84.53±31.5	85.2±25.56	0.24
Gender					
Man	4 (28.6%)	5 (35.7%)	2 (14.3%)	3 (21.4%)	0.601
Women	11 (23.9%)	10 (21.7%)	13 (28.3%)	12 (26.1%)	

BMI: Body mass index, IBW: Ideal body weight

Table 3. Comparison of Mallampati score values between groups

	Group 1	Group 2	Group 3	Group 4	p
Mallampati					
1	7 (29.2%)	5 (20.8%)	7 (29.2%)	5 (20.8%)	0.774
2-3	8 (22.2%)	10 (27.7%)	8 (22.2%)	10 (27.7%)	

Table 4. Comparison of Clarke and Mirakhur Scale, T95, T25, and T25-75 values between groups

	Group 1	Group 2	Group 3	Group 4	p
T95 (SN)	**87±35.49**	130±46.63	122±35.7	146.6±46.1	**0.001**
T25 (DK)	62.6±20.6	67.9±22.3	75.7±31.5	74.6±24.9	0.50
T25-75 (SN)	247.3±113.2	324.8±148.9	315.6±135.1	282.2±64.1	0.30

Similarly, when the ETCO2 values between the groups were compared, no statistically significant difference was detected at all times ($p>0.05$).

With regard to neuromuscular block and intubation quality, T95(sec), T25(min) and T25-75(sec) values were compared. Considering the effect on-set time between group 1 and the other groups, T95 values were found to be statistically significantly shorter for group 1 ($p<0.05$).

No statistically significant difference was detected between the groups when comparing the clinical effect duration and recovery index (T25 and T25-75) values (Table 4).

It was determined that priming dose application with rocuronium significantly accelerated the neuromuscular block caused by rocuronium, had no statistically significant effect on the rate of neuromuscular block caused by vecuronium, and had no significant effect on the clinical effect duration, recovery index, and intubation conditions.

Discussion

The time between the administration of the priming dose and the administration of the actual intubation dose is called the "priming interval". It has been suggested that a priming dose of 10% of the intubation dose and a priming interval of 3-4 minutes is safe and effective (19-21). There have been different studies on the use of rocuronium with different priming doses and priming intervals (22-24).

In our study, the effects of priming with 0.06 mg/kg rocuronium based on IBW at a 3-minute interval on rocuronium and vecuronium block and intubation quality in patients who received intravenous premedication were investigated.

In their study on 60 patients, Rao et al. (25) compared priming application with rocuronium with the use of a single dose bolus and examined the effect of priming application on intubation conditions and intubation time. The control group was administered with 0.60 mg/kg rocuronium, whereas the priming group was administered a priming dose of 0.06 mg/kg rocuronium and an actual intubation dose of 0.54 mg/kg. Intubation time was measured using TOF stimulation, and it was reported that priming with rocuronium shortened the intubation effect onset time (T95) (50±7.3 s priming group, 94 s control group). In addition, it was reported that excellent intubation conditions were achieved in both control and priming groups, and priming with rocuronium did not have any side effects. Griffith et al. (20) also compared priming application with rocuronium with the use of bolus doses. As the priming dose, 0.06 mg/kg rocuronium was used, and the actual intubation dose was given 2 min after priming. In this study, it was shown that priming with rocuronium shortened the onset time of intubation. Martin et al. (26) explored the effects of a single dose of 100 µg/kg vecuronium with an initial dose of 10, 15 and 20 µg/kg and found the intubation times to be 165, 158, 141, and 220 s, respectively. In their study where Redai and Feldman (23) investigated the effects of the first dose of rocuronium and vecuronium in the vecuronium block, they found that both drugs shortened the effect onset time.

For our study, T95, T25, and T25-75 values we recorded for the muscle strength evaluation made with TOF monitoring. A shorter T95 (onset time) means that the patient is ready for intubation in a shorter time. Our study showed that the lowest T95 time was obtained in Group 1 (87±35.49 sec), which was primed with rocuronium in the rocuronium block. It was determined that priming application with rocuronium based on IBW significantly shortened the duration of action in the rocuronium block (group 1: 87±35.49, group 4: 146±46.1 sec), but priming application in the vecuronium block did not create a significant difference compared with the bolus dose of vecuronium (group 2: 130±46.6, group 3: 122±35.7 sec).

Abdulatif et al. (27) investigated intubation time and intubation quality with atracurium while priming with rocuronium. They applied 1, 1.5, and 2 minutes as priming intervals to different groups, and as a result, it was revealed that priming with rocuronium shortened the onset time of intubation, regardless of the priming interval, and similar times were obtained with rocuronium or succinylcholine. In addition, the intubation quality of the groups was investigated, and while good-excellent intubation quality was observed in the groups where priming was applied (more than 50%), excellent intubation quality was obtained in 100% of the groups where succinylcholine was applied.

In their study on 60 patients, Leykin et al. (28) found differences in intubation quality. They divided the patients into 2 groups; the first group was administered 0.4 mg/kg rocuronium after priming with 0.04 mg/kg rocuronium. The same procedure was applied to the second group by injecting saline as the priming dose. The intubation quality was recorded in the groups. Intubation quality was determined to be statistically significantly higher in the priming group.

In our study, intubation quality was assessed using CMS, and near-perfect intubation quality was achieved in the majority of patients (CMS 6 and above). It was determined that there was no significant difference between the groups in terms of CMS value. The highest CMS values were obtained in group 3, where rocuronium priming was applied to the vecuronium block; however, it was determined that priming with rocuronium did not create a significant difference in intubation quality.

The total duration of effect, defined as the time until 25% recovery of the T1 response, and the recovery index, defined as the time from 25% recovery to 75% recovery, were recorded in all patients. No significant difference was not found in our study in terms of clinical effect duration and recovery index. These findings are in agreement with other studies (20,29,30).

In their study, Griffith et al. (20) stated that while no difference was observed in terms of recovery index between the group primed with rocuronium and the group given saline placebo, priming with rocuronium shortened the onset time of intubation. In another study (30), 80 patients were divided into two groups: group 1 was administered 0.1 mg/kg priming dose rocuronium and 0.5 mg/kg rocuronium after a 4-min priming interval, and group 2 was administered 0.6 mg/kg single dose rocuronium. The clinical effect duration is noted to be 40±3.2 minutes in the priming group, whereas it was 39.3±2.4 minutes in the 0.6 mg/kg single dose rocuronium group. It was stated that priming application does not make a difference in terms of clinical effect duration.

In our study, it was determined that priming with rocuronium according to IBW did not create a significant difference in the duration of clinical effect. The clinical effect duration of groups 1 and group 3, in which rocuronium was used as the main neuromuscular blocker, was similar, and the clinical effect duration of groups 2 and group 3, in which vecuronium was used, was also similar. The difference in clinical effect durations is believed to be due to the different pharmacological effect durations of rocuronium and vecuronium, which are used as basic neuromuscular blockers.

Furthermore, in our study, cardiovascular system effects were evaluated by comparing hemodynamic parameters (MAP and HR) between groups. No clinically significant difference was detected in terms of MAP and HR values between the priming groups and the non-priming groups. In intragroup evaluations, it was thought that the statistically significant difference in MAP after intubation was an expected result of the stress response and sympathetic discharge that developed due to intubation. Similarly, the increase in HR values after the 1st minute in the intra-group evaluation was thought to be the result of the stress response that developed after intubation. In our study, it was observed that no side effects occurred in the priming groups.

Study Limitations

The limiting factor of our study was the small number of patients included in the study.

Conclusion

It was concluded that priming dose application with rocuronium accelerates the neuromuscular block created by rocuronium, has no significant effect on the rate of neuromuscular block created by vecuronium, and provides excellent intubation conditions. It provides fast, high quality, and safe intubation in rapid induction required cases.

Ethics Committee Approval: Obtained permission from University of Health Sciences Turkey, Haseki Training and Research Hospital Ethics Committee (approval number: 43-2023, date: 09.08.2023).

Informed Consent: It wasn't obtained.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 390–2
DOI: 10.4274/imj.galenos.2023.92332

Predictive Value of Neutrophil/Lymphocyte Ratio for Developing Acute Renal Failure in Patients with Sepsis Using Colistin in Intensive Care Units

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ABSTRACT

Introduction: Sepsis affects millions of people every year all over the world, and despite increasing knowledge over the years and the use of modern antibiotics and resuscitation treatments, it is the most important cause of morbidity and mortality in intensive care units. Nephrotoxicity is a clinical condition that increases morbidity and mortality in the hospitalized patient population, particularly critically ill patients in intensive care. The neutrophil/lymphocyte ratio (NLR) has emerged as a new biomarker that has begun to be investigated in sepsis and post-surgical acute renal failure (ARF). We determined whether changes in NLR are biomarkers for developing ARF in patients using colistin with a diagnosis of sepsis.

Methods: After obtaining ethics committee permission, the files of patients who were followed up in intensive care with a diagnosis of sepsis and who used colistin in their treatment were retrospectively scanned. In our study, the files of 350 patients followed in intensive care were examined, and it was determined that 70 patients diagnosed with sepsis used colistin. The data of 48 patients included in our study were analyzed.

Results: After colistin use, it was observed that 28 (58%) patients developed ARF, and 20 (41.6%) did not develop ARF. There was no significant difference between the groups in terms of ARF development. In the comparison between the groups, although NLR1 was higher in group 2 than in group 1, and NLR2 was higher in group 1 than in group 2, no significant difference was detected. In the intra-group evaluation, although NLR2 was higher than the baseline value in group 1 and lower in group 2, no statistically significant difference was detected.

Conclusion: The NLR results do not constitute a difference that can be used as a predictive value in showing the development of ARF in patients diagnosed with sepsis and receiving colistin treatment.

Keywords: Sepsis, colistin, acute renal failure, neutrophil lymphocyte ratio

Introduction

Sepsis/septic shock affects millions of people every year all over the world, and despite increasing knowledge over the years and the use of modern antibiotics and resuscitation treatments, it continues to be the most important cause of morbidity and mortality in intensive care units (ICUs). The incidence of sepsis/septic shock; it is increasing due to prolonged intensive care stay, increase in antibiotic resistance, and increase in the number of immunosuppressed patients and the elderly population (1,2). Polymyxins are the preferred drugs for treating multidrug-resistant microorganisms such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, which develop multiple antibiotic resistance. Polymyxins were isolated from *Paenibacillus polymyxa* and became available for clinical use in the 1950s (3). Polymyxin B and polymyxin E (also known as colistin) are in clinical use. Its use gradually decreased in the 1970s with the discovery of aminoglycosides, which have fewer side effects than colistin. In the 2000s, it began to be used more frequently for treating microorganisms with multidrug resistance, especially *Pseudomonas* and *Acinetobacter* spp. (4). The most important side effect of intravenous polymyxins is nephrotoxicity (5). Nephrotoxicity is a clinical condition that increases morbidity and mortality in the hospitalized patient population, particularly critically ill patients in intensive care. The neutrophil/lymphocyte ratio (NLR) has emerged as a new biomarker that has begun to be studied in acute renal failure (ARF) that develops after sepsis and surgery.

