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A Novel Marker Triglyceride Glucose Index in Predicting the Development of No-reflow in Acute Coronary Syndrome without ST-segment Elevation

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Abstract

Aim: The triglyceride-glucose (TyG) index is a new marker that predicts adverse clinical outcomes in coronary artery disease. We aimed to investigate the relationship between the TyG index and the no-reflow phenomenon after percutaneous coronary intervention (PCI) to saphenous vein grafts (SVGs) in patients with non ST-elevation acute coronary syndrome (NSTE-ACS).

Methods: In this retrospective study, 289 patients diagnosed with NSTE-ACS who underwent PCI for SVG obstruction were included. Patients were divided into 2 groups according to the development of a no-reflow phenomenon in the infarct-related artery after PCI: group 1 normal reflow group (n=209) and group 2 (n=80) no-reflow group. The groups were then compared according to the TyG index.

Results: The TyG index (p<0.001) was significantly higher in the no-reflow group. Univariate and multivariate logistic regression identified that congestive heart failure (p<0.001), degenerated SVG (p=0.002), intraluminal thrombus (p<0.001), and TyG index (p<0.001) were independent no-reflow predictors. In the receiver operating characteristic curve analysis, the TyG index with an optimum threshold value of 0.82 detected the development of no-reflow with 70% sensitivity and 83.7% specificity.

Conclusion: The TyG index, a simple measurable laboratory variable, is an independent predictor of no-reflow development in NSTE-ACS patients undergoing PCI for SVG occlusion.

Keywords: Coronary artery disease, triglyceride-glucose index, no-reflow phenomenon

Introduction

In coronary artery bypass graft (CABG) surgery, saphenous vein grafts (SVGs) are often used when the arteries aren't good enough for bypass grafting or when there are multiple vessel lesions. However, SVG tends to degenerate over time, and the patency rate drops to 41% after 10 years (1). Failure of the SVG in the early period (up to 18 months) is mainly due to inflammation, endothelial damage, platelet aggregation, a reduction in nitric oxide production, and intraluminal foam cell deposition due to mechanical trauma (2). Late graft failure (after 18 months) occurs because of an atherosclerotic occlusive plaque that develops with the progression of intimal hyperplasia (3). For treating SVG disease, redo-CABG or percutaneous coronary intervention (PCI) treatment options are available. Percutaneous coronary intervention to the bypassed native artery should be attempted first, and if this is not possible, PCI of the SVG should be considered (4). Since redo surgery is associated with high mortality rates, it should be considered only in patients who cannot be treated with PCI (5). Percutaneous coronary intervention of SVG lesions, accounting for approximately 5-10% of all PCIs, results in a higher complication rate and worse clinical outcomes than native artery interventions. The intervention has significant limitations, such as distal embolization in the acute phase,

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lack of reflow, high restenosis rate in the follow-up, and progression of SVG disease (6). The phenomenon of no-reflow, occurring in 3.4-18.5% of SVG PCIs (4), is associated with high early and late major adverse cardiac events (MACE) and mortality rates (7). Although it is thought to be caused by no-reflow, microembolization, microvascular spasm, endothelial dysfunction, increased oxidant production, and reperfusion injury, the reasons for its development are still controversial (8). Unfortunately, a widely accepted risk classification method that can predict the no-reflow outcome is not yet available. However, because the prevention of no-reflow development is the best strategy to minimize its negative consequences, it is vital to identify modifiable factors associated with no-reflow development.

The triglyceride-glucose (TyG) index is a simple index calculated from fasting blood sugar and triglyceride (TG) levels. It has been shown that the TyG index is an independent risk factor for cardiovascular disease and can predict MACE (9,10). In addition, studies have shown that elevated blood glucose values (11) and high triglyceride levels (12) increase the risk of no-reflow development in patients with acute coronary syndrome (ACS) undergoing PCI. However, the relationship between the TyG index and no-reflow development is unknown. Because the prognosis of the no-reflow phenomenon in SVG PCIs is poor, parameters that can predict this situation are vital. Therefore, in this study, we investigated the relationship between TyG index values and the development of the no-reflow phenomenon after PCI of SVGs in patients with non-ST-segment elevation ACS (NSTE-ACS).

Materials and Methods

Study Population

This was a single-center, observational, and retrospective study. We included 408 consecutive patients who underwent PCI due to SVG disease with a diagnosis of NSTE-ACS at our center between April 2016 and July 2019.

Patients with cardiogenic shock (n=21), stent restenosis and thrombosis (n=23), ST-segment elevation myocardial infarction (STEMI; n=36), and percutaneous transluminal balloon angioplasty alone (n=39) were excluded (Figure 1). The diagnosis of NSTE-ACS was made according to the current guidelines of the European Society of Cardiology (13). Coronary blood flow was defined according to the thrombolysis in myocardial infarction (TIMI) flow degree. Blood flow below TIMI flow 3 was defined as no reflow in the absence of dissection, vasospasm, or stenosis. The Clinical Research Ethics Committee of the University of Health Sciences Turkey, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital approved the protocol for this study in accordance with the Declaration of Helsinki and good clinical practice (approval no.: 2023.02-10, date: 21.02.2023). Because the study had a retrospective design, informed consent was not obtained from the patients.

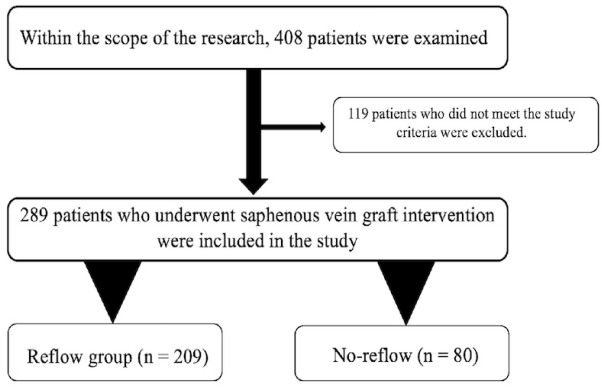

Figure 1. Flow chart of patients included in the study

Patient Characteristics

Laboratory, clinical, and demographic data were obtained from hospital records. Complete blood count, serum creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TG, and serum electrolyte levels were evaluated using the Friedewald equation. Blood samples were collected during hospitalization in the emergency room. The TyG index was calculated as fasting TG mg/dL and fasting glucose mg/dL/2 (14). In addition, echocardiographic imaging was performed on all patients during their hospitalization in the coronary intensive care unit immediately after PCI. The patients were examined using an echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway) with a 3.2 MHz adult probe. Left ventricular ejection fraction, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, left ventricular posterior wall thickness, and interventricular septum thickness were measured according to the guidelines of the American Society of Echocardiography (15).

Coronary Angiographic Evaluation

Coronary angiography was performed on each patient from the femoral or radial artery using the Judkins technique. All PCIs were performed using 6F or 7F guide catheters. After the diagnosis of NSTE-ACS was made according to the recommended guidelines, adequate antiaggregant and anticoagulant drug therapy was administered to all patients (16). The primary operator

decides on the stent length, diameter, and pre- and post-dilatation. The use of drugs such as intracoronary tirofiban, nitroprusside, and adenosine is at the discretion of the operator. Coronary blood flow was analyzed according to the degree of TIMI flow. Thrombolysis in myocardial infarction flow grades were defined as follows: grade 0, no antegrade flow beyond the lesion; grade 1, weak distal antegrade flow leading to incomplete filling of the artery; grade 2, slow antegrade flow despite complete opacification of the entire coronary bed; and grade 3, mean opacification rate of the entire coronary bed (17). Patients were divided into 2 groups according to post-intervention TIMI flow grade: group 1 included patients with TIMI flow grade 3, and group 2 included patients with TIMI flow grades 0 to 2. Digital media were used for quantitative analysis and documentation of coronary angiograms (Dicom viewer; Med-Com GmbH, Darmstadt, Turkey). Two expert interventional cardiologists, unaware of all the clinical data, analyzed the digital angiograms, and in case of disagreement, a consensus decision was made. Interobserver variability in the coronary angiographic evaluation of no-reflow was 5%.

Statistical Analysis

Statistical analysis was performed using the SPSS Version 26.0 program (SPSS Inc., Chicago, Illinois, USA). Whether the variables indicate a normal dispersion. Normally dispersion numerical variables were described as mean ± standard deviation (SD), non-normally dispersion numerical variables as median (interquartile range), and categorical variables were described as a percentage (%). Receiver operating characteristic (ROC) curve and Youden index [maximum (sensitivity + selectivity -1)] were used to identify the predictive value of the TyG index value that best detects no-reflow development. Statistical analysis of numerical variables between independent groups was performed using the Student's t-test or Mann-Whitney U test. Analysis of categorical variables such as reflow and no-reflow was performed using the chi-square or Fisher's exact test. Pearson's or Spearman's study evaluated the correlation between the TyG index and other numerical variables. Multivariate logistic regression analysis was performed to identify independent predictors of no-reflow. If the area under the ROC curve was above 0.5 and the p-value was <0.05, it was considered statistically significant.

Results

This study evaluated 289 consecutive patients who underwent PCI with the diagnosed NSTE-ACS of SVGs. Of these 289 patients, 48 (16.6%) were female, and the mean age was 63.5±9.2 years. The study patients were divided into two groups based on TIMI flow grade after PCI. The regular reflow group comprised 209 patients, and the no-reflow group included 80 patients. The baseline demographic, clinical, and laboratory characteristics of the patients are shown in Table 1. The mean (SD) age was 62.6 (8.6) years in group 1 and 66.1 (10.2) years in group 2 (p=0.004). Additionally, the number of patients with diabetes (p<0.001), history of stroke (p<0.001), previous MI (p=0.035), atrial fibrillation (p=0.031), chronic kidney disease (p=0.007), WBC (p<0.001), platelets (p<0.001), neutrophils (p<0.001), lymphocytes (p<0.001), and CHF (p<0.001) were higher in group 2 than in group 1. The mean (SD) ejection fraction was lower in group 2 (p<0.001), whereas the TyG index was higher in group 2 (p<0.001) (Figure 2). There was no significant difference in terms of gender, hypertension, dyslipidemia, smoking, peripheral arterial disease, previous PCI, COPD, serum creatinine, total cholesterol, LDL-C, and HDL-C between the groups.

Coronary angiography findings and procedural characteristics of the entire study group are shown in Table 2. Preinterventional TIMI flow grade 0 (p<0.001) and grade 3 (p<0.001), degenerated SVG (p<0.001), thrombus (p<0.001), and glycoprotein IIb/IIIa receptor antagonist use (p<0.001) were higher in group 2, whereas the number of patients implanted with drug-eluting stents (p=0.041) was larger in group 1. The stent diameter (p=0.004) was larger in group 2.

The results of univariate and multivariate regression analyses for selected preprocedural and procedural variables in the prediction of the no-reflow phenomenon are presented in Table 3. The TyG index (p<0.001), congestive HF (p<0.001) degenerated SVG (p=0.001), and intraluminal thrombus (p<0.001), were found to be independent predictors of the no-reflow phenomenon in multivariate logistic regression analysis.

To determine the cut-off value for the TyG index that best detects the presence of the no-reflow phenomenon, the ROC curve was drawn (Figure 3), and the cut-off value was determined as 5.15 using the Youden index (area under the curve: 0.821, 95% confidence interval: 0.769-0.873, p<0.001). This cut-off value could detect no-reflow with 70% sensitivity and 83.7% specificity. In addition, a positive predictive value of 62.2%, a negative predictive value of 87.9%, and an accuracy rate of 79.9% were detected.

Discussion

The main findings of this study are summarized below:

1. A higher TyG index is an independent risk factor for the no-reflow phenomenon in saphenous venous grafts in patients with acute coronary syndrome.

Table 1. The baseline demographic, clinical, and laboratory data of the study patients			
Variables	**Normal reflow (n=209)**	**No reflow (n=80)**	**p-value**
Male sex, n (%)	177 (80.4)	64 (80)	0.338
Age, year, mean (SD)	62.6±8.6	66.1±10.2	0.004
Hypertension, n (%)	156 (74.6)	68 (85)	0.059
Diabetes, n (%)	79 (37.8)	48 (60)	0.001
Dyslipidemia, n (%)	112 (53.6)	47 (58.8)	0.430
Current smoking status, n (%)	48 (23)	26 (32.5)	0.097
PAD, n (%)	40 (19.1)	23 (28.7)	0.077
History of stroke/TIA, n (%)	9 (4.3)	18 (22.8)	<0.001
Previous MI, n (%)	99 (47.4)	49 (61.3)	0.035
Previous PCI, n (%)	74 (35.4)	37 (46.3)	0.090
COPD, n (%)	28 (13.4)	8 (10)	0.434
Congestive HF, n (%)	41 (19.6)	49 (61.3)	<0.001
EF, %	51.5±9.2	42.3±11	<0.001
Atrial fibrilation, n (%)	18 (8.6)	14 (17.5)	0.031
CKD, n (%)	46 (22)	30 (37.5)	0.007
Serum creatinine, mg/dL, median (IQR)	1 (0.8-1.2)	1 (0.8-1.3)	0.062
Fasting blood glucose, mg/dL, median (IQR)	105 (91-139.5)	179 (112.3-281)	0.001
Hemoglobin, g/dL, median (IQR)	13.7 (12.2-15)	12.8 (11-14)	0.001
Total cholesterol, mg/dL, mean (SD)	186±55	187.9±55.3	0.459
LDL cholesterol, mg/dL, mean (SD)	115±46.2	115±47.6	0.994
HDL cholesterol, mg/dL, mean (SD)	39.6±8.7	38.6±10.7	0.412
Triglycerides, mg/dL, median (IQR)	132 (105-189.5)	219.5 (165-314.5)	<0.001
White blood cells, 10^6/L, mean (SD)	8±2.2	9.6±2.4	<0.001
Platelets x $10^9/mm^3$, mean (SD)	227.4±64.3	354.5±125.1	<0.001
Neutrophils, 10^9/L, median (IQR)	4.6 (3.8-5.5)	7.5 (6.1-9.7)	<0.001
Lymphocyte, 10^9/L, mean (SD)	2.3±0.7	1.8±1.2	<0.001
TyG index, mean (SD)	4.86±0.3	5.3±0.4	<0.001

Data are presented as percentage, mean ± standard deviation or median (interquartile range)
AF: Atrial fibrillation, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, HDL: High-density lipoprotein, HF: Heart failure, LDL: Low-density lipoprotein, MI: Myocardial infarction, PAD: Peripheral artery disease, PCI: Percutaneous coronary intervention, TyG: Triglyceride-glucose, TIA: Transient ischemic attack, IQR: Interquartile range, SD: Standard deviation

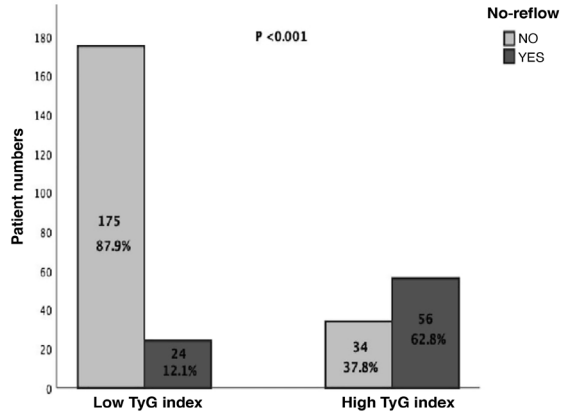

Figure 2. No-reflow development was higher in the high TyG index group than in the low TyG index group [56 (62.8%) vs 24 (12.1%); p<0.001]
TyG: Triglyceride-glucose

2. The other independent risk factors for the no-reflow phenomenon in saphenous venous grafts are congestive heart failure, intraluminal thrombus, and degenerated SVGs.

The no-reflow phenomenon is a result of endothelial dysfunction that occurs after the revascularization of epicardial coronary arteries. The main immunopathological mechanisms include capillary edema with the contribution of leukocytes and inflammation-related mediators and distal coronary embolism after percutaneous intervention. It is commonly observed in patients with acute coronary syndrome (18). Percutaneous coronary interventions, which are performed on saphenous venous grafts, carry a high risk in terms of the coronary no-reflow phenomenon and restenosis (19). Many factors have been identified that predict the no-reflow phenomenon; however, additional markers are required (11).

Table 2. Coronary angiographic findings and procedural characteristics of the study patients			
Variables	**Normal reflow (n=209)**	**No reflow (n=80)**	**p-value**
Time elapsed from surgery to angiography, y, mean (SD)	10.4±4.9	11.4±4.8	0.133
Narrowed saphenous vein graft to Left anterior descending artery, n (%) Diagonal artery, n (%) Circumflex artery, n (%) Right coronary artery, n (%)	 12 (5.8) 23 (11.1) 88 (42.5) 84 (40.6)	 7 (8.8) 8 (10) 34 (42.5) 31 (38.8)	0.832
TIMI flow grade before the intervention 0, n (%) 1, n (%) 2, n (%) 3, n (%)	 21 (10) 15 (7.2) 55 (26.3) 118 (56.5)	 22 (27.5) 8 (10) 28 (35) 22 (27.5)	<0.001
TIMI flow grade following the intervention 0, n (%) 1, n (%) 2, n (%) 3, n (%)	 0 (0) 0 (0) 0 (0) 209 (100)	 9 (11.3) 23 (28.7) 48 (60) 0 (0)	<0.001
Procedural data			
Degenerated saphenous vein graft, n (%)	45 (21.5)	51 (63.7)	<0.001
Intraluminal thrombus, n (%)	41 (19.6)	54 (68.4)	<0.001
Focal lesion, n (%)	154 (74)	39 (48.8)	<0.001
Drug-eluting stent, n (%)	121 (59)	32 (45.1)	0.041
Stent diameter, mm, mean (SD)	3.2±0.5	3.4±0.6	0.004
Stent length, mm, mean (SD)	24.2±12.2	25.6±13.9	0.413
Predilatation, n (%)	72 (34.4)	37 (46.3)	0.064
Postdilatation, n (%)	51 (24.4)	13 (16.3)	0.135
Glycoprotein IIb / IIIa inhibitor use, n (%)	34 (16.3)	40 (50)	<0.001
Antiplatelets Clopidogrel, n (%) Ticagrelor, n (%) Prasugrel, n (%)	 185 (88.5) 19 (9.1) 5 (2.4)	 74 (92.5) 5 (6.3) 1 (1.3)	0.589
Additional variables			
Distal protection device use, n (%)	8 (3.8)	3 (3.8)	0.975
Thrombectomy, n (%)	3 (1.4)	4 (5)	0.078

Data are presented as number (percentage) unless otherwise indicated
TIMI: Thrombolysis in Myocardial Infarction, SD: Standard deviation

Table 3. Independent predictors for no-reflow with univariate and multivariate logistic regression analysis				
	Univariate analysis		**Multivariate analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	1.044 (1.014-1.076)	0.004	1.033 (0.987-1.081)	0.157
History of stroke/TIA	6.557 (2.803-15.341)	<0.001	3.117 (0.939-10.354)	0.063
Congestive HF	6.477 (3.682-11.392)	<0.001	4.728 (2.139-10.450)	<0.001
CKD	2.126 (1.216-3.717)	0.008	1.080 (0.471-2.476)	0.856
TyG index	12.01 (6.571-21.949)	<0.001	13.449 (5.823-31.06)	<0.001
Degenerated saphenous vein graft	6.409 (3.651-11.250)	<0.001	4.284 (1.804-10.169)	0.001
Intraluminal thrombus	8.852 (4.934-15.875)	<0.001	5.569 (2.534-12.241)	<0.001
Focal lesion	0.334 (0.195-0.571)	<0.001	1.041 (0.434-2.498)	0.929

TyG: Triglyceride-glucose, CKD: Chronic kidney disease, HF: Heart failure, TIA: Transient ischemic attack, CI: Confidence interval, OR: Odds ratio; others, see Table 1 and Table 2

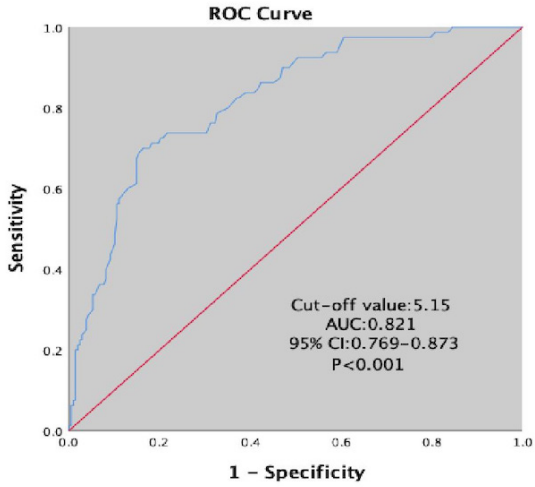

Figure 3. Receiver operating characteristics curve analysis showing the TyG index cut-off value of 5.15 that predicted no-reflow phenomenon with with 70% sensitivity and 83.7% specificity

TyG: Triglyceride-glucose, ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

The TyG index, calculated as a parameter derived from fasting blood glucose and TG levels, is a new laboratory marker. High levels of TyG ratio are considered a worse setting in various clinical syndromes, namely diabetes and metabolic syndrome (20,21). Triglyceride-glucose index is associated with high arterial pulse wave velocity, even in patients without diabetes (22). Furthermore, hospitalized diabetic patients with high TyG index levels have more frequent cardiovascular complications than patients who are not diabetic (23). As a result, the TyG index can be used as a screening tool for, in particular, the worsening clinical setting for cardiovascular disease, irrespective of diabetes.

The TyG index is a composite indicator composed of TG and is a good marker of insulin resistance (24). In addition, insulin resistance is a marker of oxidative stress and inflammation (25). The conclusion to be drawn from this connection is the close relationship between the TYG index and inflammation, which is of critical importance for the no-reflow phenomenon. There are studies showing the relationship between the TyG index and stent restenosis, especially in acute coronary syndrome patients (26). In addition to inflammation, the TyG index is an indicator of insulin resistance and a predictor of the no-reflow phenomenon. Metabolic syndrome increases the development of no-reflow in patients with STEMI. Considering the relationship between the TyG index and metabolic syndrome, this correlation with no-reflow is not surprising.

Other parameters are associated with the no-reflow phenomenon in our study. Several studies have shown that congestive heart failure is related to the no-reflow phenomenon. Consistent with previous reports, multivariate analysis in our study showed that congestive heart failure was independently associated with the no-reflow phenomenon (27). Similar to previous findings, our study also showed that the presence of intraluminal thrombus and degenerated SVGs could independently predict the no-reflow phenomenon before SVG intervention (28). Previous studies also reported a relationship between advanced age and the no-reflow phenomenon (29). Consistently, in our study, it was determined that the patients who developed no-reflow were older; however, in multivariate analysis, age was not among the factors predicting the no-reflow phenomenon.

Study Limitations

This study had several limitations. First, this was a retrospective study conducted with a relatively limited number of patients. Second, the baseline thrombus burden, an important determinant of the no-reflow phenomenon, was not evaluated in our study. Third, our current study included only patients with ACS, which may introduce selection bias and limit the generalizability of our findings to patients with chronic coronary syndromes. Finally, because fasting insulin was not routinely measured in our center, this study fails to compare the role of the Homeostasis Model Assessment of Insulin Resistance and TyG index in the setting of the no-reflow phenomenon. Despite these limitations, to the best of our knowledge, this study is the first to elucidate the relationship between the absence of reflow phenomena in venous grafts and the TyG index.

Conclusion

A simple measurable laboratory variable was related to a more frequent no-reflow phenomenon in patients with non-STEMI undergoing SVG PCI. In addition, the TyG index was an independent predictor of the no-reflow phenomenon in our study population. Triglyceride-glucose index levels higher than 5.15 have been shown to be effective in predicting the no-reflow phenomenon in such patient groups. It is a simple and non-invasive method that can be performed on either diabetic or non-diabetic patients.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of the University of Health Sciences Turkey, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital approved the protocol for this study in accordance with the Declaration of Helsinki and good clinical practice (approval no.: 2023.02-10, date: 21.02.2023).

Informed Consent: Because the study had a retrospective design, informed consent was not obtained from the patients.

Authorship Contributions

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

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Evaluation of Hematological Parameters in Children with Idiopathic Facial Paralysis: A Case-control Study

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Abstract

Aim: Idiopathic peripheral facial paralysis [Bell's palsy (BP)] is the most common cause of acute, one-sided facial paralysis, whose etiopathogenesis is currently unknown. However, inflammation is considered to play a role in etiopathogenesis. In this study, we examined the relationship between hematologic parameters and indices in children with BP.

Methods: The study included 60 pediatric patients diagnosed with BP between December 2017 and May 2022 and 60 healthy controls of the same age and gender. The relationship between the patient and control cohorts and between the severity of the disease and inflammation markers was analyzed. Low-severe BP (House-Brackmann classification grade 2-3) and high-severe BP (House-Brackmann classification grade 4-5) were grouped. Complete blood count parameters and hematologic indices [neutrophil count/lymphocyte count (NLR), platelet count/lymphocyte count (PLR), monocyte count/lymphoid count (MLR), and platelet mass index] were recorded as inflammation markers.

Results: 55% of the patients had BP on the right side, 48.3% had grade 3, and 30.0% had grade 4 facial paralysis. Leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts were significantly higher in the patient group than in the control group (p-values p<0.001, p=0.006, p=0.027, p=0.009, respectively). The low-severe BP group had significantly higher leukocyte counts than the high-severe BP group. However, there was no significant difference between the other hematologic parameters and indices (NLR, PLR, MLR, and platelet mass index).

Conclusion: Children with BP had higher counts of leukocytes, neutrophils, lymphocytes, monocytes, and platelets than children in the control group. Thus, we believe that these parameters can be used in the diagnosis, differential diagnosis, and treatment of patients with BP.

Keywords: Child, platelet count, facial paralysis, diagnosis-differential, blood cell count

Introduction

Idiopathic peripheral facial paralysis [Bell's palsy (BP)] is a sudden onset, usually partial or total muscular paralysis on either side of the face. It is the most common motor cranial neuropathy that can occur as a result of damage at any level along the anatomical course of the facial nerve from the motor nucleus in the brain stem until it reaches the facial mimic muscles (1). The incidence is 19-21 per 100,000 children younger than 18 years old. Patients usually present with a sudden onset of unilateral facial paralysis that lasts from a few hours to a day. Mild pain radiating behind the ear, numbness of the face, increased

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sensitivity to sound, and taste disturbances are other accompanying symptoms. Although the etiopathogenesis has not been fully elucidated, inflammation is considered to play a role (2). In the literature, prognostic factors for peripheral facial paralysis include age, severity of the disease, period between the onset of symptoms and treatment, electrophysiological changes, and history of recurrence (2-4). In adults, corticosteroids offer important benefits, particularly when they are administered early during the disease, whereas there are no standardized treatment guidelines for children. Peripheral facial paralysis in children generally has a good prognosis, but if it does not fully regress, it can affect quality of life in the long term, causing problems with drinking, eating, and speaking and even affecting social life (2). Magnetic resonance imaging (MRI) of patients with BP shows inflammation of the facial nerve (5).

Further evidence supporting an inflammatory etiology is the high neutrophil count/lymphocyte count (NLR) found in patients with BP (5-8). In another study, the relationship between BP and inflammatory markers such as white blood cells (WBCs), neutrophils, lymphocytes, monocytes, platelet count/lymphocyte count (PLR), NLR, mean platelet volume (MPV), and red blood cell distribution width (RDW) was evaluated, and a statistically significant difference was found between lymphocytes, NLR, and PLR between the patient and control groups (9). Although there are many studies in the literature evaluating hematologic parameters and indices as diagnostic and prognostic markers in adult patients with BP, there are not enough studies in pediatric patients.

We hypothesized that there may be a strong relationship between disease severity and hematological parameters or indices indicating inflammation in BP patients. Therefore, we aimed to analyze the relationship between pediatric patients with BP and healthy controls and between disease severity and hematologic parameters and hematologic formulas [e.g., hemoglobin (Hb), mean corpuscular volume (MCV), RDW, MPV, platelet distribution width (PDW), leukocyte, neutrophil, lymphocyte, and platelet count] to investigate the relationship between NLR, PLR, MLR (monocyte count/lymphoid count), and platelet mass index and to evaluate the prognostic utility of these parameters.

Methods

Compliance with Ethical Standards

The study was conducted in accordance with the principles of the Helsinki Declaration and was endorsed by the Afyonkarahisar Health Sciences University, Non-Conventional Clinical Research Ethics Committee (approval no.: 2022/12, date: October 7, 2022). Informed consent was obtained.

Study Design

Our study enrolled 60 pediatric patients with idiopathic peripheral facial paralysis who were admitted to the Pediatric Neurology Outpatient Clinic of Afyonkarahisar Health Sciences University Faculty of Medicine Hospital with acute unilateral facial weakness between December 1, 2017 and May 31, 2022. Sociodemographic characteristics, detailed ear-nose-throat examination, neurologic and systemic examination findings, laboratory tests (complete blood count and biochemistry analysis), audiologic evaluation and MRI results, and treatment received by all patients at the time of diagnosis were reviewed from the electronic outpatient clinic records.

Patient Selection

Children with a diagnosis of congenital facial paralysis (2 patients), otitis media (2 patients), Ramsay-Hunt syndrome (1 patient), history of trauma before paralysis (2 patients), history of systemic inflammatory diseases such as diabetes (1 patient), and additional abnormal neurological findings on neurological examination were excluded. In addition, children with underlying chronic diseases such as malignancy (1 patient) and those taking medication for these diseases were excluded. Cranial MRI was performed in every child with acute facial weakness, and tumor-related facial paralysis was excluded. Sixty pediatric patients with idiopathic BP were enrolled in our study. The control group included 60 healthy children who were admitted to the pediatric outpatient clinic for routine healthy child follow-up and had no history of any infection in the last 15 days and no chronic disease (Figure 1). The patients were evaluated by an otorhinolaryngologist according to the House-Brackmann classification of facial paralysis. According to this classification, grade 1 is classified as normal and symmetrical function in all areas, grade 2 as mild dysfunction, grade 3 as moderate dysfunction, grade 4 as moderate to severe dysfunction, grade 5 as severe dysfunction, and grade 6 as total paralysis (10,11). Paralysis staging was performed based on this classification at the time of initial admission and 1 month after treatment. Patients are considered to have responded to treatment if there is a decrease in staging in the first month after treatment compared with the staging at the time of initial admission. All patients diagnosed with BP routinely receive standard treatment in our clinic if there are no contraindications. According to Hb scoring, 1 mg/kg/day prednisolone is started in patients with grades 1-2 according to Hb scoring and discontinued by tapering in 15 days, and 2 mg/kg/day prednisolone (maximum dose 60 mg/day) is started in patients with grades 3-5 in the first week and discontinued by tapering in 15 days. No pediatric patient received antiviral treatment (12,13). The patient and control groups were not tested for coronavirus

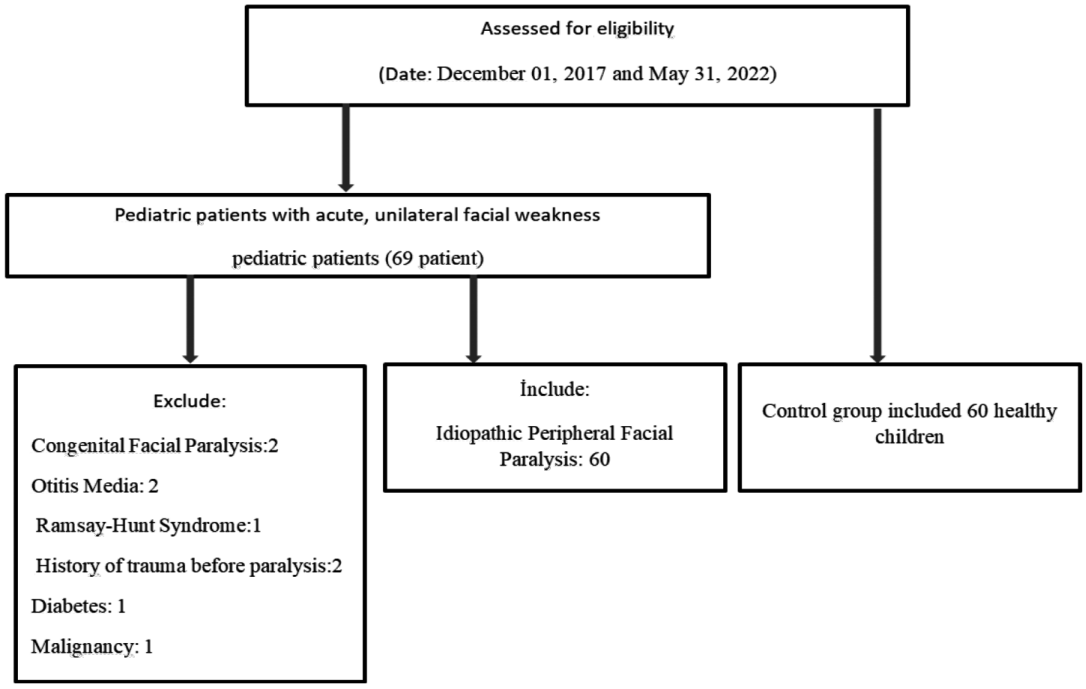

Figure 1. Patients' selection diagram

disease-2019 (COVID-19) because they did not have complaints such as fever and cough related to COVID-19.

Hematological Testing and Evaluation

The complete blood counts and C-reactive protein (CRP) values of the patients were taken before steroid treatment. Hb, MCV, RDW, MPV, PDW, leukocyte, neutrophil, lymphocyte, platelet count, and CRP were recorded from laboratory tests of the patient and control groups. Calculated leukocyte formulas include NLR, PLR, MLR, and platelet mass index (platelet count times MPV). Low-severe BP: Group 1 (House-Brackmann classification grade 2-3), and high-severe BP: Group 2 (House-Brackmann classification grade 4-5) were grouped. The relationship between hematologic parameters and indices between the patient and control cohorts was investigated.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 18.0, Chicago). Descriptive statistics are presented as percentage frequency for categorical data, mean and standard deviation (mean ± standard deviation) when continuous data conform to a normal distribution, and median and quartiles [median quartile 25-75)] when not conforming to a normal distribution. The conformity of continuous data to a normal distribution was evaluated using the Kolmogorov-Smirnov test. For continuous data that fit the normal distribution, a Student's t-test was used to compare paired groups, and a one-way analysis of variance (ANOVA) was used to compare ternary groups. In cases of statistically significant differences found as a result of ANOVA, Tukey's Honestly Significant Difference test was used for intragroup comparisons. The Mann-Whitney U test was used to compare paired groups, and the Kruskal-Wallis H test was used to compare ternary groups. In cases of a statistically significant difference because of the Kruskal-Wallis H test, the Mann-Whitney U test with Bonferroni correction was used for intragroup comparisons. The chi-square test was used to compare the distributions of categorical data. A p-value of 0.05 was accepted as statistically significant.

Results

The study included 60 pediatric patients with idiopatic facial paralysis and 60 healthy controls of the same age and gender. The sociodemographic and clinical characteristics of the patient group are summarized in Table 1. The mean age of the patient group was 10.35±3.91 years, and 56.7% were girls. 55% of the patients had BP on the right, 48.3% had grade 3, and 30.0% had grade 4 facial paralysis (Table 1). 56.7% of the patient group (n=34) and 48.3% of the control group (n=29) were female, and there was no statistically significant difference between their gender distributions (p=0.361). The mean age of

the patient group was 10.35±3.91 years and that of the control group was 10.20±3.64 years, and there was no statistically significant difference (p=0.826) (Table 2).

There were no statistically significant differences in Hb, MCV, and RDW values between the patients and controls. The median leukocyte count was 8,270/mm^3 (7,300-10,567) in the patient group and was statistically significantly higher than that in the control group (p<0.001). The median values of neutrophil, lymphocyte, monocyte, and platelet counts were significantly higher in the patient group than in the control group, and there was a statistically significant difference between the patient and control groups (p-values were p<0.001, p=0.006, p=0.027, p=0.009, respectively). There were no statistically significant differences among the MPV, NLR, PLR, MLR, CRP, and platelet mass indexes of patients and controls (Table 2).

When comparing the patient groups with the House-Brackmann classification., those with grades 2 and 3 were classified as having low-severe BP, and those with grades 4 and 5 were classified as having high-severe BP. No statistically significant difference was observed between the age, Hb, MCV, RDW, MPV, NLR, PLR, MLR, CRP, and platelet mass index values of the groups (Table 3). When leukocyte counts were compared between the control group and the low-severe BP, low-severe BP, and high-severe BP groups, leukocyte counts were higher in both patient groups than in the control group (p<0.001). A statistically significant difference was found between the neutrophil, lymphocyte, monocyte, and platelet counts between the control group and the low-severe BP group, with p-values of p=0.001, p=0.009, p=0.006,

Table 1. Sociodemographic and Bell's palsy-related characteristics of patients with facial paralysis

Demographics	n (%)
Age (years)	10.35±3.91
Gender	
Female	34 (56.7%)
Male	26 (43.3%)
Laterality (side)	
Right	33 (55%)
Left	27 (45%)
Grade	
Grade 2	9 (15%)
Grade 3	29 (48.3%)
Grade 4	18 (30.0%)
Grade 5	4 (6.7%)

Table 2. Patient and control group demographics, clinical and laboratory characteristics

Characteristic	Patient group	Control group	p-value
Age (years)	10.35±3.91	10.20±3.64	0.826[a]
Gender			
Female	34 (56.7%)	29 (48.3%)	0.361[b]
Male	26 (43.3%)	31 (51.7%)	
Hb (g/dL)	13.44±1.49	13.65±1.10	0.398[a]
MCV (fL)	81.70±5.83	83.31±4.02	0.082[a]
RDW (%)	13.20 (12.43-13.78)	13.00 (12.40-13.58)	0.229[c]
Leukocyte count (/mm^3)	8270.00 (7300-10567)	6840.00 (5615.00-7695.00)	**<0.001[c]**
Neutrophil count (/mm^3)	4335.00 (3002.50-6205.00)	3110.00 (2672.50-4115.00)	**<0.001[c]**
Lymphocyte count (/mm^3)	3010.00 (2322.50-3577.50)	2635.00 (2070.00-2875.00)	**0.006[c]**
Monocyte count (/mm^3)	575.00 (460.00-720.00)	505.00 (445.00-577.50)	**0.027[c]**
Platelets (/mm^3)	335500.00±86437.10	295233.33±80724.76	**0.009[a]**
MPV (fL)	9.68±0.95	9.99±0.89	0.071[a]
NLR	1.42 (0.98-2.29)	1.32 (0.96-1.62)	0.173[b]
PLR	120.27-47.94	117.02-35.59	0.674[b]
MLR	0.19 (0.14-0.25)	0.20 (0.16-0.25)	0.553[b]
CRP (mg/dL)	0.10 (0.02-0.30)	0.10 (0.10-0.10)	0.601[b]
Platelet mass (MPV X PLT count/1000)	3151.20 (2694.45-3623.53)	2929.45 (2347.65-3422.55)	0.069[b]

[a]: Student's t-test
[b]: Chi-square test
[c]: Mann-Whitney U test
Hb: Hemoglobin, MCV: Mean corpuscular volume, RDW: Red blood cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil count/lymphocyte count, PLR: Platelet count/lymphocyte count, MLR: Monocyte count/lymphoid count, PLT: Platelet, CRP: C-reactive protein

Table 3. Relationship between disease severity and hematologic indices and parameters (3 groups)				
Characteristic	**Control**	**Group 1**	**Group 2**	**p-value**
Age	10.20-3.64	10.65-3.69	9.82-4.28	0.699[a]
Numbers	60	38	22	
Hb (g/dL)	13.65-1.10	13.52-1.38	13.32-1.70	0.599[a]
RDW (%)	13.00 (12.40-13.58)	13.20 (12.55-13.60)	13.05 (12.30-13.80)	
Leukocyte count (/mm³)	6788-1313	9782-3709	7973-1801	**<0.001[&*a]**
Neutrophil count (/mm³)	3110.00 (2672-4115)	4610 (3047-6895)	4005 (2725-5327)	**0.001[&b]**
Lymphocyte count (/mm³)	2635 (2070-2875)	3055 (2522-3637)	2855 (2002-3452)	**0.009[&b]**
Monocyte count (/mm³)	505 (445-577)	640 (482-742)	485 (412-652)	**0.006[&b]**
Platelets (/mm³)	295233-80724	334947-76385	336454-103484	**0.035[&b]**
MPV (fL)	9.99-0.89	9.76-0.97	9.55-0.91	0.141[a]
NLR	1.32 (0.96-1.62)	1.47 (0.98-2.34)	1.33 (0.97-2.33)	0.366[b]
PLR	117.02-35.59	113.49-44.05	131.99-53.03	0.239[a]
MLR	0.20 (0.16-0.25)	0.19 (0.14-0.25)	0.17 (0.14-0.25)	0.76[b]
CRP (mg/dL)	0.10 (0.10-0.10)	0.10 (0.02-0.29)	0.12 (0.03-0.35)	0.733[b]
Platelet mass index	2939763.33-830573.94	3250500.00-745623.78	3148790.91-765966.82	0.155[a]

[&]: Between the control group and Group 1
[*]: Between Group 1 and Group 2
[a]: One-way analysis of variance (ANOVA)
[b]: Kruskal-Wallis H test
Hb: Hemoglobin, RDW: Red blood cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil count/lymphocyte count, PLR: Platelet count/lymphocyte count, MLR: Monocyte count/lymphoid count, platelet mass index (platelet count x MPV), CRP: C-reactive protein

and p=0.035, respectively. Recurrence of the disease was observed in 5 of our patients with BP; however, there was no significant association between the group of recurrent patients and disease severity.