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Cite this article as: Uçkun S, Saruhan F. Predictive Value of Neutrophil/Lymphocyte Ratio for Developing Acute Renal Failure in Patients with Sepsis Using Colistin in Intensive Care Units. İstanbul Med J 2023; 24(4): 390-2.

Received: 12.10.2023
Accepted: 06.11.2023

Table 1. Descriptive and clinical characteristics of the groups

	Group 1	Group 2	p-value
Female/male (number)	10/18	8/12	0.762
Age (years)	73±12	70±13	0.794
Height (cm)	170±10	173±10	0.777
Weight (kg)	80±13	70±13	0.498
SOFA	12±2	11±3	0.612
APACHE II	27±7	29±8	0.924

APACHE: Acute Physiological and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment Score, p<0.005 significant

Table 2. NLR values

NLR	Group 1	Group 2	p-value
NLR1	11±12	14±14	0.446
NLR2	14±12	11±16	0.151

NLR: Neutrophil/lymphocyte ratio, NLR1: NLR calculated just before starting colistin treatment, NLR2: NLR calculated at the 48th hour of colistin treatment, p<0.005 significant

In our study, we compared the NLRs of patients who developed and did not develop ARF after colistin use in patients we followed up with a diagnosis of sepsis. We determined whether changes in NLR are biomarkers for developing ARF in patients using colistin with a diagnosis of sepsis.

Methods

After obtaining permission from the Balıkesir University Faculty of Medicine Ethics Committee (approval number: 2022/02, date: 26.01.2022), the files of patients who were followed up in the ICU with a diagnosis of sepsis and used colistin in their treatment between January 2019 and December 2021 were retrospectively scanned. Patients who stayed in intensive care for more than 48 h were included in our study. Patients were diagnosed with sepsis and septic shock according to the "Sepsis Survival Campaign Severe Sepsis and Septic Shock Management 2021 guideline". Patients had to be over 18 years of age and use colistin for at least 48 h. Patients who used colistin before ICU admission, patients who were diagnosed with AKI and/or chronic renal failure before colistin treatment, and patients who used colistin for less than 48 h were not included in the study.

Risk-injury-failure-loss of renal function-End-stage kidney disease (RIFLE) criteria were used to eliminate patients diagnosed with renal failure in patients in whom colistin treatment was initiated at a standard dose of 2.5-5 mg/kg/day (maximum: 300 mg). The creatine value calculated just before colistin treatment was recorded as the baseline value and re-evaluated for ARF at the 48th hour of colistin treatment. Patients were divided into two groups: those who developed ARF (group 1) and those who did not (group 2). NLR values of the patients were calculated immediately before and 48 h after starting colistin treatment. NLR was obtained by dividing the absolute neutrophil count by the lymphocyte count. It was defined as NLR1 calculated immediately before starting colistin treatment and NLR2 calculated at the 48th hour. NLR1 and NLR2 were examined in patients in both groups to determine whether the change in NLR was a predictive value in terms of ARF.

Statistical Analysis

The SPSS 22.0 (SPSS, Inc., Chicago, IL) package program was used for the analysis of data. The descriptive statistics of the quantitative variables included in the study are as follows: arithmetic mean, standard deviation, median, minimum, and maximum values. Qualitative variables are shown as frequency and percentage (%). The suitability of quantitative variables to normal distribution was examined using the Shapiro-Wilk test. Chi-square tests were used in intergroup comparisons of qualitative variables. The Independent sample t-test was used for comparisons of variables with normal distribution between two independent groups. Those not normally distributed were compared using the Mann-Whitney U test to compare the two groups. The statistical significance level was determined as 0.05.

Results

In our study, the files of 350 patients followed up in the ICU were examined, and it was determined that 70 patients diagnosed with sepsis used colistin. Twenty patients were excluded from the study because of the diagnosis of chronic renal failure, and 2 patients were excluded because they were under 18 years of age. Data of 48 patients included in our study were analyzed. Of the patients, 18 were women and 30 were men. While the average age of all patients included in the study was 71±9, the average age of only female patients was 73±5 and only male patients was 71±3. The demographic characteristics of group 1 and group 2 patients were similar. Sequential Organ Failure Assessment Score and Acute Physiological and Chronic Health Evaluation II score distributions were similar between the groups (Table 1).

After colistin use, it was observed that 28 (58%) of the patients developed ARF, and 20 (41.6%) did not develop ARF. There was no significant difference between the groups in terms of AKI development. In the comparison between the groups, although NLR1 was higher in group 2 than in group 1, and NLR2 was higher in group 1 than in group 2, no significant difference was detected. In the intra-group evaluation, although NLR2 was higher than the baseline value in group 1 and lower in group 2, no statistically significant difference was detected (Table 2).

Discussion

The NLR results do not constitute a difference that can be used as a predictive value in showing the development of ARF in patients diagnosed with sepsis and receiving colistin treatment.

In their study, Yilmaz et al. (6) examined the data of 118 patients hospitalized in intensive care with a diagnosis of sepsis. Suggested that the

ARF development rate was 61% and that there was a statistical correlation between ARF and NLR. Bu et al. (7) suggested that ARF develops in 59% of patients hospitalized in intensive care and diagnosed with sepsis, the average NLR is 17±4, and there is a significant correlation between ARF and NLR. Various studies have reported a relationship between ARF and NLR (8-10). We believe that the different results obtained from our study are due to the difference in the number of patients, the fact that the studies were not specific to patients using colistin, and the lack of etiology discrimination. In addition, in these studies, criteria different from the RIFLE criteria were used in the diagnosis of ARF. It has been observed that more patients can be diagnosed with the Acute Kidney Injury Network criteria than with the RIFLE criteria (11-14).

Consistent with the literature, the most common growth in microbiological samples is *Acinetobacter baumannii*, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* a, respectively. For this reason, colistin is used for treating sepsis (15-17).

It has been reported that before 1975, colistimethate sodium was mostly used intramuscularly and in higher doses than today, and the nephrotoxicity rate was approximately 30% (20-50%) (4). The rates of nephrotoxicity caused by colistin vary in various studies. This is because different criteria are used in the diagnosis of renal failure and different patient groups are evaluated (18,19).

Study Limitations

The limiting factors of our study are the small number of patients included in the study, the fact that many factors may be associated with renal failure during the hospitalization period, and the fact that it was conducted as a retrospective file scan.

Conclusion

Because of our study, we concluded that it is not appropriate to use NLR as a predictive value in ARF in patients diagnosed with sepsis and starting colistin treatment in intensive care.

Ethics Committee Approval: The study was approved by the Balıkesir University Faculty of Medicine Ethics Committee (approval number: 2022/02, date: 26.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 393-8
DOI: 10.4274/imj.galenos.2023.90094

Role of Serum NT-proBNP Levels in Early Prediction of Prognosis in Severe COVID-19 Pneumonia

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ABSTRACT

Introduction: Coronavirus disease-2019 (COVID-19) infection is a viral disease characterized by fast transmission and heterogeneous clinical manifestations in people. Cardiac complications with different clinical presentations are observed during the disease course. In this study, we aimed to determine the importance of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) level to predict the prognosis in severe COVID-19 pneumonia and its optimal cut-off value.

Methods: A total of 131 patients who were admitted to a hospital with severe COVID-19 pneumonia and who did not have a history of heart failure, chronic obstructive pulmonary disease, or chronic renal disease were included in the study. Diabetes mellitus and hypertension rates were recorded. Inflammatory markers (ferritin, C-reactive protein, procalcitonin, interleukin-6) and proBNP levels were measured. In-hospital mortality and recovery rates were recorded. The relationship between proBNP levels and chronic disease existence, inflammatory markers, and in-hospital mortality was evaluated using SPSS.

Results: ProBNP levels were significantly higher in the non-survivor group than in the survivor group. The cut-off value of proBNP to predict in-hospital mortality was 650 pg/mL with 87% sensitivity and 62% specificity. The ProBNP >650 pg/mL group had higher hypertension rates, procalcitonin levels, intensive care unit admittance rates, and in-hospital mortality than ProBNP ≤650 pg/mL group ($p<0.05$).

Conclusion: This study showed that NT-proBNP levels can be used to predict prognosis in severe COVID-19 pneumonia and that it is an independent risk factor for in-hospital mortality.

Keywords: COVID-19 pneumonia, NT-proBNP, prognosis

Introduction

The coronavirus disease-2019 (COVID-19) severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) created an unpredictable health catastrophy causing a pandemic. This virus is characterized by quick transmission and affects several organ systems, especially the respiratory system. The clinical spectrum ranges from asymptomatic carriage of infection to critical diseases with multi-organ failure and ARDS resulting in mortality. Although it has been 3 years since the first case was diagnosed in Wuhan, the pandemic continues and mortal cases occur.

Respiratory diseases, particularly pneumonia, are the most common and mortal clinical presentation, but cardiac complications are also common and are related to poor prognosis (1). Cardiac complications can include acute cardiac injury or worsening of a prior cardiac condition. The cardiac injury rate was found to be 19.7% (1) and 27.8% (2) in different studies. The pathogenesis consists of the direct cytopathic effect of virus on cardiomyocytes, systemic inflammation causing oxygen deprivation, thromboinflammation, and endotel dysfunction, and microvascular dysfunction caused by high angiotensin-converting enzyme 2 expression in cardiac capillary pericytes (3-5). Clinical findings include heart failure (HF), abnormal electrocardiography changes, and acute ischemic injury (6).

Although vaccine and medical treatment studies are available, clinical biomarkers are needed to predict prognosis and mortality. Cardiac injury markers are still arguable to predict the amount of cardiac injury (7).

In this study, we aimed to search N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) as a prognostic factor in severe COVID-19 pneumonia, determine its optimal cut-off value for mortality prediction, and evaluate its relationship with common inflammatory markers.

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Cite this article as: Usta Atmaca H, Erol Çiçek N, Pişkinpaşa ME. Role of Serum NT-proBNP Levels in Early Prediction of Prognosis in Severe COVID-19 Pneumonia. İstanbul Med J 2023; 24(4): 393-8.

Received: 10.10.2023
Accepted: 07.11.2023

Methods

Study Design and Participants

This study was designed as a single center, prospective, cross-sectional study. One hundred thirty one patients who had clinical, radiological, and laboratory criteria for severe COVID-19 pneumonia according to the living guidance for clinical management of COVID-19 (3-7) and were admitted to hospital for treatment were included in the study. The protocol for this study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 99, date: 11.03.2022). Written informed consent was obtained from the participants. The study complies with relevant ethical regulations and is performed under the Declaration of Helsinki ethical principles for medical research involving human subjects.

All patients' SARS-CoV-2 infection diagnoses were confirmed by oropharyngeal and nasal swap analysis using polymerase chain reaction method. Patients with prior HF, chronic obstructive pulmonary disease, or chronic renal disease were excluded. Diabetes mellitus and hypertension (as most common accompanying diseases of COVID-19 infection) rates and general features were recorded, and inflammatory markers [ferritin, C-reactive protein (CRP), procalcitonin, interleukin-6] and NT-proBNP levels were measured (Table 1).

Primary end points (recovery, in-hospital mortality) were followed and recorded. The relationship between NT-proBNP levels and chronic disease existance, inflammatory markers, in-hospital mortality, and the optimal cut-off value of proBNP were evaluated.

Statistical Analysis

Statistical analysis was performed using SPSS 28.0 for Windows program. Descriptive statistics are reported as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of variables was tested with the Kolmogorov-Smirnov test. Quantitative independent data analysis was performed using Independent sample t-test and Mann-Whitney U test. Qualitative independent data analysis was performed using the chi-square test and Fisher's test when the criteria were not met by the chi-square test. The effect size and cut-off point are searched with the ROC curve.

Results

One hundred thirty one patients (mean age: 62.7 years; 47% women) were included in the study. The in-hospital mortality rate among patients was 26% (34 patients). The mean age of the non-survivor group was higher than that of the survivor group. ProBNP and procalcitonin levels were significantly higher in the non-survivor group than in the survivor group. There was no significant difference in gender distribution, HT presence or hemoglobin A1C (HbA1C), ferritin, and CRP levels between the survivor and non-survivor groups. The length of hospital stay showed no difference between the survivor and non-survivor groups. Thirty four patients (11.1% of survivor group and 95.7% of non-survivor group) were referred to the intensive care unit (ICU). ICU referral was significantly higher in the non-survivor group than in the survivor group (Table 2).

NT-ProBNP level was significant in determining the survivor and non-survivor patients [area under the curve: 0.781 (0.691-0.870)]. The cut-off value of NT-proBNP to predict in-hospital mortality was 650 pg/mL [area under the curve 0.745 (0.644-0.846)] with 87% sensitivity,

Table 1. General features and laboratory values of the patients

		Minimum-maximum	Median	Mean ± SD/(n, %)
Age (years)		18.0-96.0	64.0	62.7±17.8
Sex	Female			62 (47.3%)
	Male			69 (52.7%)
Diabetes mellitus	(+)			37 (28.2%)
	(-)			94 (71.8%)
Hypertension	(+)			67 (51.1%)
	(-)			63 (48.1%)
NT-proBNP pg/mL		10.0-12860.0	600.0	1311.7±1967.3
NT-proBNP pg/mL	<650			70 (53.4%)
	>650			61 (46.6%)
HbA1C		5.4-12.1	6.3	6.8±1.4
Ferritin pg/mL		12.0-2000.0	416.0	651.4±562.2
CRP mg/L		0.0-313.0	65.0	81.4±68.0
Prokalcitonin pg/mL		0.02-24.20	0.10	0.53±2.53
IL-6		2.0-376.0	16.0	38.8±62.7
Duration of hospitalization day		1.0-27.0	6.0	6.8±4.0
ICU	(+)			34 (26.0%)
	(-)			97 (74.0%)

SD: Standard deviation, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, CRP: C-reactive protein, HbA1C: Hemoglobin A1C, IL-6: Interleukin-6, ICU: Intensive care unit

positive prediction 32.8%, 62% specivity, and negative prediction 95.7% (Table 3, Figure 1-3).

The NT-ProBNP >650 pg/mL group had higher hypertension rates, procalcitonin levels, ICU admittance rates, and in-hospital mortality than the NT-ProBNP ≤650 pg/mL group ($p<0.05$). There was no significant difference for gender distribution, diabetes rates, HbA1C, ferritin, and CRP levels between the NT-ProBNP ≤650 pg/mL and NT-ProBNP >650 pg/mL groups (Table 4, Figure 4).

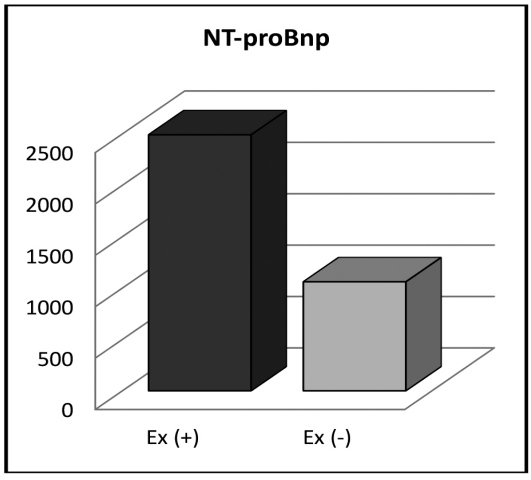

Figure 1. ProBNP cut-off value and mortality

NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide

Discussion

This single-center, cross-sectional study showed that high proBNP levels are associated with poor prognosis in patients with severe COVID-19 infection. In addition, in-hospital mortality and ICU referral rates were higher in patients with high proBNP levels. The mortality rate was as high as 26%, and there was also a relationship between age, hypertension, mortality. The hypertension rate was high among patients

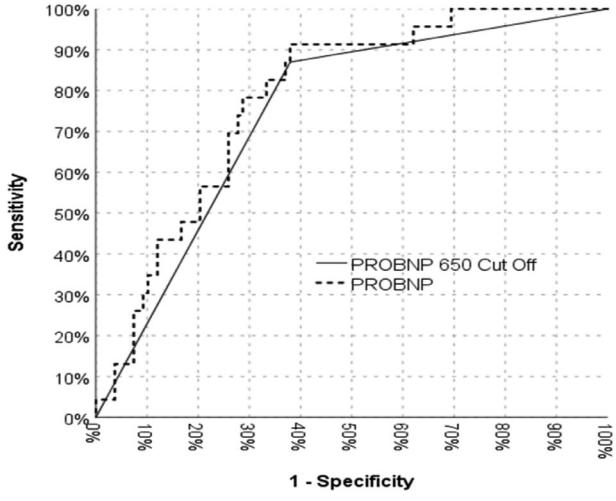

Figure 2. Ideal value of NT-proBNP in predicting in-hospital mortality in COVID-19 cases without HF

NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide, COVID-19: Coronavirus disease-2019, HF: Heart failure

Table 2. General features and laboratory values of the survivors and non-survivor groups

		Ex (+)		Ex (-)		p	
		Mean ± SD/(n, %)	Median	Mean ± SD/(n, %)	Median		
Age (years)		72.1±18.3	77.0	60.7±17.1	62.0	0.005	t
Sex	Female	10 (43.5%)		52 (48.1%)		0.684	X^2
	Male	13 (56.5%)		56 (51.9%)			
Diabetes mellitus	(+)	6 (26.1%)		31 (28.7%)		0.800	X^2
	(-)	17 (73.9%)		77 (71.3%)			
Hypertension	(+)	16 (69.6%)		51 (47.2%)		0.052	X^2
	(-)	7 (30.4%)		57 (52.8%)			
NT-proBNP pg/mL		2491.0±2760.1	1471.0	1060.5±1665.3	455.0	0.001	m
HbA1C		6.8±1.1	6.3	6.8±1.5	6.3	0.656	m
Ferritin pg/dL		819.6±613.9	673.0	615.6±547.0	380.5	0.106	m
CRP mg/dL		96.4±58.6	89.0	78.2±69.6	56.0	0.071	m
Prokalsitonin pg/mL		2.1±5.8	0.2	0.2±0.4	0.1	0.001	m
IL-6		82.0±91.6	29.0	29.9±51.1	14.0	0.001	m
Duration of hospitalization day		6.7±3.5	7.0	6.9±4.1	6.0	0.864	m
ICU	(+)	22 (95.7%)		12 (11.1%)		0.001	X^2
	(-)	1 (4.3%)		96 (88.9%)			

[t]Independent sample t-test/[m]Mann-Whitney U test/[X²]chi-square test, SD: Standard deviation, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, HbA1C: Hemoglobin A1C, CRP: C-reactive protein, IL-6: Interleukin-6, ICU: Intensive care unit

Table 3. ROC analysis of ProBNP

		Area under the curve		95% CI	p
NT-proBNP		0.781		0.691-0.870	**0.001**
NT-proBNP 650 cut-off		0.745		0.644-0.846	**0.001**
		Ex (-)	**Ex (+)**		**(%)**
NT-proBNP pg/mL	<650	67	3	Sensivity	87.0%
	>650	41	20	Pozitive prediction	32.8%
				Specivity	62.0%
				Negative prediction	95.7%

ROC: Receiver operating characteristic, proBNP: Prohormone brain natriuretic peptide, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, CI: Confidence interval

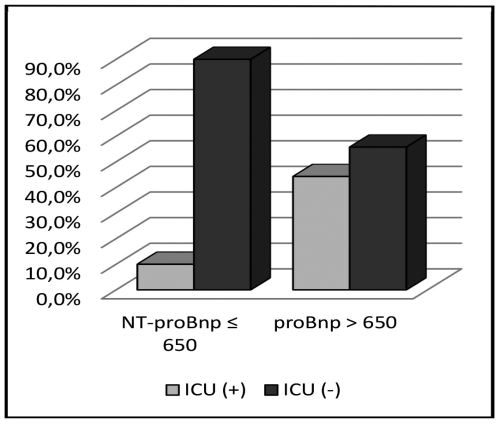

Figure 3. ICU admittance according to the ProBNP cut-off value

ICU: Intensive care unit, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide

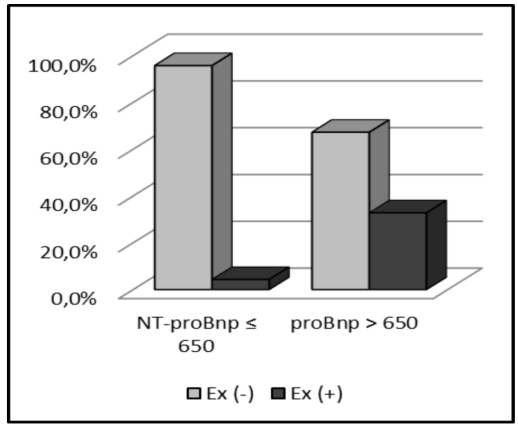

Figure 4. Mortality rates according to the proBNP cut-off value

NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide

Table 4. General features and laboratory values of proBNP ≤650 and proBNP >650 groups

		NT-proBNP ≤650		NT-proBnp >650		p	
		Mean ± SD/(n, %)	**Median**	**Mean ± SD/(n, %)**	**Median**		
Age (years)		54.3±15.5	52.5	72.4±15.1	76.0	***0.001***	t
Sex	Female	29 (41.4%)		33 (54.1%)		0.147	x^2
	Male	41 (58.6%)		28 (45.9%)			
Diabetes mellitus	(+)	17 (24.3%)		20 (32.8%)		0.281	x^2
	(-)	53 (75.7%)		41 (67.2%)			
Hypertension	(+)	30 (42.9%)		37 (60.7%)		***0.042***	x^2
	(-)	40 (57.1%)		24 (39.3%)			
HbA1C		6.8±1.5	6.2	6.8±1.3	6.3	0.687	m
Ferritin pg/mL		632.0±549.8	386.0	673.6±579.9	521.0	0.755	m
CRP mg/L		72.4±64.2	51.0	91.6±71.1	69.6	0.081	m
Prokalsitonin pg/mL		0.4±1.9	0.1	0.7±3.1	0.1	***0.001***	m
IL-6		31.0±63.4	11.5	47.3±61.3	19.0	***0.005***	m
Duration of the haspitalization day		6.4±3.6	6.0	7.4±4.5	7.0	0.211	m
ICU	(+)	7 (10.0%)		27 (44.3%)		***0.001***	x^2
	(-)	63 (90.0%)		34 (55.7%)			
Exitus	(-)	67 (95.7%)		41 (67.2%)		***0.001***	x^2
	(+)	3 (4.3%)		20 (32.8%)			

[t]Independent sample t-test/[m]Mann-Whitney U test/[x²]chi-square test, NT-proBNP: N-terminal of the prohormone brain natriuretic peptide, proBNP: Prohormone brain natriuretic peptide SD: Standard deviation, HbA1C: Hemoglobin A1C, CRP: C-reactive protein, IL-6: Interleukin-6, ICU: Intensive care unit

with high NT-proBNP levels. HT and preserved left ventricular systolic function, plasma NT-proBNP is an important cardiovascular risk marker, regardless of traditional risk factors and prevalent cardiovascular disease (8). Mortality was higher in the advanced age group with the presence of high proBNP, showing that cardiac complication rates increased in this group, especially with the presence of HT.