Discussion

Because the facial nerve has a long intracranial journey and the facial canal is anatomically close to the temporal bone, it can be easily affected by inflammation caused by diseases such as infection, trauma, and tumors (12,14,15). Although the etiopathogenesis is not yet fully understood, it has been suggested that viral, inflammatory, and immune-mediated inflammation play a major role in the etiopathogenesis of BP (15,16). Leukocytes, neutrophils, and monocytes play an active role in the proinflammatory and anti-inflammatory processes at the site of inflammation and are also essential in the initiation and maintenance of the immune response against foreign proteins (17,18). Platelets are cells generated by megakaryocytes of the bone marrow and have an active role in inflammation by producing and releasing various cytokines that affect the inflammation mechanism, similar to neutrophils and macrophages, as well as controlling bleeding (19). In our study, we demonstrated that leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts were higher in children with BP than in the control group and that an inflammatory process occurred in these patients. It has been reported that the function of platelets can be evaluated more accurately with platelet mass index than platelet count or platelet volume (20). We didn't find a significant link between BP patients and the control group or between low-severity BP patients and high-severity BP patients in our study. However, we did find that the number of platelets was higher in BP patients than in the control group. This makes us think that the platelet mass index will be higher in BP patients when it comes to inflammation in studies with more cases. Our study is the first to evaluate the platelet mass index in children with BP.

It has been demonstrated that parameters such as NLR, PLR, and MLR, which can be easily calculated from complete blood count parameters, are associated with disease severity and prognosis in inflammatory diseases (21). There are many studies showing that NLR is significantly higher in patients with BP than in the control group (1,5,9,14). Neutrophil count/lymphocyte count has also been shown to play a role in disease prognosis (8,9,14). Cayir and Kilicaslan (14) reported that NLR was higher in the non-recovery group, and WBC count and PLR were similar between the recovery and non-recovery groups. Similarly, the NRL was significantly higher in the non-recovery group, but there were no significant differences in PLRs between the recovery and non-recovery groups (22). In a recent study comparing 88 BP patients with 50 healthy control groups, it was shown that there was a statistically significant increase in systemic inflammatory index, neutrophil, and NLR levels

in the BP group and that they are useful parameters in showing the prognosis of the disease (16). Ayşel et al. (23) also reported that NLR was associated with disease severity (higher in grades 4-6) and prognosis in pediatric BP patients. Similar to our study, they did not detect any difference between MPV and PLR in relation to disease severity. Ulusoy et al. (24) found no correlation between NLR and PLR and the prognosis of the disease. In this study, we found no relationship among parameters such as NLR, PLR, MLR, and the severity of the disease between the BP and control groups or between mild and severe severity of the disease in patients with BP. Similar to our study, Atan et al. (6) also found no association between NLR, PLR, or disease severity. Although we detected significant differences in terms of leukocyte, neutrophil, lymphocyte, and monocyte numbers between the patient and control groups, we could not detect any difference in PLR, NLR, or MLR values between the patient and control groups or between the mild and severe disease groups. We attribute this to the small number of patients. Karatoprak and Yilmaz (25) followed 102 children with BP and reported that 101 children showed complete recovery and that there was no relationship between NLR and RDW and early recovery. In our study, complete recovery was observed in all children. In approximately 1-2 years of follow-up, five patients developed facial paralysis again and were re-treated. It was observed that the patients recovered completely in the follow-up, and no recurrence was observed.

Study Limitations

The limitations are the small number of patients due to the single-center design and, in particular, the small number of grade 4-5 patients. Despite these limitations, the selection of a control group of similar age and gender to the patient group in our study provides safe results in terms of hematological parameters. In addition, this study makes a significant contribution to the literature in terms of evaluating several hematological parameters in children.

Conclusion

Increased leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts in children with BP compared with those in the control group support the inflammatory process considered responsible for the etiopathogenesis of this disease. Thus, we suggest that these parameters can be used in the diagnosis, differential diagnosis, and treatment of patients with BP. We would like to emphasize that we could not detect a significant correlation between the severity of the disease and hematologic parameters and indices because of the small sample size of our study and that large-scale studies are warranted in this regard.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Helsinki Declaration and was endorsed by the Afyonkarahisar Health Sciences University, Non-Conventional Clinical Research Ethics Committee (approval no.: 2022/12, date: October 7, 2022).

Informed Consent: Informed consent was obtained.

Authorship Contributions

Surgical and Medical Practices: H.S.S., S.K., D.C., Concept: H.S.S., N.E., D.C., Design: H.S.S., Y.D.K., D.C., Data Collection or Processing: H.S.S., S.K., Y.S., D.C., Analysis or Interpretation: H.S.S., N.E., Y.S., D.C., Literature Search: H.S.S., Y.D.K., D.C., Writing: H.S.S., Y.D.K., D.C.

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Original Article

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Evaluation of the Relationship Between Diabetic Nephropathy, Hemogram Parameters, and Uric Asid

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Abstract

Aim: Inflammation plays an important role in the development of diabetic nephropathy (DNP). In our study, we aimed to analyze the relationship between the mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), uric acid-lymphocyte ratio (UALR), and uric acid level with early diagnosis of DNP and DNP progression.

Methods: Our cross-sectional study, which is a type of observational study, included patients diagnosed with type 2 diabetes mellitus and followed in the internal medicine and nephrology clinics of our hospital. Patients were divided into four groups: Group 1: estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 and albuminuria <30 mcg/day; Group 2: eGFR >60 mL/min/1.73 m^2 and albuminuria: 30-300 mcg/day; Group 3: eGFR >60 mL/min/1.73 m^2 and albuminuria >300 mcg/day; and Group 4: eGFR <60 mL/min/1.73 m^2 and albuminuria >300 mcg/day. Thirty-six patients were included in group 1, 38 patients in group 2, 35 patients in group 3, and 40 patients in group 4. Mean platelet volume, NLR, PLR, UALR, and uric acid levels were compared among the groups.

Results: A total of 149 patients were included in the study; 57.7% were female, and the mean age was 55.2±9.2 years. Significant differences were found among the groups in terms of MPV, PLR, NLR, and UALR ($p<0.001$, $p=0.023$, $p\leq0.001$, $p<0.001$, respectively). There was a negative correlation between eGFR and MPV ($r=-0.218$, $p=0.008$). While there was no relationship between eGFR and platelet values, a relationship was obtained when platelets were compared with lymphocytes ($r=-0.263$, $p=0.002$). There was a weak relationship between eGFR and neutrophil levels ($r=-0.188$, $p=0.026$), but a stronger relationship was found when neutrophil and lymphocyte values were rationed ($r=-0.414$, $p<0.001$).

Conclusion: Mean platelet volume, PLR, NLR, UALR, and uric acid levels, especially MPV, can be used in the development and progression of DNP.

Keywords: Diabetic nephropathy, lymphocyte, neutrophil, mean platelet volume, platelet, uric acid

Introduction

Diabetic nephropathy (DNP) is the most common cause of end-stage kidney disease (ESKD) (1). Although DNP may appear as a late manifestation of diabetes, physiological, pathological, and clinical symptoms arise before the development of DNP. Early detection of DNP, which is a significant cause of mortality and morbidity in patients with diabetes mellitus (DM), can slow down the progression to ESKD with appropriate measures. Cytokines such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor play an important role in the development and progression of DNP (2). However, their use in daily practice is expensive and technically difficult. However, hematological parameters can be measured almost anywhere, are inexpensive, and can be adapted to daily practice (3,4).

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Diabetes mellitus is a prothrombotic condition associated with accelerated atherosclerosis and inflammation. Prothrombotic tendencies are associated with increased platelet reactivity. Increased platelet reactivity plays a crucial role in the pathogenesis of microvascular complications, such as DNP associated with DM (5). Previous studies have reported that the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are indicators of subclinical inflammation, along with the uric acid-lymphocyte ratio (UALR) and uric acid levels (6-12). In addition, mean platelet volume (MPV), a platelet index that reflects platelet stimulation and production rates, is associated with inflammation. These parameters have been shown to be strong inflammatory markers and can be easily measured, providing rapid results and inexpensive costs, which increases the interest in studies related to these parameters.

Our study aimed to investigate the potential correlation between easily quantifiable and cost-effective measures, such as PLR, MPV, NLR, UALR, and uric acid levels, as markers of inflammation in patients with DNP at various stages. We hypothesized that these parameters may be useful in predicting the early diagnosis and progression of DNP.

Materials and Methods

Compliance with Ethical Standards

Ethical approval was received by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no.: 425, date: 05.04.2017).

Study Population

Our cross-sectional study, which is a type of observational study, included patients diagnosed with type 2 DM who were followed up in the internal medicine and nephrology clinics of our hospital between. The parameters used in the study were retrospectively obtained from hospital information management system records. Type 1 diabetic patients were not included in the study. People under 18 or over 70 years old, those with non-DNP renal disease, those with acute kidney injury, those with advanced heart, lung, or liver disease, those with an autoimmune disease, those with a cancer diagnosis, and those who had a history of systemic infectious or inflammatory events or acute ischemic vascular disease in the last three months were excluded from the study. Informed consent was obtained from all participants in the study.

Measurements and Definitions

The ADA criteria were used as the basis for the diagnosis of DM (13). Patients were divided into 4 groups based on estimated glomerular filtration rate (eGFR) and urine albumin concentration.

Group 1: Those with GFR >60 mL/min/1.73 m^2 and urine albumin <30 mcg/day,

Group 2: Those with GFR >60 mL/min/1.73 m^2 and urine albumin 30-300 mcg/day,

Group 3: Those with GFR >60 mL/min/1.73 m^2 and urine albumin >300 mcg/day,

Group 4: Those with GFR <60 mL/min/1.73 m^2 and urine albumin > Three hundred mcg/day.

Uric acid, C-reactive protein (CRP), urea, and creatinine levels were analyzed using the Architect c1600 device with spectrophotometric methods recommended by the manufacturer in our hospital's biochemistry laboratory. HbA1c levels were measured using high-performance liquid chromatography, and hematological parameters were measured using the HORIBO ABX petra dx 120 device. The eGFR was calculated using the chronic kidney disease (CKD) Epidemiology Collaboration formula (14). Proteinuria and microalbuminuria were calculated by dividing the corresponding values in the spot urine by the creatinine value. These measurements were considered significant if they were consistent with at least two measurements in the past three months.

Statistical Analysis

The SPSS program (15.0 for Windows) was used for statistical analysis. Descriptive statistics are given as mean, standard deviation, minimum, and maximum for numerical variables and as number and percentage for categorical variables. An one-way ANOVA test was used for numerical variables that met the normal distribution condition in more than two independent groups, whereas the Kruskal-Wallis test was used for numerical variables that met the normal distribution condition. Subgroup analyses were performed using the Tukey test for data that met the parametric conditions, and the Mann-Whitney U test was used for data that did not meet the parametric conditions and interpreted with Bonferroni correction. A comparison of proportional data between groups was performed using chi-square analysis. The relationships between numerical variables were examined using Spearman correlation analysis because the parametric test condition was not met. The statistical alpha significance level was set at $p<0.05$.

Results

A total of 149 patients were included in the study. The mean age of the patients was 55.2±9.2. Of the patients, 57.7% were female. Thirty-six patients were included in group 1, 38 patients in group 2, 35 patients in group 3, and 40 patients in group 4. The demographic characteristics and baseline laboratory data of the patients are presented

in Table 1. Neutrophil, hsCRP, and uric acid levels were correlated with the progression of DNP.

The differences between the groups in terms of MPV, NLR, and UALR levels and the parameters analyzed within the groups are shown in Table 2. While platelet and PLR toll-like receptor (TLR) did not differ between the groups, there were statistically significant differences in MPV, NLR, and UALR between the groups.

Correlations between eGFR and MPV, NLR, UALR, TLR, neutrophil, lymphocyte, and uric acid levels are shown in Figure 1.

Discussion

In this cross-sectional study, including patients at different stages of DNP, we analyzed the relationship between MPV, NLR, TLR, and UALR, which have previously been shown to be associated with inflammation and vascular complications in many studies, and eGFR in patients with DNP. We found no significant difference in terms of platelet count between the groups, but significant differences were observed in MPV, NLR, TLR, and UALR values. These differences were more pronounced in Group

Table 1. Baseline demographic and laboratory data of the patients

	Group 1	Group 2	Group 3	Group 4	p-value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age (years)	53.2±8.2	54.4±10.8	53.0±9.1	59.6±7.6[a, c]	0.004*
Gender, female n (%)	20 (55.6)	19 (50.0)	23 (65.7)	24 (60.0)	0.573**
Creatinine (mg/dL)	0.72±0.12	0.78±0.16	0.82±0.27	2.18±0.97[a, b, c]	<0.001*
eGFR (mL/min)	99.1±15.7[d]	95.7±15.9[d]	90.6±25.3[d]	33.1±14.5	<0.001*
Proteinuria (mg/day)	-	301.0±241.3	2451.5±1853.5[b]	3319.9±2790.3[b]	<0.001*
Microalbuminuria (mg/day)	10.7±9.7	87.3±63.1[a]	525.1±280.6[a, b]	1111.5±1497.7[a, b, c]	<0.001*
HbA1c (%)	8.1±2.5	8.5±2.0	9.1±2.0	8.9±1.7	0.120*
Leukocytes (/µL)	7.8±1.7	8.2±2.0	9.0±2.7	9.0±2.7	0.098*
Neutrophil (/µL)	4526.7±1470.8	4972.6±1907.3	5664.3±2195.6	5826.5±2363.6[a]	0.008*
Lymphocyte (/µL)	2538.1±672.7	2383.7±773.6	2497.1±761.0	2120.5±657.5	0.052*
hsCRP (mg/dL)	0.43±0.39	0.66±1.07	1.15±1.38	1.14±1.42[a]	0.003*
Uric acid (mg/dL)	4.9±1.5	4.8±1.1	5.3±1.8	6.2±1.3[a, b]	<0.001*

[a]: Group 1 vs. other group, [b]: Group 2 vs. other Group, [c]: Group 3 vs. other Group, [d]: Group 4 vs. other group
*Pearson chi-square test **One-Way ANOVA test
eGFR: Estimated glomerular filtration rate, hsCRP: High sensitive C-reactive protein, SD: Standard deviation

Table 2. Mean platelet volume, neutrophil-lymphocyte ratio, uric acid lymphocyte ratio values of the groups

	Group 1		Group 2		Group 3		Group 4	
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)
PLT*	275[a]±85	270 (218-314)	277[a]±50	270 (248-308)	285[a]±85	270 (233-333)	288[a]±91	268.5 (230-339)
OTH*	8.9[a]±1.0	8.85 (8.2-9.3)	9.5[b]±1.0	9.3 (8.6-10.4)	9.3[a, b]±1.1	9.3 (8.4-10.1)	8.9[a]±0.7	8.85 (8.4-9.3)
NLO*	1.9[a]±1	1.7 (1-2)	2.4[a, b]±2	2.0 (2-3)	2.5[a, b]±1	2.1 (2-3)	3.1[b]±2	2.5 (2-3)
UALO*	0.002[a]±0.001	0.001 (0.001-0.003)	0.002[a]±0.001	0.002 (0.002-0.002)	0.002[a]±0.001	0.002 (0.002-0.003)	0.003[b]±0.002	0.002 (0.002-0.004)
TLR*	0.12[a]±0.05	0.108 (0.08-0.13)	0.13[a]±0.05	0.1304 (0.09-0.16)	0.12[a]±0.05	0.109 (0.09-0.14)	0.16[a]±0.12	0.128 (0.10-0.16)
Uric acid* (mg/dL)	4.9[a]±1.5	4.8 (3.7-5.7)	4.8[a]±1.1	4.45 (4.0-5.7)	5.3[a]±1.8	5.1 (4.1-6.2)	6.2[b]±1.3	6 (5.5-7.1)
Neutrophil* (/µL)	4527[a]±1471	4285 (3545-5530)	4973[a, b]±1907	4870 (3720-5800)	5664[a, b]±2196	5000 (4400-7300)	5827[b]±2364	5600 (4415-6450)
Lymphocyte* (/µL)	2538[a]±673	2470 (2120-2800)	2384[a]±774	2145 (1800-2990)	2497[a]±761	2380 (1990-3100)	2121[a]±657	2160 (1800-2550)

*Kruskal-Wallis test
Note: Values in the same row and subtable not sharing the same subscript are significantly different at p<0.05 in the two-sided test of equality for column proportions.
PLT: Platelet, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, UALO: Uric acid lymphocyte ratio, TLR: Platelet lymphocyte ratio, SD: Standard deviation, IQR: Interquartile range

4, which included patients with eGFR <60 mL/min/1.73 m^2 and albuminuria >300 mcg/g, compared with the other groups. On the other hand, a positive correlation was found between eGFR and MPV and lymphocyte levels, whereas a significant negative correlation was found between eGFR and NLR, UALR, TLR, neutrophil, and uric acid levels.

The NLR has been shown to be better than routine and conventional tests such as CRP, leukocyte count, and neutrophil count in the diagnosis of bacteremia (15,16). NLR has been found to be an effective parameter in the prognosis and follow-up of myocardial infarction, gangrenous appendicitis, and colorectal carcinoma in previous studies conducted on different patient groups (17,18). The presence of a low-grade inflammatory state in CKD has been shown in studies, and given that inflammation increases as GFR decreases, it is thought that NLR can provide predictive information for the progression of CKD (19-21). Khandare et al. (22) accepted NLR as a predictive and prognostic risk marker for DNP. On the other hand, Huang et al. (23) found that increasing NLR was associated with DNP and that NLR was a reliable predictor for early-stage DNP.

Large platelets have high adhesion capabilities. Mean platelet volume, an indicator of platelet function, is associated with various prothrombotic and proinflammatory diseases. Mean platelet volume is a prognostic biomarker of cardiovascular and cerebrovascular diseases. A meta-analysis reported that increased MPV values are associated with mortality after acute myocardial infarction and restenosis following coronary angiography (23). Other studies have also reported a relationship between increased MPV and sepsis severity, stroke, hypertension, venous thromboembolism, and DNP microvascular complications (24-29). Ju et al. (30) showed that MPV increases with CKD progression. In our study, we observed that MPV values increased relatively with decreasing GFR.

Platelet-lymphocyte ratio, an easy and inexpensive biomarker, has been shown to be a prognostic factor in cardiovascular mortality and some types of cancer in previous studies (30-34). There are also studies showing that TLR is related to inflammation and can predict

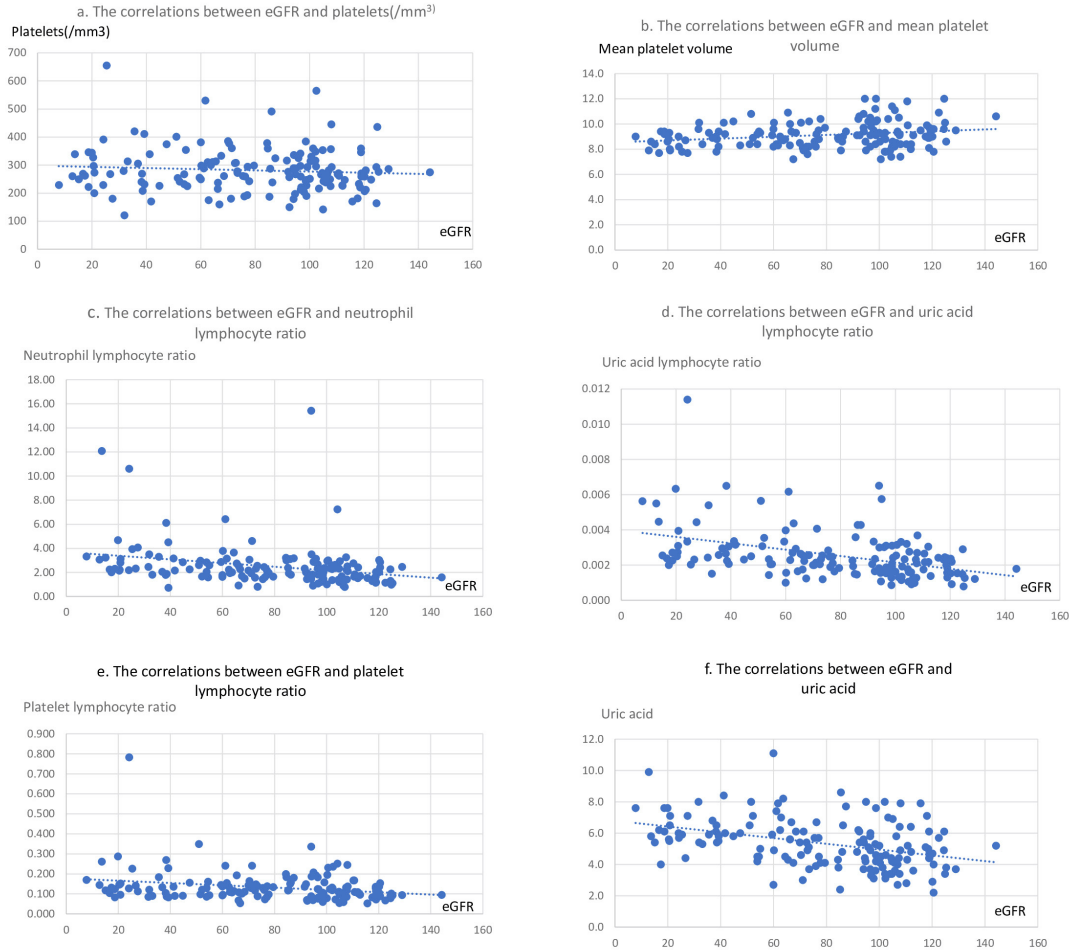

Figure 1. The correlations between eGFR and MPV, NLR, UALR, TLR, neutrophil, lymphocyte, and uric acid levels

mortality in hemodialysis patients (35,36). In our study, we did not find any relationship between platelet levels and GFR used in the classification of DNP, but we found a significant relationship between GFR and TLR obtained by rationing this parameter with lymphocyte levels. Similar to our results, Abdallah et al. (37) showed that NLR and TLR are important predictive and prognostic biomarkers for DNP.