Abnormal NT-proBNP levels show cardiac injury and cardiac dysfunction in the COVID-19 infection course and have prognostic value (7). Early studies where clinical features of patients were declared showed that an increase in cardiac biomarkers, including troponin and NT-proBNP, predicted poor outcomes in COVID-19 patients (9,10). Following meta-analyses showed that high proBNP levels were related to disease severity, mechanical ventilation, and in-hospital mortality, and evaluating NT-proBNP levels could discriminate COVID-19 patients under high risk (11,12).

Cardiac biomarkers predict worsening prognosis and in-hospital mortality risk in COVID-19 patients with and without myocardial injury (13).

Our study showed a significant relationship between mortality and NT-proBNP levels above 650 pg/mL. NT-ProBNP cut-off levels ≥650 pg/mL were found to be significant in predicting the survival of survivor and non-survivor patients.

In a study where bottom and top cut-off points were determined for proBNP, proBNP levels <331 pg/mL and >11,126 pg/mL were found to be related to the longest and shortest durations in order, starting from admittance to hospital to mortality period (14). ProBNP cut-off level to predict in-hospital mortality in the presence of cardiac disease was found to be 1022.50 pg/mL [sensitivity 87.5%, specificity (87.1%)] (15). This level is significantly higher than our finding, but it should be noted that our study excluded patients with existing HF.

Our study showed that mortality increased with advanced age and that HT was more common in patients with NT-proBNP >650 pg/mL. Similarly, COVID-19 infection is associated with advanced age, inflammatory response, underlying cardiovascular co-morbiditesand myocardial injury (16).

Multiple pathophysiological pathways are responsible for proBNP increase. Several cytokines are shown in COVID-19 patients' serum samples (17). Inflammation is the main reason for the increase (12) but also presence of pulmonary emboli, ARDS, and sepsis, which accompanies pneumonia, can also cause the increase (18,19).

In our study, procalcitonin levels but not CRP levels were found to be high in the increased proBNP level group. Caro-Codón et al. (9) CRP levels were not significantly high in the early phases of the disease but developed a correlation during proBNP pick measurement. CRP picks at 12-24 hours and lasts up to 3-7 days, but procalcitonin increases earlier than CRP and decreases to normal levels faster (20). In our study, proBNP levels did not show any correlation with CRP levels, but a strong correlation was found with procalcitonin. Because the laboratory values at admittance were evaluated in our study, procalcitonin levels should be the test of choice for early disease evaluation.

Extensive alveolar microthrombosis found postmortem in COVID-19 is one of the important reasons of mortality of the disease (9). Pro BNP is increased in pneumonia and pulmonary emboli because of cardiac shear stress but should also be accepted as an inflammation indicator because of its parallelity with inflammatory markers. Its role in direct cardiac injury, of course, requires more research.

Study Limitations

The small number of patients in our study is a limitation of the study.

Conclusion

Although vaccine and medical treatment studies are available, clinical biomarkers are needed to predict prognosis and mortality. Cardiac injury markers are still arguable to predict the amount of cardiac injury. This study showed that NT-proBNP levels can be used to predict prognosis in severe COVID-19 pneumonia and that it is an independent risk factor for in-hospital mortality.

Ethics Committee Approval: The protocol for this study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 99, date: 11.03.2022).

Informed Consent: Written informed consent was obtained from the participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - H.U.A., N.E.Ç.; Concept - H.U.A.; Design - H.U.A., N.E.Ç.; Data Collection or Processing - H.U.A., N.E.Ç.; Analysis or Interpretation - H.U.A., M.E.P.; Literature Search - H.U.A., M.E.P.; Writing - H.U.A.

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

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

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İstanbul Med J 2023; 24(4): 399-403
DOI: 10.4274/imj.galenos.2023.02185

Effect of Pericardial Effusion on Right Ventricular Functions in Oncology Patients Receiving Chemotherapy

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ABSTRACT

Introduction: Pericardial effusion is an indicator of poor prognosis in patients with cancer. We investigated the effect of pericardial effusion development on right ventricular function in oncology patients receiving chemotherapy for malignancy.

Methods: A total of 90 patients who were followed up in the oncology clinic and who applied to our outpatient clinic for routine cardiac examination were included in the study. Echocardiography was performed on the patients, and they were divided into two groups: patients with and without pericardial effusion. Demographic characteristics and, clinical and laboratory findings of the patients were recorded. The right ventricular functions of the patients were then evaluated.

Results: Pericardial effusion was in 30 (33.3%) of 90 patients included in the study. The mean age of patients without pericardial effusion was 57.33±15.59, and the mean age of patients with effusion was 60.27±13.51, and it was similar between the groups (p=0.36). No statistically significant difference was detected between the groups in right ventricular (RV) fractionated area change, RV-early peak, tricuspid annular plane systolic excursion, pulmonary artery pressure, E/E', and heart failure with preserved ejection fraction values, which are parameters that indicate right ventricular functions and diastolic dysfunction. However, RV systolic velocity and RV-AM, which are indicators of diastolic dysfunction, were found at higher rates in the patient group with pericardial effusion (p-value 0.041 and 0.001, respectively). In addition, Mitral E velocity was found to be lower in the patient group with pericardial effusion (p=0.032).

Conclusion: In malignancy patients who develop pericardial effusion, we recommend that diastolic parameters be checked and close clinical follow-up of the patients be performed before overt heart failure clinic develops. It should be kept in mind that the development of pericardial effusion in oncology patients receiving chemotherapy does not mean right ventricular failure.

Keywords: Chemotherapy, pericardial effusion, diastolic heart failure, right ventricular failure

Introduction

Death rates due to cancer have begun to decrease significantly in recent years, thanks to technological developments and newly developed drugs. However, cardiotoxic effects continue to frequently occur because of the effects of some chemotherapeutic drugs (1-3). Pericardial effusion occurs because of the inflammatory effect of pericardial fluid or disorders in lymphatic drainage. Among the most common causes of pericardial effusions, they are; they can be counted as 27% infection, 25% malignancy, 14% post-radiation inflammation, and 12% collagen tissue diseases (4,5). Pericardial effusion develops in approximately 15% of malignant patients, and this is mostly due to lung and breast cancer (6,7). The development of pericardial effusion in patients with malignancy is among the common complications and is associated with poor prognosis (8). Patients with malignant pericardial effusion usually die within 1 year of diagnosis (9). Cardiotoxicity that develops in patients receiving chemotherapy affects their treatment process of the patients and causes the development of heart failure, which is a significant cause of morbidity and mortality (10). In the literature, although there are many studies on left ventricular functions after chemotherapy, the number of studies on right ventricular functions is extremely low. In this study, we aimed to show the difference between the right ventricular functions of oncology patients who developed pericardial effusion after chemotherapy and those of patients who did not develop pericardial effusion.

Methods

Between June 2020 and October 2023, 90 patients who were followed up in the oncology clinic, received chemotherapy, and applied to our outpatient clinic for routine cardiac examination were included in the study. The patients included in the study were selected from patients

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Cite this article as: Tatar S, Yavuz YE, Oktay İ, Aydın N, Alsancak Y, İçli A. Effect of Pericardial Effusion on Right Ventricular Functions in Oncology Patients Receiving Chemotherapy. İstanbul Med J 2023; 24(4): 399-403.

Received: 19.10.2023
Accepted: 07.11.2023

who had been receiving chemotherapy for at least 3 months. Patients with known heart failure, active infection, hematological malignancy, severe valve disease, chronic renal failure, rheumatological disease, hematological disease, pulmonary hypertension, history of pericardial disease, history of acute coronary syndrome within the last month, and patients with inadequate image quality were not included in the study. Patients with solid organ tumors, without a tamponade clinic, and regardless of the type of chemotherapeutic drug they received were included in the study. A voluntary consent form was obtained from the patients participating in the study, and the Necmettin Erbakan University Ethics Committee approval was obtained for the study (approval number: 2023/4541, date: 15.09.2023). Among the patients included in the study, those without an effusion on echocardiography before chemotherapy but developed an effusion after chemotherapy were included in the group of patients who developed an effusion. The clinical, demographic, and laboratory findings of all patients were recorded. In addition to routine echocardiographic evaluation, all patients underwent detailed echocardiography, including right ventricular function. Echocardiography was performed using two-dimensional imaging, M-mode, and tissue Doppler techniques, in accordance with the recommendations of the American Society of Echocardiography (11). The fluid remaining between the pericardium and epicardium at the end of diastole was considered to be pericardial effusion. To prevent the appearance of suspicious effusion in patients with prominent epicardial fat pads, these patients were not included in the study. The right ventricular fractionated area change (RV-FAC), right ventricular systolic velocity (RV-SM), right ventricular early peak (RV-EM), and late peak (RV-AM) diastolic parameters of the patients were examined. In addition, the tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery pressure (PAP) were measured. The patients' left ventricular mitral E velocity, septal E velocity, epicardial fat thickness, and E/E' parameters were examined. Then, the diastolic characteristics of the patients were recorded by examining their heart failure with preserved ejection fraction (H 2 FPEF) score.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 20.0 for Windows (SPSS Inc, Chicago, IL). Data are presented as mean and standard deviation, median and interquartile range, or numbers and proportions. Continuous variables were evaluated using the Student's t-test or Mann-Whitney U test after their suitability for normal distribution was checked using the Kolmogorov-Smirnov test, and categorical variables were evaluated using the chi-square test. A value of $p<0.05$ was considered significant.

Results

Pericardial effusion was in 30 (33.3%) of the 90 patients included in the study. The mean age of patients without pericardial effusion was 57.33±15.59, and the mean age of patients with effusion was 60.27±13.51, and it was similar between the groups (p=0.36) (Table 1). There was no statistically significant difference between the groups and patients with additional diseases such as diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, and hyperlipidemia (Table 2). No statistically significant difference was detected between the groups in RV-FAC, RV-EM, TAPSE, PAP, E/E', and H 2 FPEF values, which are parameters that indicate right ventricular functions and diastolic dysfunction (Table 1). However, RV-SM and RV-AM, which are indicators of diastolic dysfunction, were found at higher rates in the patient group with pericardial effusion (p-value 0.041 and 0.001, respectively). In addition, mitral E velocity was found to be lower in the patient group with pericardial effusion (p=0.032).