Study Limitations

The main limitations of our study are that it is retrospective and cross-sectional. Due to the possible effects of neutrophil, lymphocyte, and platelet levels, gender, genetics, lifestyle, diet, seasonal factors, and existing diseases, the limited number of patients included in the study is another limitation. Despite these limitations, we believe that it is very valuable to use parameters such as PLR, MPV, NLR, UALR, and uric acid levels, which are easily accessible and can be used in daily clinical practice in the early diagnosis and prediction of progression in diabetics.

Conclusion

Mean platelet volume and TLR values, as well as NLR and UALR values, may have prognostic and predictive values for the development and monitoring of DM and complications such as DNP. It is cheap, easily integrated into daily practice, and reliable parameters reinforce their predictive value. However, more extensive and detailed studies are required on this topic.

Ethics

Ethics Committee Approval: Ethical approval was received by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (approval no.: 425, date: 05.04.2017).

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

Authorship Contributions

Concept: T.E.S.O., Design: T.E.S.O., S.O., Data Collection or Processing: T.E.S.O., A.A., Analysis or Interpretation: S.Y., E.C., C.C., A.A., Literature Search: T.E.S.O., E.C., S.U., Writing: T.E.S.O., A.A.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Comparison of Vitamin D and Calcium Levels Between Hospitalized Refugee Newborns and Native Newborns with Early-onset Hypocalcemia

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Abstract

Aim: Vitamin D deficiency (VDD) is mainly listed in the etiology of late-onset hypocalcemia in the neonatal period, as a probable cause of hypocalcemia in the early period, figured out in our study. We compared the vitamin D status and biochemical characteristics of refugee newborns with those of native newborns with early-onset hypocalcemia.

Methods: One hundred and forty newborns enrolled in our comparative cross- sectional study were admitted with calcium <8 mg/dL in term or <7 mg/dL in preterm infants detected at the maternity ward within 72 h postnatal age during a 3-month period from June to August in 2020. Serum calcium, phosphorus, magnesium, alkaline phosphatase, and parathormone levels were measured on the initial day. Vitamin D and calcium levels in newborns before discharge.

Results: The serum calcium levels in refugees were 7.12 mg/dL and 7.23 mg/dL in native newborns. The median vitamin D level was 8.57 µg/L in refugees and 7.99 µg/L in native newborns. Vitamin D deficiency was found in every eight in ten newborns with early-onset hypocalcemia. There was no difference in the prevalence of VDD between the refugee and native neonates. Maternal vitamin D supplementation was 12.8% in the refugee group and 13.3% in the native group. The hospital stay was similar in both groups.

Conclusion: Adequate access to preventive health services, routine screening of pregnant women for VDD, and supplementation during pregnancy and lactation should be provided to mothers from underdeveloped or developing countries because the prevalence of VDD is higher among this group.

Keywords: Hypocalcemia, newborn, refugee, vitamin D

Introduction

Calcium plays a role in several metabolic processes and bone mineralization (1,2). Hypocalcemia is one of the most common electrolyte imbalances during the neonatal period, is seen within the first three postnatal days, and is accepted as early-onset hypocalcemia (3). Causes of early-onset neonatal hypocalcemia are intrauterine growth restriction, prematurity, perinatal stress/asphyxia, being an infant of a diabetic or preeclamptic mother, septicemia, maternal history of antiepileptic use, and hyperparathyroidism (4). Although early-onset hypocalcemia is not primarily symptomatic, apnea, tremor, cyanosis, poor feeding, vomiting, and focal and generalized seizures are the main clinical symptoms of hypocalcemia (5). Treatment for newborns with any clinical symptom of hypocalcemia should be given for at least 3 days. The majority of infants with early-onset hypocalcemia improve after 48-72 hours of treatment in most cases, hopefully without any significant complications (6).

Vitamin D levels in newborns mainly depend on maternal vitamin D status, breastfeeding, and sunlight exposure (7,8). Causative factors for maternal vitamin D deficiency (VDD) include darker skin pigmentation, skin coverage with whole-body clothing, which directly affects neonatal vitamin D status, and residing at high altitude. Vitamin D deficiency results in hypocalcemia, hyperphosphatemia,

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and elevated levels of alkaline phosphatase (ALP) and parathormone (PTH) as calcium homeostasis is disrupted. In some cases, only hypocalcemia can be a manifestation of VDD.

The civil war in Syria resulted in an enormous refugee crisis, and Turkey hosts approximately 4 million Syrian refugees as the largest refugee group in the country (9). The well-being of refugee infants has been negatively affected because of the poor nutrition of their mothers. Inadequate access to preventive healthcare services also causes short- and long-term undesirable complications for both infants and mothers. Implementation of a properly organized health support program plays a crucial role in raising awareness about preventive strategies via vaccination and routine screening of mothers and infants to improve effective public health measures.

To the best of our knowledge, there is limited data on the biochemical characteristics and vitamin D status of refugee newborns hospitalized in neonatal intensive care units (NICU) in Turkey. However, VDD is mainly listed in the etiology of late-onset hypocalcemia in the neonatal period, as a probable cause of hypocalcemia in the early period is determined in our study.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee with protocol number 2020-173 and date: 09.09.2020. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patients' parents.

Study Design and Participants

A total of 2,346 newborns were born in the hospital during this study period, and 673 babies were admitted to the NICU. Among these babies, 155 infants were diagnosed with early-onset hypocalcemia; 15 of them were excluded because of incomplete data for vitamin D levels; and 140 infants were included in the study. These 140 infants were divided into two subgroups and comparatively analyzed (refugee newborns: 94, native newborns: 46) (Figure 1). Our study included newborns admitted to the NICU from June 1 to August 31, 2020, which was the summer period in Turkey. The inclusion criteria were (1) postnatal age at admission ≤3 days; (2) term infants with serum calcium levels <8 mg/dL (2 mmol/L) or ionized calcium levels <4.4 mg/dL (1.1 mmol/L); and (3) preterm infants with serum calcium levels <7 mg/dL (1.75 mmol/L) or ionized calcium levels <4 mg/dL (<1 mmol/L) detected at the maternity ward; and (4) absence of a history of calcium and vitamin D use before hospitalization. The exclusion criteria were as follows: (1) newborns admitted to the NICU for any other diseases such as transient tachypnea of the newborn, meconium aspiration syndrome, acute respiratory distress syndrome, complex congenital heart disease, and congenital malformations; (2) infants born to a preeclamptic mother or mothers using antiepileptic drugs (phenobarbitone, phenytoin sodium); (3) infants having undergone phototherapy, history of receiving diuretics, lipid infusions, or blood transfusions.

Hypocalcemia in asymptomatic babies was detected by routine biochemical tests during follow-up at the maternity ward. Neuromuscular irritability (jitteriness, seizures, exaggerated startle, and myoclonic jerks) and cardiac involvement (prolonged QT interval and/or cardiac rhythm disturbances) were accepted as symptomatic hypocalcemia findings, and infants with these symptoms were admitted to the NICU soon after the symptoms were observed.

Data Collection and Procedures

Anthropometric and clinical findings of the neonates were retrieved from the hospital records, including gestational age, birth weight and height, head circumference, gender, intrauterine growth status, postnatal day at admission, mode of delivery, presence of perinatal asphyxia, calcium normalization day, route of calcium replacement, and length of hospital stay; maternal conditions, including maternal age, number of births, history of using regular vitamin D supplementation, and maternal complications, such as gestational diabetes and preeclampsia. Gestational age of 37 weeks was accepted as preterm birth.

Daily 1200 IU vitamin D maternal intake within the first trimester, independent of vitamin D level, is accepted as regular vitamin D intake during pregnancy, as stated in the Turkish Ministry of Health Support Program (10).

Blood Sampling and Analysis

Venous blood samples were collected at the time of NICU admission, and serum levels of leukocytes [platelet count [$\times 10^3$/L, white blood cell count (10^3 /L)], C-reactive protein (CRP) (mg/L), total calcium, phosphorus, magnesium, ALP, and PTH were measured on the first day. Serum calcium levels were measured again before discharge to evaluate the normalization duration. Serum samples for 25-hydroxy vitamin D [25(OH)D] were maintained at -80 °C and measured using the enzyme immunoassay method (IDS Immunodiagnostic Systems). Neonatal 25(OH)D levels of 12 ng/mL (30 nmol/L) were considered to be VDD, levels between 12 and 20 ng/mL (30-50 nmol/L) were considered to be vitamin D insufficiency, and levels >20 ng/mL (50 nmol/L) were reported as vitamin D sufficiency according to the Global Consensus Recommendations (11).

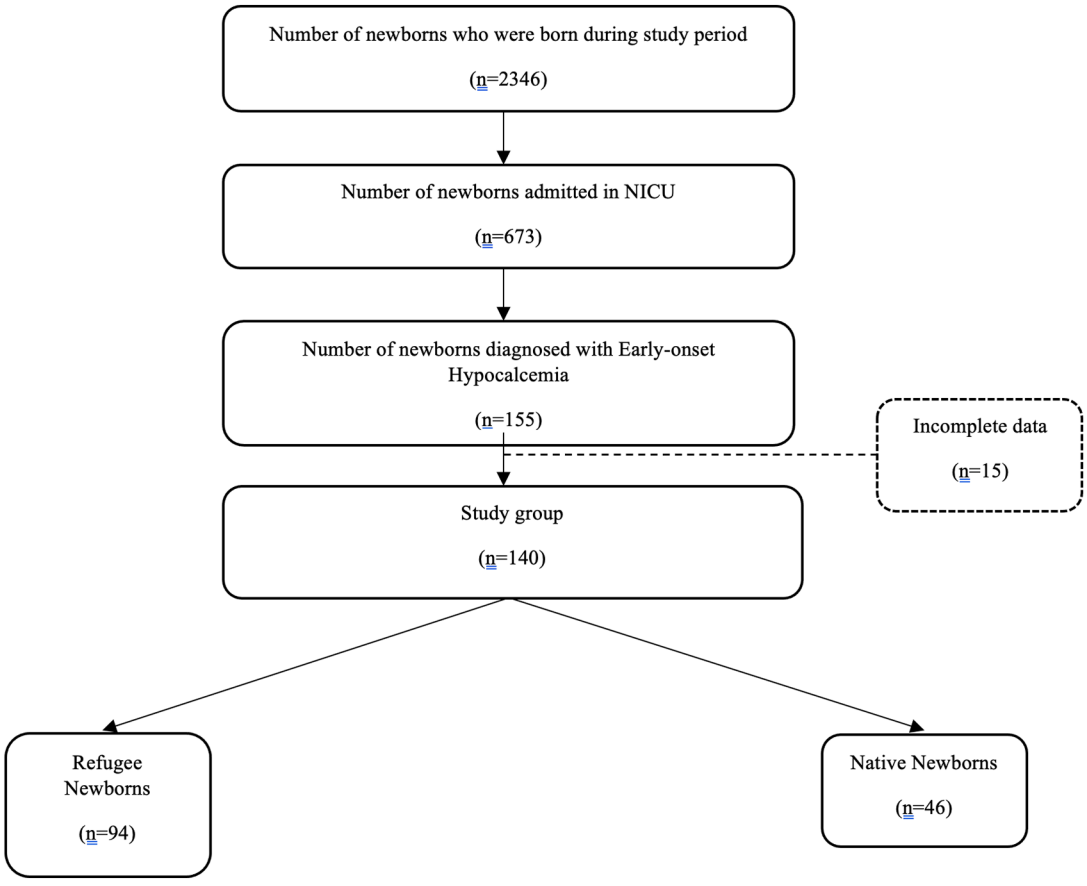

Figure 1. Flow diagram of the study

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Descriptive statistics are expressed as numbers and percentages for categorical variables. The Kolmogorov-Smirnov test was used to assess the conformity of variables to a normal distribution. If numerical variables were normally distributed, they were expressed as mean ± standard deviation, whereas if numerical variables were non-normally distributed, they were expressed as median (interquartile range: Q1-Q3). To compare categorical variables, the chi-square test was performed, and the comparison of quantitative data between the two groups was assessed using the Mann-Whitney U tests. Statistically significant was accepted as a p-value of less than 0.05.

Results

Study Population and Characteristics

A total of 140 newborns [male: 93 (66.4%), female: 47 (33.6%), with a mean gestational age of 38.1 (±2.0) weeks, a birth weight of 2933 (±665) g, and a birth height of 49.3 (±2.9) cm] were enrolled in the study.

Ninety-four (67.1%) of the babies were Syrian refugee newborns, 46 (32.9%) were native newborns, and 30 of the babies (21.4%) were preterm infants. Gestational age, birth weight, height, head circumference, gender, SGA, appropriate for gestational age, large gestational age ratios, perinatal asphyxia, gravity, parity, gestational diabetes, and maternal vitamin D supplementation use of refugees and native newborns were similar. The rates of prematurity, cesarean section, and maternal age were significantly higher in native newborns (respectively, p=0.022, p=0.001, and, p=0.002). The baseline demographic and laboratory values of the newborns and maternal features are given in Table 1.

Analysis of Vitamin D and Calcium Status

The mean calcium levels of all babies were 7.16 (0.46) mg/dL [minimum-maximum (min.-max.) 5.5-7.9], the median vitamin D levels of babies were 8.36 ng/dL (min.-max. 5.93-11.1), and 79.1% of the infants had VDD and 14.4% had vitamin D insufficiency. No significant difference was found in the prevalence of vitamin D sufficiency, insufficiency, and deficiency between term and

Table 1. Baseline demographics of newborns and maternal features					
Characteristic		**All newborns (n=140)**	**Refugee newborns (n=94)**	**Native newborns (n=46)**	**p-value**
Demographic characteristics					
Gestational age (week), mean (SD)		38.1 (2.0)	38.3 (1.9)	37.7 (2.0)	0.097*
Prematurity, n (%)		30 (21.4%)	15 (16%)	15 (32.6%)	0.024**
Gender, n (%)	Male	93 (66.4%)	66 (70.2%)	27 (58.7%)	0.175**
Birth weight (gr), Mean (SD)		2933 (665)	2921 (687)	2957 (626)	0.757*
Birth height (cm), mean (SD)		49.3 (2.9)	49.3 (3.1)	49.3 (2.5)	0.909*
Head circumference (cm), mean (SD)		34.5 (3.8)	34.1 (1.7)	35.4 (6.1)	0.06*
Weight for GA, n (%)	SGA	30 (21.4%)	22 (23.4%)	8 (17.4%)	0.715**
	AGA	98 (70%)	64 (68.1%)	34 (73.9%)	
	LGA	12 (8.6%)	8 (8.5%)	4 (8.7%)	
Mode of delivery, n (%)	Cesarian section	72 (51.4%)	42 (44.7%)	30 (65.2)	0.022**
Perinatal asphyxia, n (%)		1 (0.7%)	1 (1.1%)	0 (0%)	0.483**
Maternal features					
Maternal age (years), mean (SD)		26.5 (6.6)	24.8 (5.9)	29.9 (6.6)	<0.001*
Gravity, median (Q1-Q3)		2 (2-3)	2 (1-3)	2 (2-4)	0.195***
Parity, median (Q1-Q3)		2 (1-3)	2 (1-3)	2 (1.75-3)	0.789***
Gestational diabetes, n (%)		5 (3.6%)	3 (3.2%)	2 (4.3%)	0.664**
Maternal vitamin D supplementation, n (%)		18 (12.9%)	12 (12.8%)	6 (13%)	0.963**

*t-test, **Chi-square test, ***Mann-Whitney U test
SD: Standard deviation, GA: Gestational age, SGA: Small gestational age, AGA: Appropriate gestational age, LGA: Large gestational age

preterm infants. Symptomatic hypocalcemia developed in 5 patients (3.0%) during hospitalization, and all of these babies were refugees. Calcium, phosphorus, PTH, vitamin D, magnesium, ALP, leukocytes, platelets, and CRP levels were similar in refugee and native newborns. The mean hospital stay was 9.1 (0.6) days. Refugee babies had a longer hospital stay compared to the natives (p=0.022). Calcium was applied more frequently by the intravenous route, and the duration of calcium normalization was longer in refugee newborns than in native newborns (respectively, p=0.048 and p=0.026) (Table 2). Calcium and vitamin D levels of refugee and native newborns are shown as scatter plots (Figure 2).

Discussion

In this study, vitamin D levels, biochemical status, and clinical characteristics of neonates with early-onset hypocalcemia were evaluated, and vitamin D levels and biochemical status were compared between refugee newborns and native newborns. Vitamin D deficiency was found in every eight in ten newborns with early-onset hypocalcemia in our study. The prevalence of VDD among neonates was reported at 61% in a recently published meta-analysis including eighteen studies (12), and in the studies conducted in Iran (13) and Jordan (14), the results for VDD were found to be over 90%. A meta-analysis of vitamin D prevalence in South European countries showed an increased trend in newborns, besides, there were different rates in different countries. In particular, VDD in newborns from Spain was found to be lower compared to other countries, but Turkey also had higher rates (15). A multicenter study with 61 centers from Turkey reported that the prevalence of VDD was 86.5% in newborns with late-onset hypocalcemia (16). A recent meta-analysis of 11 studies including 452 newborns with hypocalcemia and 2,599 newborns with normal serum calcium levels revealed that VDD in newborns may be related to the higher prevalence of hypocalcemia, and maternal VDD may also be a risk factor for neonatal hypocalcemia. This meta-analysis indicates that newborns with VDD have a higher risk of hypocalcemia, and maternal vitamin D levels play a crucial role in this association (17). Our study is valuable because the data of patients with early neonatal hypocalcemia have not been evaluated before, whereas studies frequently report hypocalcemia related to VDD during all neonatal periods.

The vitamin D level of a newborn is closely related to maternal vitamin D level, breastfeeding, and sunlight exposure duration (7,8). The prevalence of VDD was 74.5% and 88.9%, and insufficiency was 17% and 8.9% in the refugee and native neonates hospitalized in the NICU, respectively (p=0.132). In a study by Abdelmageed et al. (18), 365 pregnant women were prospectively

Table 2. Laboratory findings and clinical features of the newborns					
		All newborns (n=140)	**Refugee newborns (n=94)**	**Native newborns (n=46)**	**p-value**
Laboratory finding					
Baseline calcium (mg/dL), mean (SD)		7.16 (0.46)	7.12 (0.47)	7.23 (0.45)	0.188*
Phosphorus (mg/dL), Mean (SD)		5.7 (1.1)	5.8 (1.2)	5.6 (0.9)	0.253*
Magnesium (mg/dL), Median (Q1-Q3)		2.00 (1.70-2.00)	1.95 (1.70-2.00)	2.00 (1.70-2.00)	0.849**
ALP (U/L), median (Q1-Q3)		201 (167-246)	208 (166-249)	186 (169-242)	0.706**
Calcium at discharge (mg/dL), mean (SD)		9.18 (0.68)	9.23 (0.66)	9.08 (0.69)	0.213*
Leucocyte count (10^3/L), mean (SD)		16770 (7200)	16657 (7859)	17007 (5796)	0.767*
Platelet count (10^3/L), mean (SD)		257 (86)	252 (81)	267 (96)	0.392*
C-Reactive Protein (mg/L), Median (Q1-Q3)		1.42 (0.24-11.92)	1.75 (0.32-12.2)	1.20 (0.20-11.60)	0.359**
Parathormone (U/L), median (Q1-Q3)		74.8 (46.8-114.3)	77.6 (49.4-112.7)	66 (42.9-146.8)	0.838**
25 OH Vitamin D (µg/L), Median (Q1-Q3)		8.36 (5.93-11.17)	8.57 (6.29-12.55)	7.99 (5.58-10.58)	0.317**
	Deficiency, n (%)	110 (79.1%)	70 (74.5%)	40 (88.9%)	0.132***
	Insufficiency, n (%)	20 (14.4%)	16 (17%)	4 (8.9%)	
	Sufficiency, n (%)	9 (6.5%)	8 (8.5%)	1 (2.2%)	
Clinical features					
Number of symptomatic hypocalcemias cases, n (%)		5 (3.6)	5 (5.3)	0 (0)	0.172***
Route of calcium replacement, n (%)	IV + PO	17 (12.1)	15 (16)	2 (4.3)	0.048***
Calcium normalization duration (day), median (Q1-Q3)		4.0 (3.0-5.0)	4.0 (3.0-5.0)	3.0 (2.5-4.0)	0.026**
Length of stay at hospital (day), median (Q1-Q3)		9.0 (7.0-11.0)	9.0 (7.0-12.0)	7.5 (6.0-9.2)	0.002**

*t-test, **Mann-Whitney U test, ***Chi-square test, ALP: Alkaline phosphatase, IV: Intravenous, PO: Per oral

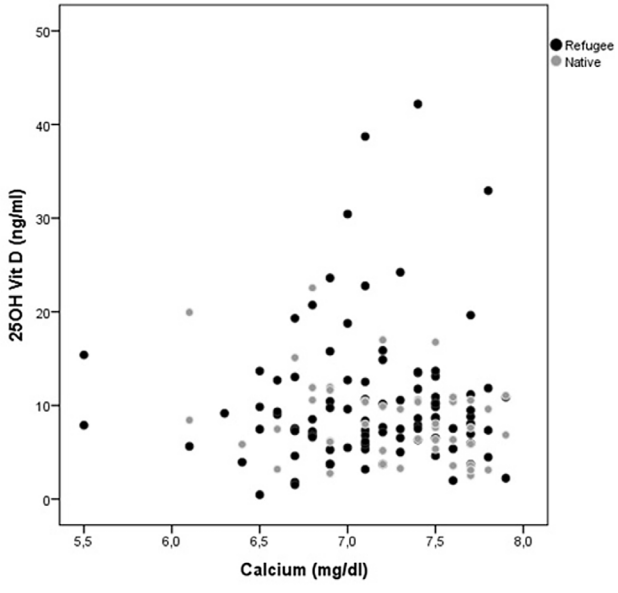

Figure 2. Vitamin D and calcium levels in refugee and native newborns

evaluated in terms of vitamin D levels, and 57.7% of the participants had VDD. They reported that vitamin D supplementation at a daily dose of 1000 IU may not adequately address VDD (18). The study of Kareem Mohammed (19) also revealed a significant prevalence of VDD among pregnant women, and the incidence of VDD was 56.0% among pregnant participants. In our study, the VDD of both refugee and native mothers was similar. Maternal vitamin D supplementation was 12.8% in the refugee group and 13.3% in the native newborns. Besides, no significant difference was found in the vitamin D supplementation of mothers, suggesting similar socioeconomic levels and poor access to public health programs. The rate of covered clothing was also frequent in both groups' mothers, and the parents of both refugee and native newborns were living in the same region, which may explain the similar sun exposure of the mother and baby dyad. Fakhoury et al. (20) examined the relationship between various measures of 25(OH)D status in maternal and neonatal populations and their associations with neonatal outcomes in a sunny Mediterranean region. The study found a link between maternal total and free 25(OH) D levels and all forms of neonatal 25(OH)D levels being positively related. This suggests that maternal vitamin D

levels may have a big effect on the vitamin D status of the newborn (20). Blarduni et al. (21), from Spain, also conducted a study that measured vitamin D levels in 745 mothers and in the umbilical cord blood of 560 newborns. Multiple pregnancies and non-European origin were found to be risk factors for maternal hypovitaminosis, whereas maternal supplementation, physical activity, and sun exposure had a preventive effect.

Hypocalcemia, hyperphosphatemia, and elevated levels of ALP and PTH are the main laboratory findings of VDD. In some cases, only hypocalcemia can be a manifestation of VDD. The mean calcium levels of refugee and native newborns were 7.1 mg/dL and 7.2 mg/dL, respectively. Parathormone, ALP, and phosphorus levels were found within the normal range in both groups, which may be explained by the fact that if VDD was not detected and persisted for a long time, it would increase the levels of these parameters. In a case report including 2 newborns with early-onset hypocalcemia who presented with hypotonia, lethargy, and pathologic tremors, vitamin D levels were low, but PTH was found to be high in one newborn, and both maternal vitamin D levels were deficient. A possible association between ethnicity, maternal vitamin D levels, and neonatal serum calcium levels has been shown; therefore, maternal vitamin D levels and neonatal calcium levels may vary depending on the maternal phototype or cultural factors (22).

Study Limitations

We cannot fully present all maternal biochemical statuses, including vitamin D, calcium, magnesium, phosphorus, and PTH levels, because of financial issues that affect neonatal calcium levels and are thought to be associated with early-onset neonatal hypocalcemia. The sunlight exposure rates of the mothers included in the study were not known, but all pregnancy periods were in similar seasons in both groups. Babies born during the summer period were included in the study. Although a limited number of newborns were enrolled in our study, we showed that VDD in newborns also caused early-onset hypocalcemia.

Conclusion

Neonatal VDD in both native and refugee newborns should also be considered for early-onset hypocalcemia. Maternal regular vitamin D supplementation during pregnancy and lactation and neonatal vitamin D supplementation as soon as after birth should be recommended as the main components of preventive public health policies. Unfortunately, the increased prevalence of VDD is mostly present among women from underdeveloped or developing countries; therefore, health education programs should be established to raise awareness about nutritional and health conditions. Because the majority of hypocalcemic infants have no symptoms related to hypocalcemia, calcium levels must be monitored routinely in newborns born to mothers who have no regular follow-up or vitamin D supplementation. While evaluating the causes of hypocalcemia, treatment for hypocalcemia should be initiated as soon as low calcium levels are obtained. There is a need for further studies to assess the expanded biochemical evaluation of the mother and infant dyad in many patients.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee with protocol number 2020-173 and date: 09.09.2020.

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

Authorship Contributions

Design: B.C., Data Collection or Processing: M.C.U., Analysis or Interpretation: B.C., Literature Search: B.C., M.C.U., Writing: B.C., M.C.U.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Evaluation of Sharp and Needle-stick Injuries in A Tertiary Care Hospital: A Two-year Analytical Cross-sectional Study

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Abstract

Aim: Healthcare workers are at risk of infections due to needle-stick and sharp injuries (NSSIs) and through contact with blood and contaminated body fluids. This study aimed to investigate NSSIs and associated factors in healthcare workers.

Methods: This single-center analytical cross-sectional study included healthcare workers who were admitted to "the Hospital Infections Control Committee" following NSSIs at University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, between January 1, 2020, and December 31, 2021. Demographic and epidemiological data, serological tests, and routine follow-up results were retrospectively collected from NSSI surveillance. Healthcare workers were divided into two groups according to the occurrence of stab wounds (injury or no injury). The age, sex, occupation, and working area of healthcare workers were compared.

Results: A total of 232 (7%) experienced NSSIs among 3,312 healthcare workers. The NSSI was 35.0 [confidence interval (CI)=34.9-35.2] per 1000 person-years. Needle-stick and sharp injuries were most frequently observed in nurses (n=148, 63.8%). Nurses [odds ratio (OR)=5.97, CI=4.51-7.90, p<0.001], cleaning staff (OR=1.64, CI=1.13-2.37, p=0.009), medical waste personnel (OR=10.79, CI=2.88-40.46, p<0.001), and medical technicians/technologists (OR=1.92, CI=1.03-3.57, p=0.039) were at increased risk for NSSIs.

Conclusion: This study highlights the need for assigning sufficient healthcare workers, prioritizing vaccination programs for high-risk groups, and providing regular hands-on training as crucial measures to prevent injuries.

Keywords: Sharp injuries, needle-stick injuries, healthcare workers

Introduction

Healthcare workers are at risk of infections due to contact with blood and contaminated body fluids during service provision. The main risk of infections transmitted through blood is injuries from needle-stick and sharp injuries (NSSIs). The Centers for Disease Control and Prevention (CDC) estimate that approximately 385,000 injuries occur among healthcare workers each year (1). According to the World Health Organization, more than two million professional NSSIs occur among 35 million healthcare workers annually (2). Factors leading to infection because of injury include major viruses such as hepatitis B, hepatitis C, and the human immunodeficiency virus (3). A systematic review on NSSIs among healthcare workers has shown that in developed countries, the incidence of injury is lower because of appropriate budget programs and the supply of preventive equipment (4).

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However, inadequate information on the prevention and management of professional exposure increases the risk of injury. Despite regular training for healthcare professionals on professional exposure and measures to be taken from the onset, NSSIs continue to be a significant problem. In addition, the CDC emphasizes the importance of a lack of notification after injury among healthcare workers (5).

Needle-stick and sharp injuries are common problems among healthcare professionals (6). Following occupational exposure, the exposed individual should promptly report the incident, and necessary follow-up and treatment should be planned. Hospitals should establish appropriate emergency intervention mechanisms to ensure timely reporting and treatment of exposures, as well as regular monitoring and follow-up (6,7). Therefore, it is critical to conduct regular NSSI surveillance and identify risky groups and situations that increase risk. This study aimed to investigate NSSIs and associated factors in healthcare workers.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval no.: 159-2022, date: 10.08.2022).

Study Design

This single-center analytical cross-sectional study included healthcare workers who were admitted to "the Hospital Infections Control Committee (HICC)" following NSSIs at Haseki Training and Research Hospital between January 1, 2020, and December 31, 2021. 232 (7%) healthcare workers with NSSIs were included in the study. The study excluded 45 (1.4%) healthcare workers who were injured by contaminated body fluids (Figure 1). Demographic and epidemiological data (age and sex) and routine follow-up results were retrospectively collected from medical data sheets for NSSI surveillance. Healthcare workers were routinely monitored for six months following the injury. They were divided into two groups according to the occurrence of stab wounds (injury or no injury) during the 2-year period. The gender and age characteristics of these two groups were compared. Healthcare workers who were injured were evaluated according to their professional group, the unit in which they worked, and the type of injury. In addition, injured healthcare workers were divided into 3 groups: 18-30 years old, 30-45 years old, and >45 years old, and the frequency of injuries was compared between age groups.

Statistical Analysis

The statistical software IBM SPSS-21 (Statistical Package for Social Sciences, Chicago, IL, USA) facilitated the execution of these analyses. Quantitative variables were delineated through the calculation of the median (minimum-maximum) in the context of continuous data, whereas categorical data were articulated in terms of percentages (%) and frequencies (n). The Pearson chi-squared test was employed to compare qualitative characteristics. The odds ratio (OR) was calculated, and risk values were given. The Student's t-test was applied to analyze continuous data among more than two independent non-parametric groups. Results were provided within a 95% confidence interval (CI), with the predetermined level of statistical significance set at a p-value of <0.05.

Results

A total of 232 (7%) experienced NSSIs among 3,312 healthcare workers. Of the 232 healthcare workers

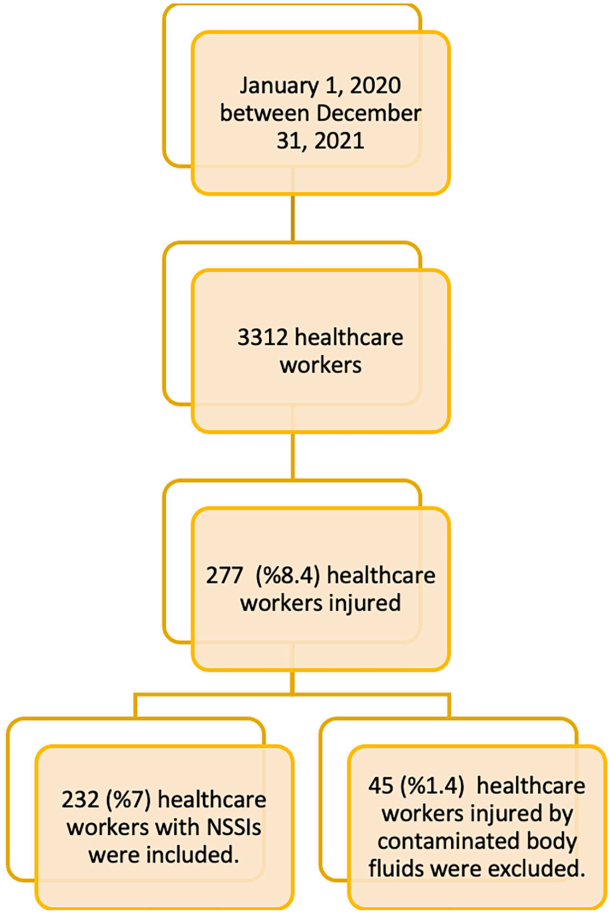

Figure 1. The flow chart regarding the study design

included in the study, 155 (66.8%) were female, with a median age of 27 (18-62) years. The demographic data of healthcare workers in our hospital, their distribution according to occupational groups, and the clinics where they worked are presented in Table 1. When injuries were grouped by age, the highest incidence occurred in the 18-30 age group (n=159, 68.5%) (Table 2). The NSSI was 35.0 (CI=34.9-35.2) per 1000 person-years.

The NSSIs were most frequently observed in nurses (n=148, 63.8%), followed by cleaning staff (n=37, 15.9%), and physicians (n=15, 6.5%) (Table 3). Working in general wards (OR=2.08, CI=1.58-2.72, p<0.001) and working in the intensive care unit (ICU) (OR=3.71, CI=2.69-5.10, p<0.001) were associated with an increased risk of NSSIs (Table 4). When injuries were evaluated by region, the hand was the most frequently injured area (n=230, 99.1%). Needlestick injuries accounted for 82.8% of cases (n=192). Six healthcare workers were injured during the breakage of a drug ampule. The material causing the injury was contaminated in 89.6% of cases (n=208), whereas in 14 cases (6.03%), the contacted material was not contaminated. In eleven cases, it was unknown whether the material was contaminated. No cases of infection transmitted through blood were recorded during the 2-year study period associated with the injury.

Table 1. Demographic characteristics of healthcare workers

		n	%
In total		3312	100
Sex	Female	1977	59.7
	Male	1335	40.3
Median age, years (min.-max.)		30 (18-69)	
Distribution by Professions			
Nurse		850	25.7
Doctor		672	20.3
Patient receptionist		440	13.3
Cleaning staff		357	10.8
Medical secretary		323	9.8
Administrative staff		180	5.4
Laboratory technician		170	5.1
Security guard		150	4.5
Medical technician		97	2.9
Dining hall staff		64	1.9
Medical waste personnel		9	0.3
Distribution by Units/Departments			
Clinics		982	29.7
Intensive care unit		325	9.8
Emergency department		292	8.8
Outpatient clinics		283	8.5
Operating room		207	6.3
Laboratory		170	5.1
Other departments		**1053**	**31.8**

Discussion

This single-center analytical cross-sectional study was designed to assess the prevalence of NSSIs and associated factors among healthcare workers in our hospital. We found that the NSSI was 35.0 (CI=34.9-35.2) per 1000 person-years. Factors significantly associated with NSSIs were occupation (being a nurse) and working area (working in general wards and the ICU).

In the study by Erturk Sengel et al. (8), the incidence of occupation-related injuries was 34.1 (CI=33.1-37.5). In the study by Yunihastuti et al. (9), the NSSI incidence rate was 13.3 per 1000 people per year. In our study, the NSSI was 35.0 (CI=34.9-35.2) per 1000 person-years. Injury rates among different centers varied. In addition, the extent to which injuries are reported or followed up for treatment and testing may vary among healthcare professionals. There are problems with reporting among healthcare professionals, probably because of a lack of time, a lack of belief in the infection transmitted through NSSIs, and several other reasons (10). In a questionnaire, at least one-third of health workers had at least one reported injury, and the most common reason for not being notified was time-consuming (11). Although the relatively low ratio seen in physicians in our center is required, it may be thought that they may not be notified for various reasons.

Table 2. Comparison of injured and uninjured healthcare workers in terms of sex and age

In total (n=3,312)	**Injured (n=232)**		**Uninjured (n=3,080)**		**OR**	**CI**	**p-value**
	n	**%**	**n**	**%**			
Sex							
Female (n=1,977)	155	66.8	1822	59.2	1.39	1.05-1.84	0.022*
Male (n=1,335)	77	33.2	1258	40.8			
Age							
Median age, years (min.-max.)	27 (18-62)		31 (18-69)		-	-	0.186**

OR: Odds ratio, CI: Confidence interval, min.-max.: Minimum-maximum, *: Pearson chi-quare test, **: Student's t-test

In our study, 82.8% of NSSIs were caused by needlestick injuries. In the study of Aiken et al. (12), it was found that 36.9% of NSSIs occurred through needlestick injuries during drug preparation, injection, and blood collection. Karabay et al. (13) showed that 85% of the tools that caused NSSIs were contaminated. In our study, it was determined that nurses, medical technicians, and cleaning personnel constituted approximately 85% of penetrating injuries. Kaya et al. (14) reported that NSSIs were distributed as follows: 48% are nurses, 22% are servants, 14.5% are technicians, 8.5% are health officers, and 7% are doctors. Güngör Özdemir and Şengöz (15) demonstrated that nurses constituted the most frequent occupational group exposed to NSSIs, accounting for 57.5%.

In a retrospective study conducted by HICC in a hospital in India over a period of 9 years, 78 NSSIs were reported, with nurses constituting 61.5% of these incidents. This study revealed a higher incidence of injuries among females (1.6:1). The higher proportion of female healthcare workers overall and in the nursing profession can both help to explain this situation (16). In another study, Alshehri et al. (17) showed that the NSSI rate was 2.05. Also, they found that 68.8% of the cases were female and 66.6% were under 39 years old (17). In our study, the rate of women's health workers in our hospital was higher, and more injuries were seen in females.

In numerous studies in the literature, it has been shown that NSSIs most frequently occur among nurses (9,16-19). In our study, the most commonly injured occupational group was also found to be nurses. This situation can be explained by the fact that nurses constitute the highest proportion in terms of the number of employees, coupled with their frequent and direct patient contact and the relatively high patient load per nurse. Another retrospective study by Stallard et al. (20) included 47 injuries, and the most common injuries were seen in nurses.

Saadeh et al. (19) demonstrated that two-thirds of the injuries were among health workers under 30 years of age. Alshehri et al. (17) reported that 66.6% of the injuries

Table 3. Comparison of injured and uninjured healthcare workers terms of occupation

In total (n=3,312)	Injured (n=232)		Uninjured (n=3,080)		OR	CI	p-value*
	n	%	n	%			
Doctor (n=672)	15	6.5	657	21.3	0.25	0.15-0.43	<0.001
Nurse (n=850)	148	63.8	702	22.8	5.97	4.51-7.90	<0.001
Cleaning staff (n=357)	37	15.9	320	10.4	1.64	1.13-2.37	0.009
Medical waste personnel (n=9)	4	1.7	5	1.5	10.79	2.88-40.46	<0.001
Patient receptionist (n=440)	4	1.7	436	14.2	0.11	0.04-0.29	<0.001
Medical technician (n=97)	12	5.2	85	2.8	1.92	1.03-3.57	0.039
Dining hall staff (n=64)	0	0	64	2.1	0.10	0.01-1.63	0.106
Security guard (n=150)	1	0.4	149	4.8	0.09	0.01-0.61	0.014
Administrative staff (n=180)	0	0	180	5.8	0.03	0.002-0.56	0.018
Medical secretary (n=323)	1	0.4	322	10.5	0.04	0.01-0.26	0.001
Laboratory technician (n=170)	10	4.3	160	5.2	0.82	0.43-1.58	0.557

OR: Odds ratio, CI: Confidence interval, *: Pearson chi-quare test

Table 4. Comparison of of injured and uninjured healthcare workers terms in terms of working area

In total (n=3,312)	Injured (n=232)		Uninjured (n=3,080)		OR	CI	p-value*
	n	%	n	%			
Emergency department (n=292)	24	10.3	268	8.7	1.21	0.78-1.88	0.395
Operating room (n=207)	16	6.9	191	6.2	1.12	0.67-1.90	0.673
Clinics (n=283+478+221)	105	45.3	877	28.5	2.08	1.58-2.72	<0.001
Intensive care unit (n=325)	60	25.9	265	8.6	3.71	2.69-5.10	<0.001
Laboratory (n=170)	10	4.3	160	5.2	0.82	0.43-1.58	0.557
Outpatient clinics (n=283)	3	1.3	280	9.1	0.13	0.04-0.41	<0.001
Other departments (n=1,053)	14	6.0	1039	33.7	0.13	0.07-0.22	<0.001

OR: Odds ratio, CI: Confidence interval, *: Pearson chi-quare test

were among health workers under 39 years of age. In our study, 68.5% of injuries occurred in health workers aged 30 years. In another study evaluating NSSIs over 19 years in Japan, 58.5% of the injuries occurred in people with less than 5 years of experience (21). The median age of healthcare workers in our hospital is 30 (range: 18-69) years, suggesting a relatively young healthcare workforce. It is also thought that the work experience of the cases can be a factor. Contrary to these studies, in a single-center cross-sectional study conducted in Ethiopia, it was found that being older (>40 years) increased the risk of NSSI by three times. The reason for this has been suggested as loss of muscle strength and sensory nerve endings, loss of concentration, loss of attention, and increasing structural and functional changes due to chronological age in elderly caregivers (22).