Table 1. Distribution of the clinical, demographic, echocardiographic, and laboratory characteristics of patients according to the pericardial effusion status

	Without pericardial effusion	Pericardial effusion	p-value
Age	57.33±15.59	60.27±13.51	0.36
Size	162.82±7.866	165.53±8.025	0.133
BMI	27.24±5.11	26.56±7.01	0.636
Alb/CRP	1.63±2.49	1.52±2.39	0.842
RV-FAC	42.73±9.40	42.63±9.09	0.960
RV-SM	13.88±3.35	15.25±2.69	**0.041**
RV-EM	10.94±3.13	11.51±3.65	0.473
RV-AM	14.26±4.25	17.28±3.50	**0.001**
Septal E	8.83±2.39	8.45±2.24	0.466
Mitral E	73.53±19.05	63.73±20.17	**0.032**
TAPSE	2.22±0.41	2.25±0.49	0.812
PAP	27.95±6.04	29.37±8.10	0.402
Epicardial fat	0.45±0.18	0.46±0.21	0.717
H 2 FPEF	33.15±20.85	32.77±20.08	0.934
E/E'	8.53±3.07	9.53±7.21	0.470

BMI: Body mass index, Alb: Albumin, CRP: C-reactive protein, RV-FAC: Right ventricular fractionated area change, RV-SM: Right ventricular systolic velocity, RV-EM: Right ventricular early peak, RV-AM: Right ventricular late peak, TAPSE: Tricuspid annular plane systolic excursion, PAP: Pulmonary artery pressure, H 2 FPEF: Heart failure with preserved ejection fraction

Table 2. Distribution of clinical, demographic, and laboratory characteristics of patients according to the pericardial effusion status

	Without pericardial effusion	Pericardial effusion	p-value
Sex			
Female	41 (68.3%)	16 (53.3%)	0.164
Male	19 (31.7%)	14 (46.7%)	
DM	9 (15.0%)	6 (20.0%)	0.549
HT	17 (28.3%)	8 (26.7%)	0.868
AF	1 (1.7%)	0 (0.0%)	0.477
HL	3 (5.0%)	4 (13.3%)	0.164
Smoke	10 (16.9%)	6 (20.0%)	0.892
Alchol	3 (5%)	2 (6.7%)	0.340
CAD	8 (13.3%)	2 (6.7%)	0.343
COPD	4 (6.7%)	4 (13.3%)	0.295

DM: Diabetes mellitus, HT: Hypertension, AF: Atrial fibrillation, HL: Hyperlipidemia, CAD: Coronary arterial disease, COPD: Chronic obstructive pulmonary disease

Discussion

This study is important because it shows that the development of pericardial effusion in patients with oncological malignancies receiving chemotherapy does not cause right ventricular failure or diastolic heart failure.

In clinical studies, pericardial effusion was detected in 5-20% of cancer patients (12). The development of pericardial effusion in patients with cancer is considered an indicator of poor prognosis. These patients are more likely to develop pericardial tamponade, especially those receiving cardiotoxic chemotherapy. There are several different mechanisms of pericardial effusion development in patients with malignancy. The most common is the spread of the tumor to the pericardium. In addition, chemotherapeutic drugs, radiotherapy, heart failure, and renal failure are among other conditions that are effective in the development of effusion. In a study conducted in 35 patients with pericardial effusion, Pradhan et al. (13) showed that the patients had improvement in both right and left ventricular functions after pericardiocentesis (14-16). This situation is important because pericardial effusion indicates right ventricular dysfunction. Cardiac dysfunction associated with cancer treatment can be classified into two ways. Type 1 effusion begins as soon as the drug is started and increases with the cumulative effect of the drug. It is more common in anthracycline-like chemotherapeutic areas. When the effect of the drug reaches its maximum, myofibrils become disorganized and apoptosis occurs (17). This results in ventricular failure and irreversible cardiac damage. In type 2, the myocardium becomes hibernated without cell death and cardiac contractility decreases. This condition is a reversible process, and the likelihood of cardiac failure is low (18). Many studies in the literature have been conducted on left ventricular failure, but there are almost no studies on right ventricular failure and diastolic failure. Pericardial effusion causes insufficient relaxation of the pericardium and impairs diastolic filling in patients. In a meta-analysis by Theetha Kariyanna et al. (10), they found a decrease in RV radial systolic functions and RV-FAC values in patients receiving anthracycline and trastuzumab treatment (19). In addition, a significant decrease was detected in the RV free wall longitudinal strain value, which is an indicator of diastolic dysfunction. Results similar to those of Theetha Kariyanna et al. (10) were obtained in the literature (1,20,21). In our study, different results were obtained from the study of Theetha Kariyanna et al. (10) While there was no statistically significant difference in the RV-FAC value, which was among the parameters we examined, a statistically significant difference was detected in the RV-SM, RV-AM, and mitral E speed, which indicate diastolic dysfunction. However, the effectiveness of these parameters in indicating diastolic dysfunction is low. In studies, the development of right ventricular failure is less common than that of left ventricular failure. If right ventricular failure develops, it causes serious symptoms that impair the quality of life of patients and is a significant cause of morbidity and mortality (22,23). Echocardiographic evaluations of the right ventricle have become more important in recent years as an important indicator of mortality (24,25). Because two-dimensional echocardiographic evaluation of the right ventricle is difficult, it is necessary to evaluate both systolic and diastolic functions with tissue Doppler echocardiography. In our study, it was observed that there was no significant change in the right ventricular functions of patients with pericardial effusion after chemotherapy. Although statistically significant changes were detected in some diastolic parameters and right ventricular tissue Doppler parameters, these parameters are insufficient to indicate heart failure. For this, advanced examinations such as strain echocardiography are required. Right ventricular functions are expected to be suppressed because of the development of serious effusion, both in patients receiving chemotherapy and in those not receiving chemotherapy. However, in our study, it was observed that there was no significant suppression of right ventricular functions in patients who developed effusion after chemotherapy compared with patients who did not develop effusion. This can be explained by the fact that the patients did not have serious pericardial effusion. If deterioration in diastolic parameters can be detected at the beginning in patients who develop effusion, precautions can be taken and undesirable events can be prevented before the clinical picture of heart failure appears in the patients. This is especially important in oncology patients. Because ventricular functions are important for patient treatment continuity. The H 2 FPEF score is a scoring system developed for the diagnosis of HFpEF. This score consists of body mass index >30 kg/m^2, use of two or more anti-hypertensive drugs, paroxysmal or persistent AF, pulmonary artery systolic pressure >35 mmHg by echocardiography, age >60, E/E.

The higher this score, the higher the morbidity and mortality rates in the patients. In a study conducted by Suzuki et al. (26) suggested that the H 2 FPEF score is an independent predictor of future heart failure-related events. In our study, we examined the H 2 FPEF score of patients with and without pericardial effusion and did not detect a statistically significant difference between the results. This is important because it shows that it does not pose an extra risk of heart failure in patients who do not develop serious pericardial effusion after chemotherapy. Even in untreated cancer patients, increased pro-inflammatory markers, hormonal effects, and reactive oxygen radicals have negative effects on right ventricular functions (4,27,28). In a study by Oliveira et al. (16) they revealed that more support devices were needed in patients who developed chemotherapy-related right ventricular failure. This reveals that the prognosis is worse in patients receiving chemotherapy if right ventricular failure develops. In a study by Milano et al. (29), they found a decrease in both right and left ventricular wall thickness in patients receiving doxorubicin and trastuzumab. In the same study, they showed that fibrosis developed in the right ventricular free wall. The results of this study are different from those of our study. The development of pericardial effusion in patients after chemotherapy does not directly mean right ventricular failure and diastolic dysfunction. Although the development of pericardial effusion in cancer patients is considered a poor prognostic indicator, there is no need to change treatment if there is no suppression of right ventricular functions in the patients.

Study Limitations

Our limitations include not evaluating the basal right heart functions of the patients and not separately classifying the type of chemotherapeutic drug. Because the main purpose of our study was to evaluate right ventricular diastolic function parameters, even if the effusion was mild, patients were recruited regardless of the type of chemotherapeutic drug. Conducting studies in more homogeneous patient groups may provide additional information regarding cardiotoxicity.

Conclusion

Pericardial effusion is an indicator of poor prognosis in patients with cancer. In malignancy patients who develop pericardial effusion, we recommend that diastolic parameters be examined and close clinical follow-up of the patients is performed before the clinical picture of overt heart failure develops. It should be noted that the development of pericardial effusion in oncology patients receiving chemotherapy does not mean right ventricular failure.

Ethics Committee Approval: the Necmettin Erbakan University Ethics Committee approval was obtained for the study (approval number: 2023/4541, date: 15.09.2023).

Informed Consent: A voluntary consent form was obtained from the patients participating in the study.

Peer-review: Externally and internally peer-reviewed.

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

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

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

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İstanbul Med J 2023; 24(4): 404–11
DOI: 10.4274/imj.galenos.2023.55889

Hyperkalemia: A Cause of Non-adherence to Renin-Angiotensin-Aldosterone System Inhibitors in Chronic Kidney Disease: A Retrospective Study

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ABSTRACT

Introduction: There is increasing awareness of non-adherence to renin-angiotensin- aldosterone system inhibitors (RAASi) in chronic kidney disease (CKD). This study aimed to evaluate the incidence of hyperkalemic adult CKD patients who were prescribed RAASi and to determine variations in pharmacological interventions to uncover reasons for non-adherence to RAASi treatment.

Methods: The incidence of hyperkalemia and non-adherence to RAASi [angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blockers (ARBs)] in CKD patients was examined among 471 patients over the age of 18 years who had estimated-glomerular filtration rate (e-GFR) measurements and were diagnosed with CKD between stages 1 and 5. Hyperkalemia was defined as serum potassium ($K+$) ≥5 mmol/L. The number of hyperkalemic patients not reaching the target dose, hyperkalemia as a reason for not reaching the target dose, patients receiving sodium polystyrene sulfonate patients discontinuing ACEi/ARBs, having a decreased dose of ACEi/ARBs, or treated with the addition or increasing dose of diuretics were compared between the hyperkalemia groups.

Results: Hyperkalemia was detected in 29.1% of the patients (n=137), being mild in 21.7%, moderate in 6.2%, and severe in 1.3%. The main finding was that the frequency of patients not reaching the target dose of ACEi/ARBs treatment due to hyperkalemia, hypotension, or e-GFR increase higher than 30% was dramatically higher among patients having moderate/severe hyperkalemia ($p<0.0001$). In 12.41% of hyperkalemic patients, hyperkalemia was cited as the cause for not achieving the target dosage of ACEi/ARB therapy. 25.71% of these patients discontinued ACEi/ARBS treatment, 14.29% had decreased dose of this treatment, and 11.43% had increased dose of diuretics or newly prescribed diuretics. However, none of the patients with mild hyperkalemia experienced these events during treatment.

Conclusion: These findings suggest that serum K^+ concentration may be related to major adverse clinical outcomes and affect the type of pharmacological intervention in CKD, resulting in ACEi-ARB discontinuation and halting to reach the target dose.