In Saadeh et al. (19), 91.1% of NSSIs occurred in the hand. Another study by Sharma et al. (16) also found that hand injuries were the most common location for NSSIs. In another retrospective cross-sectional study, hand injuries were observed in 94.3% of cases (18). In the study by Iwamatsu-Kobayashi et al. (21), the most frequently injured area was the hand. In our study, 99.1% of injuries occurred in the hand, which is consistent with the existing literature.

Study Limitations

There are some limitations to our study. This study was conducted in a single center and cannot be generalized to the entire population. However, the fact that injury hours were not evaluated in the study was insufficient to elucidate the relationship between injuries and shifts. Additionally, the number of cases was found to be lower in our study than in some studies in the literature. Despite this limitation, there was a hospital infection control committee that strictly monitored NSSIs.

Conclusion

This study highlights the need for assigning sufficient healthcare workers, prioritizing vaccination programs for high-risk groups, and providing regular hands-on training as crucial measures to prevent injuries. Needle-stick and sharp injuries among healthcare workers remain an important problem. Efforts should be made to raise awareness among healthcare professionals and increase reporting rates.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval no.: 159-2022, date: 10.08.2022).

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

Authorship Contributions

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

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Comparison of Different Surgical Incision Choices and Their Effects on Surgical Treatment Outcome in Tibial Plateau Fractures

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Abstract

Aim: Our hypothesis was that the treatment results would be superior to those of other methods in the patient group treated with a single anterior midline approach. The aim of this study was to assess the clinical and radiological results of surgical methods used to treat tibial plateau fractures.

Methods: This retrospective study included 60 patients who underwent tibial plateau fracture surgery between 2019 and 2021. The Schatzker fracture classification was used to analyze and compare the association between surgical incisions and clinical and radiological outcomes in terms of complication rate.

Results: The study included 60 patients (35 males and 25 females). The mean age of the patients was 44.8 years. The lateral incision is almost always preferred for Schatzker type 1-2-3 fractures, whereas the midline incision is used extensively for type 4-5-6 fractures. Better clinical and radiologic results were observed in Schatzker type 1 and 3 fractures. There were no significant differences in complications between anterior midline single-incision and double-incision surgeries.

Conclusion: Tibial plateau fractures require anatomical joint reduction and rigid fixation of fracture fragments. A single anterior midline incision for bicondylar plateau fractures can be safely utilized, although larger patient series studies are needed.

Keywords: Tibial plateau fractures, surgical approach, midline incision

Introduction

Tibial plateau fractures account for 5-8% of lower limb fractures and 1% of all adult fractures and frequently necessitate surgical intervention (1). High-energy trauma is the main cause of these fractures, which can significantly impair knee stability and function (2,3). The surgical treatment plan for tibial plateau fractures may vary depending on the type and location of the fracture and the general health status of the patient (4). Advances in surgical techniques and fixation methods have improved the treatment of tibial plateau fractures (5).

In tibial plateau fractures, the anatomical location of the fracture, fragmentation status, and soft tissue damage are the most important parameters affecting the results of surgical treatment (6). Therefore, patient-specific surgical approaches are used for treating patients with tibial plateau fractures (7). Many studies in the literature compare approaches to surgical treatment of tibial plateau fractures (8,9). However, clinical studies involving a single anterior incision, particularly for bicondylar fractures, are limited.

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This study aimed to evaluate the clinical and radiological results of all surgical approaches used in the surgical treatment of tibial plateau fractures, including the single anterior midline approach. Our hypothesis was that the treatment results would be superior to those of other methods in the patient group treated with a single anterior midline approach.

Methods

Compliance with Ethical Standards

This study was conducted in accordance with the Declaration of Helsinki, revised in 2013, and approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (decision no.: 2023-276, date: 27.12.2023).

Study Design

Sixty patients who underwent surgery for a tibial plateau fracture between 2019 and 2021 were included in the study (Figure 1).

The Inclusion Criteria were

- Patients treated surgically for a tibia plateau fracture.
- Patients with adequate clinical and radiological data at postoperative follow-up visits.

The Exclusion Criteria were as Follows:

- Open fractures.
- Those with concomitant vascular nerve damage.
- Patients without sufficient follow-up data.
- Conservatively treated patients.
- Pathological fractures.

Age, sex, fracture side, fracture type, surgical treatment approach, time from fracture to surgery, follow-up, duration of surgery, Rasmussen score, visual analogue scale (VAS), range of motion, postoperative pivot shift, and Lachman test results were analyzed (10,11). Radiologically, fracture union time, femorotibial angle, posterior tibial slope, and medial plateau diaphyseal angle were analyzed.

Statistical Analysis

SPSS 20.0 for Windows was used for statistical analysis. Because the numerical variables did not meet the normal distribution condition, comparisons of the independent groups were made using the Kruskal-Wallis test. The data were tested for normality using the Kolmogorov-Smirnov test. The ratios of categorical variables between the groups were tested by chi-square analysis. The statistical alpha significance level was set at $p<0.05$.

Results

A total of 60 patients, 35 (58.33%) males and 25 (41.66%) females, were included in the study. The mean age of the participants was 44.81±12.64 (19-89). The comparison of patients grouped using the Schatzker classification according to age, gender, and surgical incision selection is summarized in Table 1. Although the patients grouped according to the Schatzker classification were similar in terms of age and gender, there was a significant difference between the groups in terms of side effects. The lateral incision is almost always preferred for Schatzker type 1-2-3 fractures, whereas the midline incision is used extensively for type 4-5-6 fractures.

When the clinical and radiological results of the patients grouped according to the Schatzker classification were compared, there was a significant difference between the groups in terms of radiological union time, VAS score, special surgery hospital knee rating scale, Rasmussen score, flexion knee joint and knee joint score, and complication rate. Analysis of the time between fracture and surgery

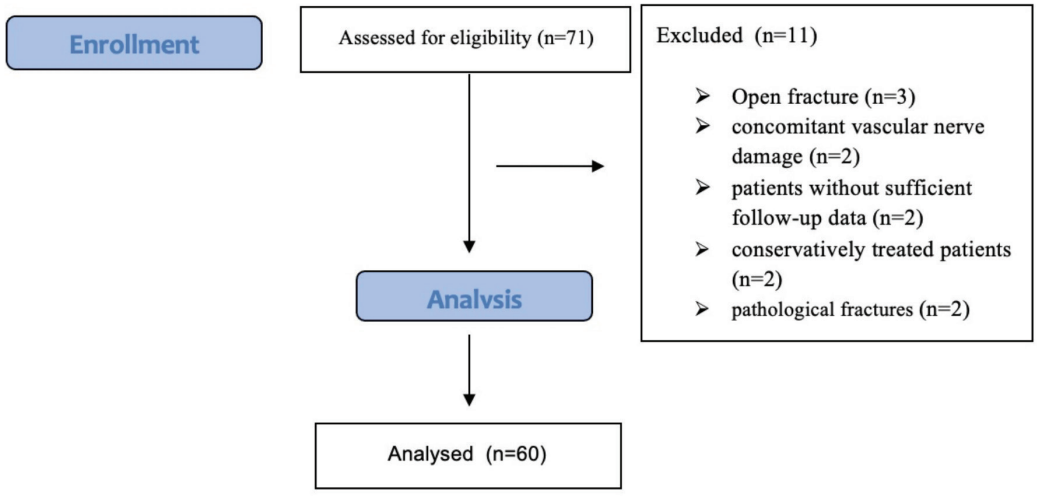

Figure 1. Consort flow diagram

showed that the more complex the fracture, the longer the time. Better clinical and radiologic results were observed in Schatzker type 1 and 3 fractures (Table 2).

When the clinical and radiological results of the patients grouped according to surgical incision selection were compared, a statistically significant difference was observed between the groups in terms of Rasmussen score, Hospital for Special Surgery knee rating scale, and radiological union time (Table 3).

Discussion

Patients who underwent different surgical approaches for tibial plateau fractures were evaluated in our study. When patients were assessed on the basis of the Schatzker classification, it was found that type 5 and 6 fractures were associated with longer preoperative waiting times, longer union times, and worse clinical and radiologic outcomes, as expected. Although type 4 fractures were less complex, comparable outcomes were noted with type 5 and 6 fractures. After surgical treatment of lateral plateau fractures, no complications were observed in our patients, whereas higher complication rates were found in fractures with medial plateau involvement.

The lateral approach is undoubtedly the most accepted method for treating isolated lateral plateau fractures and has been shown to achieve satisfactory results (12). It is possible to achieve improved results with the assistance of arthroscopy. Significant improvement has been reported with arthroscopic-assisted percutaneous fixation (13). Although the common approach involves lateral and medial double incisions, it has been reported that the same success can be achieved with a single anterior incision in fractures involving the medial and lateral columns of the tibial plateau (14,15). Anterior midline incisions were performed on 11 patients who had affected lateral and medial columns of the tibia. Five patients underwent surgery with a lateral and medial double incision, three patients underwent surgery with a medial and posterior incision, and one patient underwent surgery with a lateral and posterior incision. There was a significant difference in the postoperative radiological and clinical results of patients who underwent different incision options. However, considering the selection of different incisions according to the type of fracture, this situation was considered quite natural. The most critical concern of orthopedic surgeons regarding the anterior midline incision is that the fracture cannot be adequately controlled and skin necrosis may occur. However, our study shows that adequate reductions can be achieved with comparable complication rates using this method. No infection or skin necrosis was observed with the double and single midline incisions. Guild et al. (14) compared single and double midline incision techniques in tibial bicondylar plateau fractures. They found no significant difference in revision and infection rates. Similar findings were reported in a comparative study involving hyperextension injuries in the bicondylar plateau of the tibia (16). In addition to achieving comparable clinical and radiological results, our study highlights that the use of a single anterior midline incision reduces surgical time by approximately half. Although we did not observe

Table 1. Comparison of patients grouped using the Schatzker classification according to age, gender and surgical incision selection

	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	p-value
Age	38.67±4.04	42.91±12.48	40.67±14.05	47.17±7.44	50.89±17.78	45.06±12.02	0.951*
Gender							
Male	0 (0%)	15 (68%)	3 (100%)	5 (83%)	5 (56%)	7 (41%)	0.054**
Female	3 (100%)	7 (32%)	0 (0%)	1 (17%)	4 (44%)	10 (59%)	
Side							
Right	3 (100%)	3 (14%)	1 (33%)	2 (33%)	5 (56%)	3 (18%)	0.014**
Left	0 (0%)	19 (86%)	2 (67%)	4 (67%)	4 (44%)	14 (82%)	
Surgical technique							
Lateral incision	3 (100%)	20 (91%)	3 (100%)	0 (0%)	0 (0%)	6 (35%)	0.001**
Medial incision	0 (0%)	0 (0%)	0 (0%)	3 (50%)	0 (0%)	2 (12%)	
Midline incision	0 (0%)	2 (9%)	0 (0%)	3 (50%)	1 (11%)	5 (29%)	
Posterior incision	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (33%)	0 (0%)	
Lateral + medial	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (33%)	2 (12%)	
Medial + posterior	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)	2 (12%)	
Lateral + posterior	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)	

*Kruskal-Wallis-H test
**Pearson's chi-square test

Table 2. Comparison of clinical and radiological results of patients grouped using the Schatzker classification							
	Type 1	**Type 2**	**Type 3**	**Type 4**	**Type 5**	**Type 6**	**p-value**
Mean time from injury to surgery days	2±0	4.73±2.07	4.33±0.58	6.17±4.62	3.56±2.3	8.94±8.61	0.591*
Mean follow up months	31±0	16.86±9.52	12.67±9.87	22.5±12.41	15±9.14	22±14.9	0.188*
Mean operative time min	120±0	160.23±41.24	75±39.69	215±108.03	238.89±177.94	157.06±50	0.188*
Time to clinical union months	4±0	4.5±1.7	2.67±1.15	5.33±1.75	4.11±1.76	5.65±2.83	0.162*
Time to radiological union weeks	6±0	7.18±1.3	4.67±2.89	8±1.1	5.67±1.87	8.24±3.19	0.022*
Mean VAS	0±0	3.27±2.27	0±0	3.67±1.21	2.56±1.42	4.12±1.87	0.001*
Femoral tibial angle	2±0	5.77±4.6	5±1	6±4.05	3.89±2.37	3.88±2.26	0.306*
Posterior slope angle	75±0	82.5±3.92	81.67±1.53	81.17±4.12	82.33±2.87	82.06±3.83	0.053*
Hospital for special surgery knee rating scale	98±0	80.18±14.09	100±0	75.83±9.06	75.67±16.81	73.71±12.46	0.007*
Rasmussen score	44±0	38.73±4.96	47.33±1.15	34.5±3.45	39.33±7.04	36.76±6.18	0.012*
Flexion knee joint	160±0	131.14±15.65	150±0	107.5±27.7	121.67±20.77	123.24±17.41	0.001*
A extension knee joint	0±0	-2.27±2.73	0±0	-5.83±7.36	-2.56±2.51	-1.82±2.32	0.076*
Pivot shift test							
+	0 (0%)	4 (18%)	0 (0%)	2 (33%)	1 (11%)	1 (6%)	0.507**
-	3 (100%)	18 (82%)	3 (100%)	4 (67%)	8 (89%)	16 (94%)	
Lachman test							
+	0 (0%)	8 (36%)	0 (0%)	2 (33%)	1 (11%)	3 (18%)	0.379**
-	3 (100%)	14 (64%)	3 (100%)	4 (67%)	8 (89%)	14 (82%)	
Complication							
None	3 (100%)	22 (100%)	3 (100%)	3 (50%)	5 (56%)	11 (65%)	0.01**
Skin necrosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Malunion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Non union	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	
Infection	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (18%)	
Traumatic arthritis	0 (0%)	0 (0%)	0 (0%)	2 (33%)	4 (44%)	3 (18%)	
*Kruskal-Wallis-H test **Pearson's chi-square test							

any infection after a single midline incision in our study, infection rates ranged between 5-88% in other studies with larger patient series (1,17,18). Although a higher rate of soft tissue abrasion may increase the likelihood of infection, a shorter surgical time may balance this disadvantage. In a study analyzing the correlation between surgical duration and infection rates following open reduction and fixation of tibial plateau fractures, a significant relationship between surgical duration and infection occurrence was demonstrated (19). In this context, it is conceivable that the surgical infection rates of anterior single incisions may be lower or the same as those of double incisions.

Bicondylar tibial plateau fractures, similar to other intra-articular fractures, require rigid fixation. In high-energy fractures, the surgeon's primary goal is to achieve rigid fixation while minimizing soft tissue problems. The anterior midline method with full-thickness incisions allows rigid fixation without compromising the blood supply to the skin. According to a recent study, single and double incisions have the same risk of wound complications; however, double incisions allow greater joint restoration (1). However, in this study, anatomical joint reduction in bicondylar fractures was accomplished with a single anterior incision, and there was no reduction loss during follow-up with rigid fixation. The gold standard in tibial plateau fractures is to protect the soft tissue, ensure joint reduction, and obtain adequate stability (2). For all these purposes, an anterior midline single incision is an important option that should be considered in bicondylar tibial plateau fractures.

Study Limitations

The limitations of our study are that the patient population is limited, more specific groups cannot be created according to fracture types and surgical incision

Table 3. Comparison of clinical and radiological results of patients grouped according to surgical incision selection

	Surgical approach								
	Lateral	**Medial**	**Midline**	**Posterior**	**Lateral + medial**	**Medial + posterior**	**Lateral + posterior**	**Total**	**p-value**
Rasmussen score	38.54±5.87	27±0	39±3.85	31±0	41.6±5.03	44.33±1.15	46±0	38.53±5.92	0.002*
Hospital for special surgery knee rating scale	80.86±14.24	52±0	82.73±10.86	58±0	72.6±9.66	89.33±1.15	98±0	79.12±14.49	0.002*
Mean VAS	3.34±2.36	7±0	2.18±1.33	4±0	2.6±0.89	2.33±0.58	0±0	3.12±2.13	0.053*
A extension knee joint	-2.57±3.98	0±0	-1.36±2.34	-5±0	-2±2.74	-3±0	0±0	-2.32±3.38	0.562*
Flexion knee joint	126.57±22.42	115±0	131.36±18.04	100±0	131±10.84	146.67±2.89	150±0	127.5±20.7	0.094*
Time to radiological union weeks	7.43±2.1	13±0	6.64±2.01	5±0	6±0.71	7.33±2.31	3±0	7.15±2.31	0.001*
Time to clinical union months	5.09±2.45	7±0	3.73±1.1	4±0	4.2±0.84	5.33±2.31	2±0	4.73±2.13	0.250*
Complications									
None	26 (74.3)	2 (100.0)	10 (90.9)	0 (0.0)	5 (100.0)	2 (66.7)	1 (100.0)	46 (76.7)	0.239**
Non-union	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	
Infection	3 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.0)	
Traumatic artritis	5 (14.3)	0 (0.0)	0 (0.0)	3 (100.0)	0 (0.0)	1 (33.3)	0 (0.0)	9 (15.0)	
Instability	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	

*Kruskal-Wallis-H test
**Pearson's chi-square test

selection, and the study is retrospective and a single-center study. Despite these limitations, this is one of only a few trials on anterior midline incision for treating tibial plateau fractures.

Conclusion

Open reduction and internal fixation using a single anterior midline incision in the surgical treatment of bicondylar plateau fractures can be safely performed in selected patients. Because complications such as infection or skin necrosis are not observed with this surgical method, we can say that this surgical method can be safely used in selected patients; however, we still believe that studies with larger patient populations are needed.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, revised in 2013, and approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (decision no.: 2023-276, date: 27.12.2023).

Informed Consent: The study is retrospective and a single-center study.

Authorship Contributions

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

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Original Article

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Evaluation of Pulmonary Embolism Risk Stratification Scores in Patients Admitted to the Internal Medicine Clinic

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Abstract

Aim: Pulmonary embolism (PE) is a common cardiovascular emergency, and a broad range of conditions must be included in the differential diagnosis because of the frequent and highly non-specific symptoms of PE. Risk stratification scores were created because unnecessary procedures are often performed during the diagnostic process. Modified Geneva and Wells scores are widely used scoring systems, but their reliability remains controversial. In our study, we evaluated these scoring systems according to the predictability of the diagnosis and its correlation with mortality in patients diagnosed with PE.

Methods: Our study was conducted in a single center with a retrospective, cross-sectional design. We included 108 patients diagnosed with PE and admitted to the internal medicine clinic between January 2016 and October 2019. The median follow-up period was 19 months. The patients' initial demographic, clinical, and radiological findings were recorded. The modified Wells, Wells, and Modified Geneva risk scores were calculated according to this information. The relationships among laboratory findings, risk scores, and mortality were evaluated.

Results: It was determined that 48 (44%) of the patients died, and 57 (53%) survived during the follow-up period. The death or survival information of three patients could not be obtained because of their foreign nationality. There was no significant difference between the mean ages of female and male patients (p=839). The relationship between patient evaluations according to the score systems and mortality was examined. The analysis determined that only the Modified Geneva score had a significant association with mortality (p=0.001). In contrast, the Wells and Modified Wells scores had no statistically significant relationship with mortality (p=0.396 and 0.391, respectively). Age, malignancy, and dyspnea at admission were independent factors affecting mortality (p=0.001, 0.026, and 0.023, respectively).