Keywords: Chronic kidney disease, hyperkalemia, renin-angiotensin-aldosterone system inhibitors

Introduction

Hyperkalemia is a potential metabolic disease and a fatal complication of chronic kidney disease (CKD). It is defined as an elevated potassium (K^+) concentration in the blood serum. Recent studies have shown that K^+ fluctuation may be related to increased mortality or poor cardiovascular (CV) outcomes in patients with CKD (1,2). Hyperkalemia also arises because of renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, which is commonly used to treat CKD (3,4). The use of RAASis in treating CKD is usually recommended by current treatment guidelines because it has been demonstrated to lower blood pressure and proteinuria, delay the decline in estimated-glomerular filtration rate (e-GFR), and lessen the risk of kidney failure (5).

The CREDIT study (Chronic Renal Disease in Turkey) conducted by Süleymanlar et al. (6) depicted that RAASis [especially angiotensin-converting enzyme (ACE) inhibitors (ACEs) and angiotensin II receptor blockers (ARBs)] need to be used in CKD treatment due to their successful renoprotective properties, despite the risk of severe side effects such as hyperkalemia. Therefore, raising awareness about RAASis non-adherence has to be enlightened.

For this purpose, this study aimed to evaluate the incidence of hyperkalemic adult CKD patients who were prescribed RAASi, to determine the variations in the pharmacological interventions, which included the ratio of patients who could reach the maximum RAASi dose, and to uncover the reasons for drug non-adherence to RAASi treatment.

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Cite this article as: Gülçiçek S, Seyahi N. Hyperkalemia: A Cause of Non-adherence to Renin-Angiotensin-Aldosterone System Inhibitors in Chronic Kidney Disease: A Retrospective Study. İstanbul Med J 2023; 24(4): 404-11.

Received: 10.10.2023
Accepted: 09.11.2023

Methods

Study Design and Patient Selection

The data of patients with chronic renal failure diagnosed at the outpatient clinic of a tertiary hospital between 31.01.2021-31.01.2022 were retrospectively collected. The electronic database of the automation system of the tertiary hospital was examined between these dates, including patients with newly initiated ACEi/ARBs, and the potassium levels of these patients within 180 days after the start of treatment were screened. A total of 512 patients over the age of 18 years who had a baseline e-GFR measurement, were diagnosed with CKD between stages 1 and 5, and were receiving RAASi treatment were recruited to the study. Patients were included if they received one of the following treatments within 180 days of the initial measurement of hyperkalemia: RAASi discontinuation, RAASi dose reduction, diuretic dose increase, or new diuretic or sodium (Na) polystyrene sulfonate (SPS) prescription. Patients who received the same dose of RAASi without receiving any extra medication to address hyperkalemia were also included.

The exclusion criteria wereas follows:

- A disease other than CKD, including a known inflammatory disease and/or severe psychological disorder,

- Being on dialysis,

- History of kidney transplantation,

- Taking SPS and/or diuretic prescriptions started earlier than 30 days or exclusively in the emergency room,

- Having an initial hyperkalemia value greater than 7.0 mEq/L,

- No repeat K^+ measures,

- Hospitalization within 30 days of the initial measurement.

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee of Non-invasive Clinical Research (approval number: 311, date: 14.10.2022) in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net).

Data Collection

All data were collected from the hospital database. The patients' characteristics included gender, age (years), body mass index (BMI) (kg/m^2), their comorbidities [diabetes mellitus (DM), hypertension, CV disease (CVD) and cerebrovascular event]. The laboratory findings included the hematocrit (HCT), white blood cells, glucose, urea, creatinine, uric acid, total protein amount, albumin, albumin/creatinine ratio, calcium (Ca^{+2}), phosphor (P), Na^+, K^+, parathyroid hormone (PTH), bicarbonate (HCO_3), hemoglobin (Hb), hemoglobin A1C (HbA1C), and e-GFR levels. To assess the patients' laboratory results, fasting blood samples were collected from all individuals during the examination and then centrifuged. Roche Cobas 8000 e602 analyzers (Roche Diagnostics, Mannheim, Germany) were used to analyze parameters such as whole blood count, blood urea, creatinine, uric acid, total protein, and albumin. Levels of HCO_3, Hb, and HbA1C were determined using a photometric method, whereas an electrochemiluminescence assay was used to measure PTH.

The e-GFR was calculated using equations established by the CKD epidemiological collaboration (CKD-EPI) (7). CKD was defined as the presence of persistent proteinuria or a reduced e-GFR (<90 mL/min per 1.73 m^2) determined by the CKD-EPI creatinine equation, confirmed in two separate measurements within a 3-month interval. The CKD-EPI equation, presented as a single formula, is as follows: GFR= 141 x minimum (Scr/κ, 1)α x maximum (Scr/κ, 1)-1.209x0.993 age x 1.018 (if female), where Scr represents serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males. The min function indicates the smaller value between Scr/κ and 1, and the maximum function indicates the larger value between Scr/κ and 1.

Diagnosis of Hyperkalemia and Classification

To estimate the peak level of K^+, blood K^+ was measured at least once 180 days after beginning ACE/ARB intake. Hyperkalemia was characterized by a serum K^+ level equal to or greater than 5 mmol/L. It was further categorized as mild (>5.0 to <5.5 mmol/L), moderate (5.5 to <6.0 mmol/L), or severe (≥6.0 mmol/L) based on the K^+ concentration. Patients who had serum K^+ <5 mmol/L were selected as the control group. The patient characteristics and laboratory findings were compared between the control and hyperkalaemic patients. As the target dose, we accepted the maximum dose stated in the prospectus or product information sheet. Among the patients with serum K^+ ≥5 mmol/L, the number of patients not reaching the target dose, hyperkalemia as cause of not reaching the target dose, patients receiving SPS, patients discontinuing ACEi/ARBs, having a decreased dose of ACEi/ARBs, or treated with addition or increasing dose of diuretics were compared between the groups of hyperkalemia.

Statistical Analysis

The Graph Pad Instat application was used to statistically evaluate all data. The mean, standard deviation, median, minimum, and maximum values were identified as descriptive statistics. The homogeneity of the variance and the normality of the variable distribution were examined using the Kolmogorov-Smirnov test. The parametric analysis of variance test (Student's t-test) was used to evaluate two groups after the assumption was satisfied. Non-parametric testing (Mann-Whitney U test) was used to evaluate the two groups when the requirements for parametric tests were not satisfied. Categorical variables are analyzed by the chi-square test. At a 95% confidence interval, $p<0.05$ was considered statistically significant level.

Results

Among 512 patients over the age of 18 years who had baseline e-GFR and hyperkalemia measurements and were diagnosed with CKD, 41 patients were excluded according to the exclusion criteria. Among the 471 patients diagnosed with CKD and receiving RAASi, hyperkalemia was identified in 29.1% of the cases (n=137) during the initial assessment. Specifically, 21.7% of these cases were categorized as mild (n=102), 6.2% as moderate, and 1.3% as severe (n=6). The general characteristics of patients classified according to hyperkalemia diagnosis are

presented in Table 1. The mean age, BMI, distribution of sex, and comorbidities were comparable between the control group including normokalemic patients and the hyperkalemia group including hyperkalemic patients, except that the ratio of patients with CVD in the hyperkalemia group was significantly higher than that in the control group (25.55% vs. 7.49%, p<0.0001). The mean HCT, total protein, HCO_{3^-}, Hb, and e-GFR levels significantly decreased, whereas the median urea and K^+ levels significantly increased in the hyperkalemia group compared with those in the control group (p<0.05) (Table 1). The distribution of CKD stage significantly varied between the two groups (p<0.0001). The ratios of patients at stages 4 and 5 were 16.06% and 2.92% in the hyperkalemia group and 7.78% and 0.60% in the control groups, respectively.

The distribution of medications classified according to hyperkalemia diagnosis is presented in Table 2. The most common drugs prescribed in the control group were ARBs, thiazide, beta-blockers and ACEi (59.9%, 46.7%, 41.0% and 40.1%, respectively). The most common drugs prescribed in the hyperkalemia group were ARBs, beta-blockers, Ca channel blockers, oral antidiabetics and ACEi (55.5%, 52.6%, 51.8%, 47.4% and 44.5%, respectively).

Table 1. General characteristics of normokalemic and hyperkalaemic patients

Characteristics	Total, (n=471)	Control, (n=334)	Hyperkalemia, (n=137)	p-value
Age (y), $\bar{x}$ ± SD	66.07±10.37	66.17±10.86	66.17±10.86	0.309
Sex, (n, %)				
Male	211 (44.80)	149 (44.61)	62 (45.26)	0.979
Female	260 (55.20)	185 (55.39)	75 (54.74)	
BMI (kg/m^2), $\bar{x}$ ± SD	31.64±5.61	31.86±5.88	31.44±5.37	0.546
Comorbidities (n, %)				
DM	270 (57.32)	185 (55.39)	85 (62.04)	0.221
HT	463 (98.30)	328 (98.20)	135 (98.54)	0.797
CVD	60 (12.74)	25 (7.49)	35 (25.55)	**<0.0001**
CVE	5 (1.06)	4 (1.20)	1 (0.73)	0.653
Laboratory findings				
Urea (mg/dL), $\bar{x}$ (min.-max.)	50.8 (18-180)	48 (18-120)	55.2 (25.7-180)	**0.0011**
Creatinine (mg/dL), $\bar{x}$ (min.-max.)	1.28 (0.55-8.2)	1.29 (0.55-4.00)	1.28 (0.66-8.2)	0.182
e-GFR (mL/min/1.73 m2), $\bar{x}$ ± SD	48.01±16.46	49.21±16.88	45.08±15.04	**0.0095**
Uric acid (mg/dL), $\bar{x}$ ± SD	6.45±1.61	6.47±1.68	6.42±1.54	0.793
Total protein (g/L), $\bar{x}$ ± SD	7.10±0.47	7.20±0.41	7.00±0.51	**0.0007**
Albumin (g/L), $\bar{x}$ ± SD	4.44±0.34	4.44±0.35	4.43±0.33	0.867
Ca (mg/dL), $\bar{x}$ (min.-max.)	9.5 (7.9-11)	9.42 (7.9-11.0)	9.5 (8.4-10.6)	0.490
P (mmol/L), $\bar{x}$ ± SD	3.69±0.66	3.65±0.72	3.73±0.61	0.374
Na (mg/dL), $\bar{x}$ ± SD	139.76±3.11	139.81±3.16	139.74±3.09	0.894
K (mmol/L), $\bar{x}$ (min.-max.)	4.76 (2.9-6.38)	4.6 (2.9-4.99)	5.28 (5.0-6.38)	**<0.0001**
Glucose (mg/dL), $\bar{x}$ (min.-max.)	115 (72-375)	116 (79-312)	113.55 (72-375)	0.631
PTH (ng/L), $\bar{x}$ (min.-max.)	61.3 (9.5-1405)	61 (14.3-1405)	62.2 (9.5-458)	0.805
HCO_3^- (mmol/L), $\bar{x}$ ± SD	25.54±3.00	25.73±2.99	25.02±2.98	**0.0293**
A/C ratio (mg/gr), $\bar{x}$ (min.-max.)	146 (0-11665)	145 (0-11665)	153 (1-9326)	0.391
Hb (g/dL), $\bar{x}$ ± SD	12.71±1.71	12.84±1.74	12.39±1.59	**0.0062**
HCT (%), $\bar{x}$ ± SD	38.63±4.74	39.50±4.73	37.83±4.64	**0.0043**
WBC (10^9/L), $\bar{x}$ (min.-max.)	7,770 (3,690-17,100)	7,750 (3,690-17,100)	7,930 (4,150-12,470)	0.856
HbA1C (%), $\bar{x}$ ± SD	7.40±1.59	7.44±1.52	7.29±1.94	0.855
CKD stage (n, %)				
1 (≥90 mL/min/1.73 m^2)	9 (1.91)	9 (2.69)	0 (0)	**<0.0001**
2 (60-89 mL/min/1.73 m^2)	49 (10.40)	26 (7.78)	23 (16.79)	
3 (30-59 mL/min/1.73 m^2)	359 (76.22)	271 (81.14)	88 (64.23)	
4 (15-29 mL/min/1.73 m^2)	48 (10.19)	26 (7.78)	22 (16.06)	
5 (<15 mL/min/1.73 m^2)	6 (1.27)	2 (0.60)	4 (2.92)	