Conclusion: The risk stratification scoring systems' diagnosis and mortality predictability are insufficient. These scoring systems must be improved to prevent underdiagnosis and unnecessary testing.

Keywords: Pulmonary embolism, mortality, risk stratification

Introduction

Pulmonary embolism (PE) is a common cardiovascular emergency in which the pulmonary artery or its branches are blocked by substances originating from any body part (such as a thrombus, air, tumor, or fat). The most common cause is occlusion by a thrombus (1). Unnecessary tests performed during the diagnostic process lead to complications and financial losses. While PE mortality is 25-30% in untreated cases, this rate drops to 2-8% in treated patients (2,3). It is very often confused with other diseases at the admission clinic. Differential diagnoses are broad because PE findings are non-specific and are expected in different diseases (4-6). In addition, most cases do not present with the classic symptoms of PE, such as shortness of breath, chest pain, and hypoxia (7). All conditions included in this differential diagnosis (such as acute coronary syndrome, acute pericarditis, acute respiratory distress syndrome, and dilated cardiomyopathy)

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should be considered as alternative diagnoses in patients with suspected PE.

For this reason, risk scoring systems have been created. The widely accepted ones are the revised Geneva, Wells, and modified Wells scores (8). However, the reliability of these scoring systems in predicting both diagnosis and possible mortality risk remains controversial.

This study aimed to compare the predictive features of PE, evaluate their relationship with mortality in patients hospitalized with the suspicion or diagnosis of PE, and assess the factors affecting mortality in patients hospitalized with the diagnosis of PE during follow-up.

Materials and Methods

Compliance with Ethical Standards

The study protocol and subject matter were reviewed and approved by the Institutional Ethics Committee of the University of Health Sciences (ref no./date: 243/2019). The ethics committee anonymized and approved the database information without needing consent.

Study Design

Our study was conducted in a single center with a retrospective, cross-sectional design. A total of 108 patients, 60 (55.6%) women and 48 (44.4%) men, hospitalized with a diagnosis of PE in the Internal Medicine Clinic of University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital between January 2016 and October 2019, were included in our study. PE was diagnosed or excluded by evaluating the patients' anamnesis, physical examination findings and biochemistry, echocardiography, and pulmonary computed tomography (CT) angiography examinations. Patients hospitalized with a preliminary diagnosis of PE and diagnosed with a different condition during hospitalization and those under the age of 18 were excluded from the study. According to the data obtained from the hospital information operating system, the patient's age, gender, family history, and existing comorbidities (such as hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, inflammatory bowel disease, cirrhosis, viral hepatitis, malignancy, venous thromboembolism, rheumatological diseases, and autoimmune diseases) were recorded. The patients' complaints, past medical history, vital signs at admission, and imaging results (Doppler ultrasonography, pulmonary CT angiography, echocardiography) were recorded. Serum urea, creatinine, uric acid, alanine aminotransferase, aspartate aminotransferase, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, sodium, potassium, calcium, total protein, albumin, blood gas parameters, C-reactive protein (CRP), procalcitonin levels, and hemogram results of the patients were recorded. The Wells Score, Modified Wells Score, and Modified Geneva Score were calculated based on the information recorded when the patients first applied to the emergency department. The predictive properties of these scoring systems were evaluated. Patients were followed for a median of 19 months to determine whether mortality occurred after discharge and, if so, why. Mortality information was obtained using the national death notification system and the hospital information operating system. Mortality data could not be obtained for the three patients because they were not Turkish citizens. Therefore, analyses regarding mortality were performed on 105 patients (Figure 1).

Statistical Analysis

All data obtained in the study were recorded on a computer and evaluated using the Statistical Package for Social Sciences for Windows 20.0. In descriptive statistics, continuous variables are expressed as means. Standard deviations and categorical variables are expressed as percentages. Their distribution was evaluated using the Kolmogorov-Smirnov test. To compare the two groups, numerical data with a normal distribution were evaluated using the Student's t-test. If the distribution was abnormal, the Mann-Whitney U test was used for pairwise

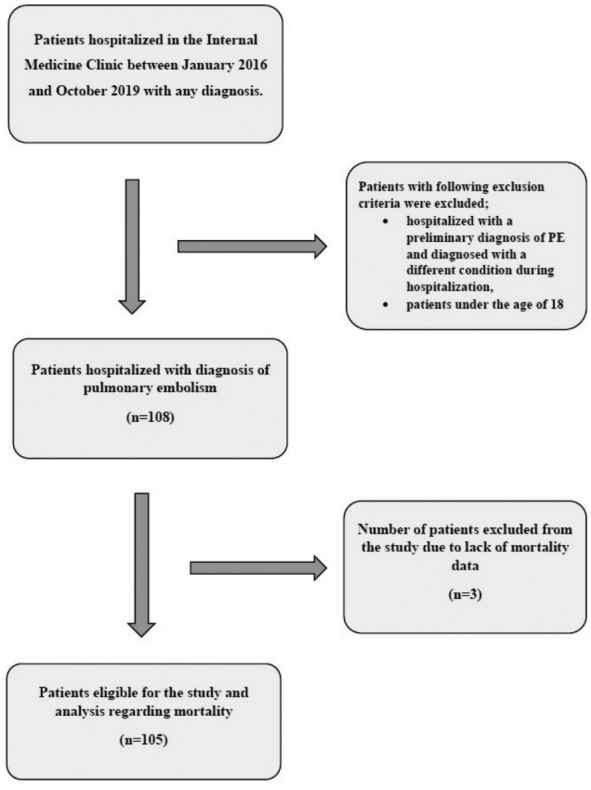


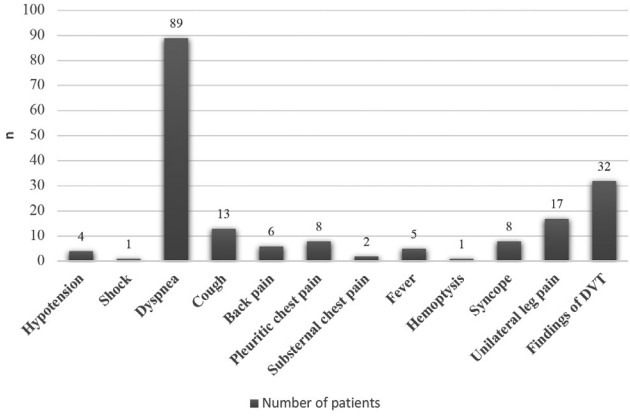
Figure 1. Flow diagram of patient selection
PE: Pulmonary embolism

comparisons of numerical data. Categorical variables were assessed using the chi-square test. P<0.05, or 95% confidence interval, was considered statistically significant.

Results

A total of 108 patients, 60 women (55.6%) and 48 men (44.4%), were included in the study. The average age was calculated as 66.34±16.5 [minimum (min.) 24, maximum (max.) 91]. Patients admitted with a diagnosis of PE were followed for a median of 19 months after discharge from the hospital (min.: 0, max.: 51 months). Forty-three of the patients (39.8%) were under 65 years of age, and 65 (60.2%) were over 65 years of age. A patient was pregnant. Thirteen patients had an operation history within the last six months. There were bone fractures in the lower extremities in four patients. Eight had a hip or knee prosthesis history. Eighteen patients had solid malignancies, and two patients had hematological malignancies. Five patients had a history of trauma within the last six months. Two patients had a history of laparoscopic surgery within the previous three months. There was immobilization in the history of 22 patients (20.4%). Concomitant infections were detected in 63 patients (52.3%). Respiratory failure was detected in 16 patients (14.8%) at admission or during hospitalization. Atrial fibrillation was present in 10 patients (9.3%). A provoking cause was detected in 16 patients (14.8%). Four patients presented with hypotension, and one patient presented with shock. Eighty-nine patients (82.4%) had shortness of breath at admission. Cough was present in 13 patients (12%), and 6 had back-chest pain (5.6%). Fever was detected in 5 patients (4.6%). Unilateral leg pain was observed in 17 patients (15.7%), and ultrasound imaging revealed deep vein thrombosis in 32 patients (29.6%) (Graphic 1).

It was determined that 48 patients died and 57 survived. Ten patients died within the first month after the diagnosis of PE. Four patients died during hospitalization.



Graphic 1. Symptoms and findings at admission

The average age of the non-survived patients was 74.9±10.8 years. The average age of surviving patients was found to be 60.04±17.2 years (p<0.001). White blood cell, neutrophil, CRP, and lactate values were higher in the patient group who did not survive during follow-up (p=0.008, 0.004, 0.023, and 0.039, respectively). Triglyceride and HDL cholesterol values were elevated in patients who survived (p=0.020 and 0.014, respectively), as shown in Table 1.

The Cox regression analysis performed to evaluate the risk factors affecting mortality showed that for those over 65 years of age, mortality risk increased by 3.78 times (p=0.001). We also observed that having malignancy increased mortality by 2.03 times (p=0.26), and having respiratory failure when the patient first came to the hospital increased mortality by 2.23 times (p=0.023) (Table 2).

According to the Modified Geneva Score, 14 patients were classified as low-risk. There were no deaths among

Table 1. Relationship between demographic data and initial laboratory parameters and mortality

Demographic data and laboratory values	Survivor (n=57)	Non-survivor (n=48)	p-value
Age	60.04±17.22	74.90±10.84	**<0.001**
Age >65 [n (%)]	24 (42.1%)	40 (83.3%)	**<0.001**
Sex (F/M)	32/25	26/22	0.839
Hemoglobin (g/dL)	12.01±1.83	11.75±2.3	0.534
WBC (10^3 uL)	8.99±3.15	11.6±5.96	**0.008**
Neutrophils (10^3 uL)	6.41±3.11	9.18±5.71	**0.004**
Lymphocyte (10^3 uL)	1.71±0.68	1.46±0.72	0.070
Glucose (mg/dL)	130.81±70.57	141.18±76.2	0.471
Urea (mg/dL)	40.05±20.26	61.8±30.59	**<0.001**
Creatinine (mg/dL)	0.86±0.34	1.02±0.55	0.067
Uric acid (mg/dL)	6.07±1.87	6.89±2.69	0.112
CRP (mg/L)	56.85±62.65	89±79.38	**0.023**
Glucose (mg/dL)	130.81±70.57	141.18±76.2	0.471
Total cholesterol (mg/dL)	179.7±47.27	160.33±42.65	**0.050**
Triglyceride (mg/dL)	156.42±82.34	121.49±46.09	**0.020**
HDL (mg/dL)	38.76±10.88	33.02±10.15	**0.014**
LDL (mg/dL)	112.56±37.35	101.74±36.45	0.181
PaO_2 (mmHg)	85.23±31.1	80.44±36.5	0.525
$PaCO_2$ (mmHg)	38.72±35.52	33.27±7.5	0.298
SpO_2 (%)	93.9±5.5	93.06±5.1	0.478
Lactate (mmol/L)	1.39±0.7	2.12±1.88	**0.039**
pH	7.43±0.05	7.43±0.1	0.885
Homosistein	15.06±3.9	5.35±7.56	**0.008**

F: Female, M: Male, CRP: C-reactive protein, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, PaO_2: Partial pressure of oxygen, $PaCO_2$: Partial pressure of carbon dioxide, SpO_2: Oxygen saturation

them. While 33 of 72 patients (47.1%) who were considered medium risk were alive, 37 (52.9%) died. According to this scoring system, 77.1% of the total mortality consisted of patients evaluated as medium risk. Twenty-two patients were assessed as high-risk. Mortality information was obtained for 21 patients. It was determined that ten patients (47.6%) survived and 11 patients (52.4%) died (p=0.001) (Tables 3 and 4).

Table 2. Cox regression analysis of factors affecting mortality

	Sig.	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
Age >65	**0.001**	3.78	1.76	8.11
Presence of malignancy	**0.026**	2.03	1.08	3.80
Admission with dyspnea	**0.023**	2.23	1.11	4.45

CI: Confidence interval

Table 3. Distribution of patients according to the clinical scoring systems

Clinical Scoring Systems	Number of patients n (%)
Modified Geneva Score	
Low probability	14 (13%)
Intermediate	72 (66.7%)
High probability	22 (20.3%)
Wells Score	
Low probability	44 (40.7%)
Intermediate	62 (57.4%)
High probability	2 (1.9%)
Modified Wells Score for PE	
PE unlikely	87 (80.6%)
PE likely	21 (19.4%)

PE: Pulmonary embolism

Table 4. Association between clinical scoring systems and mortality rates

		Survivor (n=57)	Non-survivor (n=48)	p-value
Modified Geneva Score	Low probability	14	0	**0.001**
	Intermediate	33	37	
	High probability	10	11	
Wells Score	Low probability	20	23	0.396
	Intermediate	36	24	
	High probability	1	1	
Modified Wells Score	PE unlikely	45	41	0.391
	PE likely	12	7	

PE: Pulmonary embolism

According to the Wells Score, out of 44 low-risk patients for whom mortality information was available, 20 were found to be alive and 23 were found to be dead. Patients determined to have low risk constituted 21.9% of the total deaths. Sixty-two patients were considered to have medium risk. It was determined that 36 (60%) of the patients who were considered to have medium risk survived, and 24 (40%) had died. In total, 50% of those who died were patients whose Wells score was determined to be at medium risk. Two patients were evaluated to have high risk, and one survived (p=0.396) (Tables 3 and 4).

According to the Modified Wells Score, 87 patients (80.6%) were evaluated as PE unlikely and 21 (19.4%) as PE likely. It was determined that 45 (52.3%) patients survived and 41 (47.7%) patients died among the patients who were considered PE unlikely. Mortality information for one of them could not be obtained. Deaths accounted for 85.4% of the total mortality among patients with unlikely PE. It was determined that 12 (63.2%) of the patients evaluated as having possible PE survived, and 7 (36.8%) died. 14.6% of the total mortality consisted of patients considered PE likely (p=0.391) (Tables 3 and 4).

Discussion

Pulmonary embolism is a cardiovascular emergency that is difficult to diagnose unless suspected. It is also a disease for which primary prevention can be provided and treated.

In our study, no statistically significant difference was found regarding the gender distribution of patients. In a study by Santosa et al. (9) with PE patients in Germany, PE incidence was not different between both genders.

In the regression analysis, we found that patients over 65 years of age had a significant relationship with mortality. In addition, when we did not use 65 as the cut-off age, mortality increased with age. Studies have shown that mortality in patients with PE is generally associated with malignancy, accompanying chronic cardiopulmonary comorbidities, and advanced age (10,11). We found that concomitant malignancies were also associated with mortality. This condition may be caused by malignancies, and sometimes chemotherapeutic agents increase the risk of thromboembolism.

In different studies, it has been observed that short-term mortality in treated patients diagnosed with PE can decrease below 8% (3,12). The mortality rate among those treated was 45.7% in our study. This may be because of the high average age of our patients, multiple comorbidities, and the fact that our study examined long-term mortality in addition to the short period after diagnosis.

Triglyceride, HDL, and LDL cholesterol levels were higher in the surviving patient group. It was thought

that this was because patients who developed mortality had worse nutritional status due to accompanying comorbidities, increasing age, and, therefore, lower lipid levels. In some studies conducted with different patient groups, triglyceride and LDL cholesterol levels were lower in patients who developed mortality, supporting the results of our research (13,14).

In our study, 82.4% had shortness of breath at admission. This was followed by tachycardia, cough, pleuritic chest pain, and hemoptysis. Similarly, in the article in which Dalen JE interpreted the results of the Prospective Investigation of PE Diagnosis study, it was stated that dyspnea was the most common disease in patients with PE, followed by tachypnea, tachycardia, chest pain, cough, and hemoptysis (15). Compared with the aforementioned large-scale study, the proportionally lower incidence of symptoms and findings other than shortness of breath may be because our patients were hospitalized in the internal medicine clinic and did not require intensive care. As mentioned before, the spectrum of clinical findings is highly variable depending on the severity of the disease (12). Although some studies found that symptoms were not associated with mortality, a study conducted by Zuin et al. (16) showed that acute onset dyspnea and chest pain were associated with mortality. Omar et al. (17) found that hospital admission for syncope was associated with the severity of pulmonary embolism.

Because the symptoms and clinical findings used in calculating these risk scores can be seen in many other diseases, and PE may present with different presentations, we believe that these scoring systems are not sufficiently effective in diagnosis and treatment decisions. Other studies have also reached the same results (18,19). Despite the diagnosis of PE in all our patients, the predictive features of these scoring systems are not up to the mark.

According to the modified Wells score, the diagnosis of PE was considered unlikely in 80.6% of the patients, and the diagnosis of PE was deemed unlikely in 40.7% of the patients. According to the modified Geneva score, PE diagnosis was highly likely in only 20.3% of the patients. In contrast to our study, Naderi et al.'s (20) study from 2023 found that the Geneva score used to assess the risk of PE was insufficient to predict mortality in patients diagnosed with PE. In the study conducted by Girardi et al. (18) with patients hospitalized in intensive care with a diagnosis of PE, these scoring systems were found to be unreliable in predicting the diagnosis. Ishimaru et al. (21) found that these clinical scores had low sensitivity in the diagnosis of PE and had limited prognostic values.

Our study found that the Modified Geneva score had a statistically significant relationship with long-term mortality. According to this score, no deaths among patients were considered low-risk. It was determined that the modified Wells and Wells scores did not have a significant relationship with mortality, consistent with previous studies. This can be attributed to the fact that there is no age in the Wells scoring system, and age is among the criteria in the Modified Geneva system.

Study Limitations

There are some limitations to our study. Because this was a retrospective study, the data were based on hospital information and operating system records. The study only reflects patients admitted to the internal medicine clinic; therefore, it excludes patients who are followed up in the intensive care unit with a more severe course. In addition, the small number of patients may reflect something other than the general population.

Conclusion

Pulmonary embolism is a disease that may have high mortality, and the possibility of missing a diagnosis is increased. However, risk stratification scores cannot provide the desired level of prediction when making a diagnosis. Novel scoring systems, or biomarkers, should be developed to prevent missed diagnoses and unnecessary examinations.

Ethics

Ethics Committee Approval: The study protocol and subject matter were reviewed and approved by the Institutional Ethics Committee of the University of Health Sciences (ref no./date: 243/2019).

Informed Consent: The ethics committee anonymized and approved the database information without needing consent.

Authorship Contributions

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

Conflict of Interest: No conflicts of interest were declared by the authors.

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Case Report

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Succesful Resusication with Veno-arterial Extracorporeal Membrane Oxygenation in Cardiac Arrest After Metformin Overdose: A Case Report and Current Literature Review

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Abstract

Metformin can cause gastrointestinal system symptoms, hyperlactatemia, and lactic acidosis even at therapeutic doses, and toxicity can result in serious complications and high mortality with massive infections. The prognosis for undifferentiated lactic acidosis is poor, with an expected case fatality rate of 30-50%. We present the case of a patient who was admitted to the emergency department with a large intentional metformin overdose. The patient was initially asymptomatic, but deteriorated rapidly during the observation period, developed cardiac arrest, and required extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy. Considering this case, we aim to emphasize that metformin overdoses may worsen in the late stages and that the follow-up period should be performed in a monitored setting that can provide, if needed, advanced cardiac support therapies such as ECMO.

Keywords: Metformin overdose, suicide, lactic acidosis, extracorporeal membrane oxygenation, continuous renal replacement therapy

Introduction

Metformin is a biguanide-derived drug and is the most commonly used oral antidiabetic drug for treating type 2 diabetes worldwide (1). Biguanides lower blood glucose levels by decreasing glucose absorption in the intestine by decreasing gluconeogenesis, and peripheral use of glucose. Because biguanides do not enhance insulin release, disorders of glucose homeostasis are rare with metformin, as occurs with the sulfonylurea and meglitinide classes of medications (2). Metformin can cause gastrointestinal symptoms, hyperlactatemia, and lactic acidosis even at therapeutic doses. Toxicity can lead to serious complications and high mortality with massive ingestion. The prognosis for undifferentiated lactic acidosis is poor, with an expected case fatality rate of 30-50% (3).

In this case report, we present the case of a patient admitted to the emergency department with a large intentional metformin overdose. The patient was initially asymptomatic but deteriorated rapidly during the observation period, developed cardiac arrest, and required extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy. Considering this case, we would like to emphasize that metformin overdose may worsen in the late stages, and the follow-up should be performed in a monitored setting that can provide advanced cardiac support therapies, such as ECMO, if needed.