$\bar{x}$ ± SD: Mean ± standard deviation, $\bar{x}$ [min.-max.]: Median [minimum value-maximum value], min.: Minimum, max.: Maximum, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CHD: Coronary heart disease, CVE: Cerebrovascular event, e-GFR: Estimated-glomerular filtration rate, min.: Minute, Ca: Calcium, P: Phosphorus, Na: Sodium, K: Potassium, PTH: Parathyroid hormone, HCO_3^-: Bicarbonate, A/C: Albumin/creatinine ratio in spot urine, Hb: Hemoglobin, HCT: Hematocrit, WBC: White blood cells, HbA1C: Hemoglobin A1C, CKD: Chronic kidney disease

The general characteristics of patients classified according to the severity of hyperkalemia are presented in Table 3. The mean age of patients with moderate/severe hyperkalemia was significantly lower than that of patients with mild hyperkalemia (p=0.0034). The mean BMI, distribution of comorbidities, and medications did not differ according to the severity of hyperkalemia, except the number of sodium-glucose transport protein 2 (SGLT2) inhibitor users, which was significantly lower among patients with moderate/severe hyperkalemia than among patients with mild hyperkalemia (14.29% vs. 32.35%, p=0.0488). The mean e-GFR level was significantly lower, whereas the median Na^{+2} and K^{+} levels were significantly higher in patients with moderate/severe hyperkalemia compared to the mild hyperkalemic patients (p<0.05). The other laboratory findings were comparable between the two groups (Table 3). The distribution of CKD stage did not differ between the two groups (p=0.538).

Among the hyperkalemic patients receiving a pharmacologic intervention with RAASi (Table 4), 54 (39.42%) could not reach the target dose of ACEi/ARBs. This ratio was significantly higher in patients with moderate/severe hyperkalemia than in those with mild hyperkalemia (74.29% vs. 27.45%, p<0.0001). The cause of not reaching a target dose was hyperkalemia in 48.57% of patients with moderate/severe hyperkalemia, whereas none of the mild hyperkalemic patients had this cause. 27 (19.71%) hyperkalemic patients were prescribed SPS as treatment for hyperkalemia, which did not differ between the two groups (p=0.076). Among the patients with moderate/severe hyperkalemia, 9 (6.57%) underwent ACEi/ARBs discontinuation, 5 (3.65%) underwent ACEi/ARBs dose decrease, 4 (2.92%) were newly prescribed a diuretic or prescribed an increased dose of a preexisting diuretic. None of the patients with mild hyperkalemia did not undergo ACEi/ARBs discontinuation or ACEi/ARBs dose decrease or were newly prescribed a diuretic or had an increased dose of a preexisting diuretic.

Discussion

In this retrospective study, the outcomes of hyperkalemia and non-adherence to RAASi (ACEi/ARBs) in patients with CKD were examined. The study found a hyperkalemia prevalence of 29.1% (n=137). Mild hyperkalemia was detected in 74.5% of the hyperkalemic patients, whereas 29 had moderate hyperkalemia (21.2% of hyperkalemic patients), and 6 had severe hyperkalemia (4.4% of hyperkalemic patients). These ratios were consistent with other studies in the literature (8,9). Patients with CKD cannot reach the target dose of treatments with ACEi/ARB mainly because of hyperkalemia. However, hypotension and e-GFR increases higher than 30% also seem to be related to inappropriate ACEi/ARB dosing (10). The key finding of the present study was that the frequency of patients not reaching the target dose of ACEi/ARB treatment was moderate/severe hyperkalemia. Second, within this patient group, it was discovered that hyperkalemia was the presumed cause for the failure to achieve the target dosage of treatments with ACEi/ARBs. Third, 25.71% of these patients discontinued ACEi/ARBS treatment, 14.29% had a decreased dose of this treatment, and 11.43% had an increased dose of diuretics or newly prescribed diuretics. However, none of the patients with mild hyperkalemia experienced these events during treatment.

Several factors can affect serum K^{+} concentration in CKD patients, including demographic variables, e-GFR level, medications frequently prescribed, acid- base status, BMI, and the existence of comorbidities (11). In our study, no relationship was found between age, gender, BMI, and hyperkalemia. However, the prevalence of CVD was significantly higher among hyperkalemic patients (25.55% vs. 7.49%), probably because of the medications used in these patients. In fact, in a previous study, hyperkalemia was reported to be frequent in patients with established CVD who were using antihypertensive drugs and was associated with increases in all-cause mortality and hospitalizations. Advanced CKD, diabetes mellitus, CVD, and peripheral vascular disease were also found to be independent predictors of hyperkalemia (12).

Table 2. Distribution of medications classified according to hyperkalemia diagnosis

Medications (n, %)	Total, (n=471)	Control, (n=334)	Hyperkalemia, (n=137)
ACEi	195 (41.4)	134 (40.1)	61 (44.5)
ARBs	276 (58.6)	200 (59.9)	76 (55.5)
CCBs	130 (27.6)	59 (17.7)	71 (51.8)
Alpha-blocker	27 (5.7)	7 (1.5)	20 (14.6)
Beta-blocker	209 (44.4)	137 (41.0)	72 (52.6)
Allopurinol	23 (4.9)	15 (4.5)	8 (5.8)
Thiazide	203 (43.1)	156 (46.7)	47 (34.3)
Furosemide	48 (10.2)	29 (8.7)	19 (13.9)
Spironolactone	12 (2.6)	9 (2.7)	3 (2.2)
ASA	84 (17.8)	33 (9.9)	51 (37.2)
Statin	69 (14.6)	28 (8.4)	41 (29.9)
Oral antidiabetics	123 (26.1)	58 (17.4)	65 (47.4)
Insulin	42 (8.9)	19 (5.7)	23 (16.8)
SGLT2 inhibitor	137 (29.1)	99 (29.6)	38 (27.7)

ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blockers, CCBs: Calcium channel blockers, ASA: Acetylsalicylic acid, SGLT2: Sodium-glucose transport protein 2

Table 3. General characteristics of patients classified according to the severity of hyperkalemia

Characteristics	Mild, (n=102)	Moderate/severe, (n=35)	p-value
Age (y), $\bar{x} \pm$ SD	67.17±8.86	61.91±8.77	**0.0034**
Sex (n, %)			
Male	48 (47.06)	14 (40)	0.598
Female	54 (52.94)	21 (60)	
BMI (kg/m^2), $\bar{x} \pm$ SD	31.45±5.26	31.40±5.75	0.968
Comorbidities (n, %)			
DM	62 (60.78)	23 (65.71)	0.751
HT	101 (99.02)	34 (97.14)	0.424
CHD	26 (25.49)	9 (25.71)	0.979
CVE	0 (0)	1 (2.86)	0.574
Medications (n, %)			
ACEi	45 (44.12)	16 (45.71)	0.870
ARBs	57 (55.88)	19 (54.29)	0.870
CCBs	50 (49.02)	21 (60)	0.355
Alpha-blocker	18 (17.65)	2 (5.71)	0.148
Beta-blocker	52 (50.98)	20 (57.14)	0.664
Allopurinol	7 (6.86)	1 (2.86)	0.650
Thiazide	39 (38.24)	8 (22.86)	0.148
Furosemide	14 (13.73)	5 (14.29)	0.934
Spironolactone	1 (0.98)	2 (5.71)	0.326
ASA	38 (37.25)	13 (37.14)	0.991
Statin	31 (30.39)	10 (28.57)	0.839
Oral diabetics	45 (44.12)	20 (57.14)	0.256
Insulin	17 (16.67)	6 (17.14)	0.948
SGLT2 inhibitor	33 (32.35)	5 (14.29)	**0.0488**
Laboratory findings			
Urea (mg/dL), $\tilde{x}$ (min.-max.)	55.55 (25.7-180)	54.4 (30.6-151.4)	0.696
Creatinine (mg/dL), $\tilde{x}$ (min.-max.)	1.27 (0.66-8.2)	1.5 (0.69-4.52)	0.494
e-GFR (mL/min/1.73m^2), $\bar{x} \pm$ SD	46.56±14.94	40.76±14.68	**0.049**
Uric acid (mg/dL), $\bar{x} \pm$ SD	6.48±1.60	6.27±1.36	0.489
Total protein (g/L), $\bar{x} \pm$ SD	7.03±0.50	6.94±0.54	0.420
Albumin (g/L), $\tilde{x}$ (min.-max.)	4.5 (3.3-5.1)	4.5 (3.5-4.9)	0.755
Ca (mg/dL), $\tilde{x}$ (min.-max.)	9.5 (8.4-10.6)	9.6 (8.5-10.3)	0.581
P (mmol/L), $\bar{x} \pm$ SD	3.70±0.62	3.82±0.55	0.352
Na (mg/dL), $\tilde{x}$ (min.-max.)	140 (130-145)	142 (135-148)	**0.0386**
K (mmol/L), $\tilde{x}$ (min.-max.)	5.2 (5.0-5.49)	5.6 (5.12-6.38)	**<0.0001**
Glucose (mg/dL), $\tilde{x}$ (min.-max.)	113 (72-375)	122 (72-301)	0.148
PTH (ng/L), $\tilde{x}$ (min.-max.)	61.65 (9.5-458)	67.2 (12.2-179.3)	0.913
HCO_{3^-} (mmol/L), $\bar{x} \pm$ SD	25.06±3.09	24.88±2.65	0.767
A/C ratio (mg/gr), $\tilde{x}$ (min-max)	143 [1.0-7483)	213.5 (6.0-9326)	0.337
Hb (g/dL), $\bar{x} \pm$ SD	12.42±1.60	12.29±1.55	0.661
HCT (%), $\bar{x} \pm$ SD	37.89±4.69	37.64±4.53	0.777
WBC (10^9/L), $\bar{x} \pm$ SD	7833.9±1893.6	7744.6±1918.3	0.812
HbA1C (%), $\tilde{x}$ (min.-max.)	7.15 (6.4-11.4)	6.7 (5.3-6.9)	0.478
CKD stage (n, %)			
2 (60-89 mL/min/1.73 m^2)	19 (18.63)	4 (11.43)	0.538
3 (30-59 mL/min/1.73 m^2)	66 (64.71)	22 (62.86)	
4 (15-29 mL/min/1.73 m^2)	14 (13.73)	8 (22.86)	
5 (<15 mL/min/1.73 m^2)	3 (2.94)	1 (2.85)	

$\bar{x} \pm$ SD: Mean ± standard deviation, $\tilde{x}$ (min.-max.): Median [minimum value-maximum value), BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, CHD: Coronary heart disease, CVE: Cerebrovascular event, ACEi: Angiotensin-converting enzyme inhibitor, ARBs: Angiotensin II receptor blockers, CCBs: Calcium channel blockers, ASA: Acetylsalicylic acid, SGLT2: Sodium-glucose transport protein 2, e-GFR: Estimated-glomerular filtration rate, Ca: Calcium, P: Phosphorus, Na: Sodium, K: Potassium, PTH: Parathyroid hormone, HCO_3^-: Bicarbonate, A/C: Albumin/creatinine ratio in spot urine, Hb: Hemoglobin, HCT: Hematocrit, WBC: White blood cells, HbA1C: Hemoglobin A1C, CKD: Chronic kidney disease

Table 4. Distribution of patients classified according to treatment progress

Characteristics	Total, (n=137)	Mild, (n=102)	Moderate/severe, (n=35)	p-value
Patients not reaching the target dose (n, %)	54 (39.42)	28 (27.45)	26 (74.29)	**<0.0001**
Hyperkalemia as a cause of not reaching target dose (n, %)	17 (12.41)	0 (0)	17 (48.57)	**<0.0001**
Patients receiving SPS (n, %)	27 (19.71)	16 (15.69)	11 (31.43)	0.076
Discontinuation of ACEi/ARBs (n, %)	9 (6.57)	0 (0)	9 (25.71)	**<0.0001**
Decreasing dose of ACEi/ARB (n, %)	5 (3.65)	0 (0)	5 (14.29)	**0.0008**
Addition or increasing dose of diuretics (n, %)	4 (2.92)	0 (0)	4 (11.43)	**0.0039**

SPS: Sodium polystyrene sulfonate, ACEi: Angiotensin-converting enzyme inhibitor, ARBs, Angiotensin II receptor blockers

In this study, the urea level was significantly higher in hyperkalemic patients, probably because of a prerenal condition resulting from CVD. We can explain the low Hb and HCT levels in hyperkalemic patients by the fact that the anemia increases as the CKD stage progresses because the rate of hyperkalemia was higher in advanced CKD patients.

The factors linked to K^+ levels in patients under nephrological care were renal function, nephropathy type, age, diabetes mellitus, and plasma HCO_{3^-} concentration, listed in descending order of significance. Among these main factors, only one seems to be modifiable: the plasma HCO_{3^-} level, which reflects the body acidity of patients with CKD (13). This study also supported these statements by showing that hyperkalemic patients have significantly lower HCO_3 concentrations than normokalemic patients. However, HCO_3 concentrations did not differ depending on the severity of hyperkalemia.

The risk of hyperkalemia was discovered to be inversely related to renal function, escalating from 2-fold in stage 2 to 16-fold in stage 5 kidney failure (14). We observed a significantly higher ratio of patients in stages 4-5 in the hyperkalemia group than in the control group, indicating an anticipated complication of advancing CKD. To prevent hyperkalemia in these patients, who gradually lose their ability to excrete dietary K^+, it is advisable to maintain a low dietary K^+ intake (13).

Hyperkalemia may develop in patients with CKD due to hyporeninemic hypoaldosteronism. While beta blockers, NSAIDs, and renin inhibitors reduce renin production in these people, ACEis and ARBs reduce angiotensin 2 production, and the use of these drugs increases the risk of developing hyperkalemia (15). In our study, no significant relationship was found between medications and hyperkalemia. Moranne et al. (16) recruited 1,038 CKD patients and found that the prevalence of hyperkalemia was 2% in the group with a GFR >60 mL/min/1.73 m^2, while it was 42% in the group with GFR <20 mL/min/1.73 m^2 (16). In another study including 13,500 patients with CKD, it was shown that every 5 mL/min/1.73 m^2 decrease in GFR increased the risk of hyperkalemia by 26% (17). In a study including 388 patients whose serum K^+ value was ≥5.1 mEq/L and without renal replacement therapy, as the GFR value decreased, the K^+ value increased (8). Consistent with the literature, we determined that the mean e-GFR level of hyperkalaemic patients was significantly lower than that of normokalemic patients. In addition, patients with moderate/severe hyperkalemia had significantly lower e-GFR levels than those with mild hyperkalemia.

SGLT2 inhibitors have demonstrated significant nephroprotection and cardioprotection in both diabetic and non-diabetic CKD patients, as indicated by reports evaluating long-term outcomes (18). Consequently, these inhibitors might be recommended for non-diabetic CKD patients in the future (19). Research has shown that SGLT2 inhibitors are linked to lower serum K^+ levels in patients with CKD (20-22). The effect of SGLT2 inhibitors on serum K^+ levels appears to be more substantial in clinical trials involving CKD patients than in trials focusing on high CV risk (23). Remarkably, SGLT2 inhibitors seem to have a neutral or even decreasing effect on hyperkalemia in CKD patients (22). This might explain the finding that the prescription of SGLT2 inhibitors in mild hyperkalemic patients was significantly higher than that in those with moderate/severe hyperkalemia.

The most common ambulatory pharmacologic treatment changes for hyperkalemia include discontinuation or dose decrease of RAASi, initiation or dose increase of K^{+-} wasting diuretics, or initiation of K^{+-} binding medications such as SPS. The selection of ambulatory intervention varies widely among professionals, the progression of CKD, and the availability of the treatments (13). Hyperkalemia frequently restricts the use of RAASi and can cause a dose reduction or discontinuation of medication, thereby diminishing its possible benefits. Consequently, hyperkalemia poses a significant concern for clinicians, especially in the context of ACEi and ARB usage (24). In a study conducted by Delgado-Jiménez et al. (25), hyperkalemia was cited as the cause for not prescribing or failing to achieve the target dose of mineralocorticoid receptor antagonists (MRAs) in 34.8% and 12.5% of patients, respectively. The impact of hyperkalemia on the prescription or achieving the target dose with ACEi, ARBs, and angiotensin-neprilysin inhibitors was notably lower than that with MRAs (25). In a retrospective cohort study by Hundemer et al. (26) recruiting older adults who developed hyperkalemia, the most frequently employed strategy in response to hyperkalemia was discontinuation of RAASi, accounting for 74% of 11,317 patients who received a pharmacologic intervention. This was followed by reducing the RAASi dosage (15%), increasing the diuretic dosage (7%), prescribing a new diuretic (3%), and using SPS (1%) (26). Consistent with the literature, we found that 39.42% of hyperkalemic patients did not reach a target dose, and hyperkalemia was the reason for not reaching the target dose of RAASi in 12.41% who had moderate/severe hyperkalemia. Moreover, 6.57% of hyperkalemic patients discontinued ACEi/ARB treatment, and 3.65% were prescribed a decreased dose of ACEi/ARBs, all of whom had moderate/severe hyperkalemia. 19.71% of hyperkalemic patients received SPS, which is a safe and tolerable gastrointestinal K^+ binder that enables the long-term control of hyperkalemia, perhaps facilitating the optimization of RAASi medication, and probably altering the existing CKD situation.

The best method for managing RAASi-related hyperkalemia in outpatient settings is still under debate. When it comes to choosing which intervention to employ, the specialists and clinics differ greatly from one another. In patients on RAAS inhibitors, the concurrent use of loop or thiazide diuretics has been linked to a lower incidence of hyperkalemia (22). The addition of diuretics to the treatment regimen to mitigate the risk of hyperkalemia may also enhance the effectiveness of RAAS blockade. Thiazides, in particular, have been found to reduce albuminuria by 42% when combined with RAAS blockade in short-term studies (lasting 4 weeks) (18), and they are recommended for improving the antihypertensive effectiveness of RAAS blockers (27). However, the ability of thiazides to lower K^+ levels may be limited in patients with lower e-GFR values, although serum K^+ levels in these patients may still respond to loop diuretics. It is important to note that K^{+-} sparing diuretics such as triamterene, amiloride, and those targeting the mineralocorticoid receptor can increase the risk of hyperkalemia (28). Hundemer et al. (26) also pointed out that among elderly patients (with an average age of 79 years), the most common intervention was the discontinuation of RAAS inhibitors (74%). Nevertheless, 10% of patients received new or increased doses of diuretics (26). This finding aligns with our results, where the proportion of hyperkalemic patients who were prescribed new or increased doses of diuretics was 11.43%.

Study Limitations

There are indeed several limitations to our study. First, it is essential to acknowledge that this study is retrospective and observational in nature. As a result, we could only find correlations between the study treatments and outcome measures-not causes and effects. We used a single definition of hyperkalemia and grouped a limited number of patients by severity, although the results were consistent across these groups.

Second, the outcome measures in our study were confined to a 180-day timeframe. This temporal limitation might restrict our capacity to establish correlations between outpatient interventions for RAAS inhibitor-associated hyperkalemia and long-term outcomes, which could differ from the short-term outcomes observed in this study. For instance, the long-term effects of RAAS inhibitor discontinuation on diseases such as proteinuric CKD and congestive heart failure, where RAAS inhibitors are recognized for slowing disease progression, might necessitate a longer timeframe to become fully clear.

Third, because our study concentrated on the influence of hyperkalemia severity on ambulatory interventions, patients who were acutely ill or had experienced acute kidney injury at the time of the hyperkalemia episode were excluded, as well as patients hospitalized within 30 days of the initial hyperkalemia diagnosis.

Additionally, it is worth noting that newer K^{+-} binding agents such as patiromer and zirconium cyclosilicate were not included in our study because they were not widely available in our clinic or country during the timeframe of our research. These agents provide an alternative approach for the management of outpatient hyperkalemia.

These limitations should be considered when interpreting the findings and implications of our study.

Conclusion

In conclusion, among 471 patients with CKD, hyperkalemia was detected in 29.1% of the patients, mild in 21.7%, moderate in 6.2%, and severe in 1.3%. Among non-adherence to RAASi treatment, RAASi discontinuation was the pharmacologic intervention in 27.45% of patients with mild hyperkalemia and in 74.29% of patients with moderate/severe hyperkalemia. The main reason for not reaching the target dose of RAASi was hyperkalemia in 48.57% of patients with moderate/severe hyperkalemia. These findings suggest that serum K^+ concentration may be correlated with major adverse clinical outcomes and affect the type of pharmacological intervention in patients with CKD. It should be considered that hyperkalemia may cause ACEi-ARB discontinuation, and halting to reach the target dose, and close monitoring of hyperkalemic patients in clinics is advisable. Confirming the short- and long-term effects of several treatment options for RAASi-related hyperkalemia requires several prospective investigations. Further randomized controlled trials are necessary to determine the ideal blood K^+ levels for patients with CKD.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethical Committee of Non-invasive Clinical Research (approval number: 311, date: 14.10.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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

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

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

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2023 Referee Index

2023 Author Index

2023 Author Index

2023 Author Index

2023 Author Index

2023 Subject Index

2023 Subject Index

2023 Subject Index

2023 Subject Index