Case Report

A 55-year-old, 90-kg male patient with a medical history of diabetes and hypertension was admitted to the emergency department because of an intentional

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ingestion of 90 g of metformin (90 tablets of Glifor® 1000 mg, Bilim Pharmaceuticals) approximately 8 hours prior to presentation. On arrival, he had a Glasgow Coma Scale of 15 and was cooperative and oriented. He expressed only slight discomfort in his abdomen. The vital signs of the patient were recorded as follows: blood pressure of 166/95 mmHg, heart rate of 95 beats/min, respiration rate of 20 breaths/min, temperature of 36.7 °C, and oxygen saturation of 97% on room air. The patient's physical examination did not reveal any significant findings. The electrocardiogram indicated sinus rhythm. The blood gas analysis was normal except for the lactate level, which was 9.0 mmol/L. The biochemical parameters were unremarkable except for the creatinine level (Table 1). The other laboratory results were normal. The patient was admitted to the medical toxicology intensive care unit (ICU) for close monitoring and treatment. A jugular vein dialysis catheter and a subclavian central venous catheter were placed. Intra-arterial catheterization was performed for invasive blood pressure monitoring. Based on the amount of metformin consumed and the lactate elevation at the time of admission, the patient was determined to have severe toxicity. The patient's oral intake was stopped, and a low-dose dextrose treatment was administered to prevent the development of hypoglycemia. 200 cc/h isotonic maintenance fluid and 50 cc/h %5 dextrose therapy were started. During follow-up, urine output was 200 mL/h. Blood gas was checked at regular intervals, and the results are shown in Table 1.

At the 12th hour of admission, sudden hypotension (65/40 mmHg) occurred on intra-arterial monitoring. Intravenous bolus fluid administration was performed using the Trendelenburg position. As the blood pressure did not increase, maximum doses of norepinephrine and dopamine were started, respectively. Despite this, blood pressure was 65-70/40-45 mmHg. At the 15th minute of hypotension development, the blood gas control showed a pH of 7.40, bicarbonate of 19.6 mEq/L, glucose of 98 mg/dL, and lactate of 8.4 mmol/L. A seizure lasting 5 seconds occurred in the 20th minute of an unstable condition. Bradycardia and sudden cardiac arrest occurred after the seizure. Endotracheal intubation was performed, and advanced cardiac life support was performed by administering 50 mEq of bicarbonate of soda every 5 minutes. After 9 cycles of cardiopulmonary resuscitation, spontaneous circulation was achieved in the 18th minute. In the follow-up period, he had three more seizures that lasted for approximately 10 seconds each. The patient

Table 1. Clinical course, arterial blood gas results and inotropic support of the patient during hospitalization.

		Laboratory Values	pH	Bicarbonate (mEq/L)	Lactate (mmol/L)	Glucose (mg/dL)	Creatinine (mg/dL)	CK (U/L)
	Reference Values		7.35-7.45	22-26	0.5-2	74-106	0.7-1.2	0-190
Time	**Course of events**	**Treatment**						
-8 h	Metformin ingestion	-						
0	Admission	-	7.37	20	9	160	1.22	171
2 h	Stable clinic	-	7.31	24.1	7.6	243	-	-
6 h	Stable clinic	-	7.37	20.6	9.4	161	-	-
10 h	Stable clinic	-	7.39	21.6	7.7	104	1.42	174
12 h	Hypotension	N/D	7.40	19.6	8.4	98	-	-
13 h	Cardiac arrest	N/D/E	**7.04**	12.3	**21**	138	-	-
14 h	ECMO + CRRT	N/D/E	7.12	**10.7**	**19**	135	-	-
18 h	ECMO + CRRT	N/D/E	7.13	12.6	**15**	161	-	-
30 h	ECMO + CRRT	N/D	7.34	18.3	**14**	167	-	-
36 h	ECMO	D	7.36	27.5	6.8	161	0.97	**830**
48 h	ECMO	D	7.47	33	4.5	157	-	-
54 h	ECMO	-	7.48	37.2	2.1	135	-	-
72 h	-	-	7.44	37.1	1.9	153	0.67	**5498**
96 h	-	-	7.46	33.6	1.5	164	0.83	**8630**
144 h	Extubation	-	7.47	23	1.6	165	0.95	**5033**
240 h	Discharge	-	7.40	24.9	1.3	145	0.71	685

CK, creatine kinaz; CRRT, continuous renal replacement therapy; D, dopamine; E, epinephrine; ECMO, extracorporeal membrane oxygenation; N, norepinephrine.

was initiated on a sodium bicarbonate drip at a rate of 30 milliequivalents per hour. The arterial blood gas analysis revealed a pH of 7.05, a bicarbonate level of 13.3 mEq/L, a glucose level of 208 mg/dL, and a lactate level of 19.0 mmol/L. Despite the administration of a full dose of noradrenaline and an adrenaline infusion, no hemodynamic improvement was observed. The patient's blood pressure was 60/40 mmHg. A consultation for cardiovascular surgery was performed, and the patient was placed on venoarterial ECMO in the ICU. Continuous renal replacement therapy was initiated promptly. Based on the bedside ultrasonography, the diameter of the inferior vena cava was 14 mm, so fluid therapy was continued at the same infusion rate.

In the first 2 hours of ECMO, blood pressure remained at 70-75/45-50 mmHg. From the second hour of ECMO, the blood pressure progressively increased every hour, with a systolic blood pressure of 10 mmHg/h and a diastolic blood pressure of 5 mmHg/h. The heart rate was in the range of 65-70/min. Blood pressure reached 140/90 mmHg at the 10th hour of triple (adrenalin, noradrenalin, and dopamin) inotropic support and ECMO. Starting from the 10th hour of ECMO, inotropic support was gradually reduced. Adrenaline infusions at the 16th hour of ECMO, neuradrealin infusions at the 24th hour, and finally dopamine infusions at the 36th hour of ECMO were stopped. Table 1 displays the times for the initiation and discontinuation of inotropic support therapy. At the 58th hour of treatment, the patient was successfully weaned off ECMO. On the 6th day, the patient's laboratory values improved and no additional pathology developed, leading to successful extubation. There was no pathology in the vital parameters or system examinations. Psychiatric recommendations were made. On the 10th day of follow-up, the patient was discharged without any sequelae. Informed consent was obtained from the patient for the publication of this case at the time of discharge.

Discussion

Despite stable conditions, metformin overdose can result in unexpected and sudden cardiopulmonary arrest in the late stages. So, earlier extracorporeal elimination methods like hemodialysis can be thought about even when there are no symptoms and only a mild rise in serum lactate in a metformin overdose.

Metformin overdose causes symptoms such as nausea, vomiting, abdominal pain, and myalgia in mild cases; in severe toxicity, lactic acidosis, renal failure, respiratory failure, liver failure, and ventricular dysrhythmias may occur. Hypoglycemia due to the use of antidiabetic drugs and hyperglycemia due to the underlying disease can be seen. However, metformin does not cause hypoglycemia. In this study, the amount of metformin taken and the high lactate level at the time of admission were predictive of a poor outcome. Therefore, the oral intake of the patient was stopped, and a low-dose dextrose treatment was administered to prevent the development of hypoglycemia in the follow-up period. The most common and life-threatening complication of metformin toxicity is lactic acidosis. Lactic acidosis occurs because of the activation of anaerobic metabolism when mitochondrial oxygenation cannot be achieved. The etiology of lactic acidosis includes several disease processes. These include sepsis, hemorrhagic shock, cardiac arrest, trauma, intoxication, burns, diabetic ketoacidosis, cancer, intense muscular activity, and mitochondrial toxicants such as cyanide (4). Metformin overdoses can cause type B lactic acidosis in the early period, and type A lactic acidosis can be seen in the late period due to hypotension and hypoxia due to its cardiovascular effects.

The therapeutic adult dose of metformin is a maximum of 2.550 mg/day (5). In this study, 90 g of metformin intake at one time constitutes the expectation that severe toxicity will develop. However, an asymptomatic course was observed for several hours, with abdominal pain that regressed from the time of admission to the emergency department. Isolated serum lactate elevation was accompanied by an asymptomatic course without acidosis with normal hemodynamic and laboratory findings. However, in the late period (20th hour) after ingestion, the hemodynamic status suddenly deteriorated, and cardiac arrest developed with a seizure. In our case, although adequate fluid (200 mL/h) resuscitation was performed after hospitalization, the hypotension that developed at the 20th hour was controlled with inotropes, and ECMO was performed at the 21st hour after the sudden cardiac arrest that developed. Considering the case of a patient who developed pulseless electrical activity and cardiac arrest approximately 25 hours after ingestion in the late period of ingestion (2), in addition to focusing on metabolic acidosis for treating metformin poisoning, it is necessary to be prepared for hemodynamic instability and sudden cardiac arrest that may occur in the late period and to develop preventive treatment protocols.

Extracorporeal methods are used for treating metformin overdoses. However, hemodialysis is mainly applied for correcting metabolic acidosis and not for the removal of metformin in overdoses. The clearance of metformin by renal replacement therapies is controversial because of the high volume of distribution of metformin, up to more than 3 L/kg (63-646 L/kg), as it is predominantly located in the intracellular compartment (6). There is no prognostic correlation between serum lactate levels and metformin-induced lactate acidosis, even at lactate

levels up to 35.5 mmol/L (7). The focus of treatment is to correct metabolic acidosis.

Hemodialysis with bicarbonate replacement fluid has been successfully used for treating metformin-induced acidosis because it not only corrects the acidosis but also efficiently removes metformin from plasma, preventing further lactate overproduction. The EXTRIP criteria for extracorporeal methods of metformin dosage therapy are recommended (8). According to EXTRIP, hemodialysis is recommended in the presence of lactate concentrations >20 mmol/L (recommendation, 1D), >15 mmol/L (suggestion, 2D), or pH ≤7.0 (recommendation, 1D), or pH ≤7.1 (suggestion, 2D). However, in our case, despite high-dose metformin ingestion, the clinical and laboratory progress was mild, the pH level did not deviate from the normal range, and lactate levels did not rise above 9 mmol/L. However, in the following hours, both clinical and laboratory values deteriorated rapidly. The patient experienced cardiopulmonary arrest. Despite administering high-dose vasopressors and inotropes, there was no response. Therefore, the patient was connected to ECMO to stabilize hemodynamics and allow extracorporeal treatments to be applied for the treatment of acute hyperlactatemia and metabolic acidosis.

Recommendations for the management of metformin overdose include supportive care and the correction of metabolic acidosis (9). In our case, it was observed that creatinine values deteriorated in the early period and urine output decreased in the late period of clinical observation (a few hours before hypotension). Increased urea-creatinine values and decreased urine output can also be considered indicators of a poor prognosis. The follow-up period for metformin overdose should be at least 24 hours because the clinical status is normal in the early period, sudden hemodynamic instability and lactic acidosis may occur, and seizures may accompany the late period of clinical observation.

Conclusion

Note that hemodynamics may suddenly and rapidly deteriorate in the late phase of a metformin overdose, leading to severe lactic acidosis. Hemodialysis should be performed in patients with a large volume of ingestion who may experience an abrupt deterioration in condition due to severe metabolic acidosis. Preparation for initiating ECMO should be considered in cases of refractory hypotension and in cases of shock due to a severe metformin overdose.

Ethics

Informed Consent: Informed consent was obtained from the patient for the publication of this case at the time of discharge.

Authorship Contributions

Concept: I.A., R.C., Z.K., S.K., A.S., Design: R.C., Z.K., S.K., A.S., Data Collection or Processing: I.A., R.C., I.H.T., A.S., Analysis or Interpretation: I.H.T., Z.K., S.K., A.S., Literature Search: I.A., I.H.T., Z.K., A.S., Writing: I.A., Z.K., A.S.

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Case Report

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Potential Failure of Novel-generation Oral Anticoagulants in Preventing Pulmonary Embolism: A Case Report and Current Literature Review

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Abstract

In this case report, we evaluated the risk of pulmonary embolism in patients using new-generation anticoagulant drugs. Laboratory tests for follow-up and effective dose measurement of new-generation oral anticoagulants, which are very popular in the medical community today, are not available. Therefore, patients can be at risk for effective doses and drug selection. Although our cases received novel oral anticoagulant treatment, it was determined that they had thromboembolism. We emphasized that we do not have enough information about the complications and effective use of these drugs, which are advantageous in terms of use and side effects. This situation may lead us to negative situations that we cannot manage in the future.

Keywords: Pulmonary embolism, NOAC, warfarine

Introduction

The treatment landscape for pulmonary embolism faces challenges, particularly regarding patient adherence, complicated warfarin titration, high follow-up costs, and the predominant risk group of elderly patients (1). This has led to a shift toward considering novel oral anticoagulants (NOACs) as alternatives to warfarin (2). Novel oral anticoagulants, such as dabigatran (a direct factor IIa inhibitor) and rivaroxaban, apixaban, and endoxaban (direct factor Xa inhibitors), offer comparable efficacy to warfarin but don't need to be dose-monitored and don't interact as much with food. Despite these advantages, there have been reported cases from various countries highlighting potential failures in embolism protection with NOAC treatment. The two cases presented highlight the ongoing controversy surrounding the effectiveness of NOACs as a replacement for warfarin.

Case 1

A 72-year-old female patient presented to our emergency department with complaints of dyspnea. When the patient's medication history was queried, it was found that she was regularly taking furosemide, ramipril, metoprolol, and rivaroxaban 20 mg. It was emphasized that the patient has been consistently using rivaroxaban for 5 years, along with other medications, for the diagnoses of congestive heart failure and atrial fibrillation for approximately 10 years. It was learned that she did not have a history of tobacco or cigarette use or surgery. In the physical examination, respiratory sounds were not detected in bilateral basal breath sounds in pretibial edema ++/++; other system examinations were normal. The patient's vital signs were as follows: blood pressure was 130/80 mmHg, and fingertip oxygen saturation was 97%. In the examinations performed, D-dimer=2.65 mg/L (normal range: 0-0.5

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mg/L), creatinine=0.85 mg/dL, eGFR=68.3 mL/min/m^2, and troponin T=0.037 ng/mL were detected. Bilateral pleural effusion was observed on the chest X-ray, and pulmonary angiography was performed on the suspicion of pulmonary thromboembolism. A computed tomography scan showed a filling defect that was consistent with a pulmonary embolism in the segmental branches that extended to the lower lobe of the right lung. There was also pleural effusion that was about 4 cm thick on the right side and 2 cm thick on the left (Figure 1). The patient, who was admitted to our service for further examination and treatment, was referred to the cardiology department; electrocardiogram: atrial fibrillation, ejection fraction (EF) 50%, PABS: 22 mmHg, tricuspid annular plane systolic excursion (TAPSE): 18 mm on echocardiography (ECHO), widening of the right heart chambers, advanced tricuspid regurgitation, and moderate mitral valve regurgitation were detected. Diltiazem tablets 90 mg 2x1 and furosemide ampoules 20 mg 2x2 were recommended. Deep vein thrombosis was not observed on lower venous Doppler ultrasonography. We started the patient on a dose regimen of 100 IU/kg (1 mg/kg) of enoxaparin sodium twice daily, and based on the international normalized ratio (INR) result, we added warfarin 5 mg loading dose therapy after 24 hours.

Case 2

A 75-year-old female patient had been hospitalized for 15 days because of coronavirus disease (COVID) 1 month before her admission, and after discharge, dyspnea continued and intensified for 1 week. When her anamnesis was questioned, it was learned that she had a diagnosis of hypertension and atrial fibrillation, and she has been regularly using edoxaban 30 mg and furosemide 40 mg for 2 years, metoprolol 50 mg after COVID, and methylprednisolone 16 mg. It was learned that she did not have a history of tobacco or cigarette use or surgery. In the physical examination, respiratory sounds decreased bilaterally, and other system examinations were unremarkable. In the examinations performed, D-dimer: 12.82 mg/L (normal range: 0-0.5 mg/L), creatinine=1.12 mg/dL, eGFR=50.4 mL/min/m^2, troponin T=0.022 ng/mL, and other laboratory tests were found. The patient, who was evaluated in the emergency department and had a Wells score of 3, stable vital signs, and no suspicion of high-risk pulmonary embolism, did not undergo pulmonary angiography because of acute kidney failure. The patient was admitted to our service and started on hydration, and low-molecular-weight heparin at the treatment dose was initiated because of our suspicion of pulmonary embolism. In terms of etiological investigation, lower extremity venous Doppler ultrasonography was performed. A homogeneous acute thrombus was detected in the right superficial femoral vein. She was consulted on cardiology, and ECHO was performed with cardiology consultation; EF 60%, moderate mitral valve regurgitation, moderate-severe tricuspid valve regurgitation, TAPSE: 19 mm, and PABs: 25 mmHg were detected. Diltiazem 90 mg 2x1 was recommended. After hydration, the patient's creatinine levels returned to normal levels. There were "filling defects consistent with thromboembolism, showing lobar and segmental branches extending from the distal of both pulmonary arteries" on the pulmonary angiography (Figure 2). The outpatient follow-up of our patient, who was started on warfarin with INR follow-ups after enoxaparin treatment, continues.

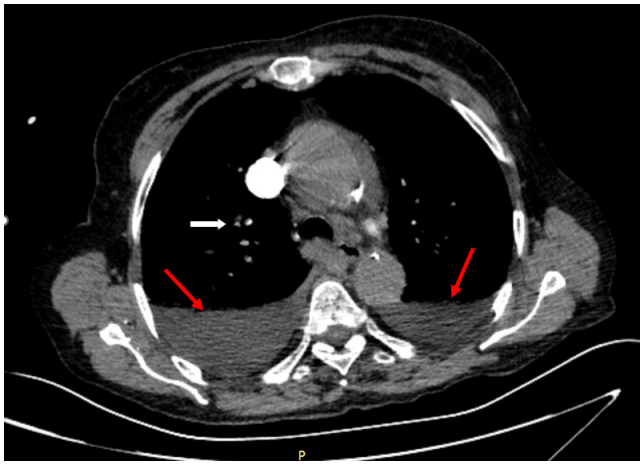

Figure 1. Computed tomography; it was reported as "Filling defect compatible with pulmonary embolism in the segmental branches going to the lower lobe of the right lung and pleural effusion with a thickness of approximately 4 cm on the right and approximately 2 cm on the left bilaterally"

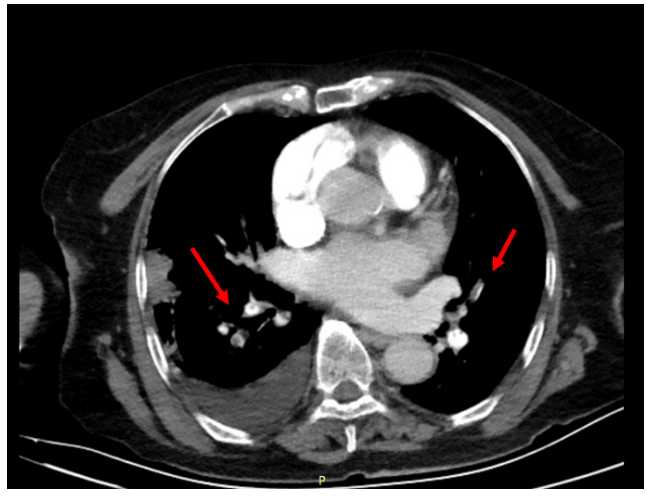

Figure 2. At computer CT filling defects consistent with thromboembolism were observed, showing lobar and segmental branches extending from the distal of both pulmonary arteries
CT: Computed tomography

Discussion

Novel oral anticoagulants have shown that they are equally effective at treating heart disease as warfarin in the EINSTEIN-PE, AMPLIFY-EXT, and HOUKASI-VTE studies. However, there aren't enough studies on them yet because there have only been non-inferior studies on follow-up and antagonist mechanisms and no superior studies (3-6). Randomized double-blind multicenter studies of these drugs, which benefit many patients with their advantages, are not enough in terms of the number of cases.

In these cases, because the patients used their drugs regularly, it was observed that the novel-generation oral anticoagulants they used were insufficient in terms of protection. In terms of embolism risk, we do not have any data or studies in terms of adequate dose intake, except that the use of edoxaban and rivaroxaban once a day facilitates regular use. Especially in our second case, we observed that despite the use of effective anticoagulants, the tendency for advanced inflammation and thrombosis in COVID could not be prevented by the NOACs. In NOACs that do not have follow-up laboratory analysis, it cannot be clearly determined whether the effective dose is reached in patients, as in warfarin (2). In the research conducted by Murtaza et al. (7), no significant difference was found in terms of resolution of the left atrial appendage thrombus between warfarin and rivaroxaban. Simultaneously, in the case series by Rankin et al. (6), potential failures of NOACs for treating pulmonary embolism have been reported.

The biggest question mark in our cases is that patients are more likely to skip at least 4 doses of NOAC drugs, which have a shorter half-life compared with warfarin, due to their multiple drug use and age. Changes in cytochrome p450 metabolism are known to reduce the effectiveness of NOACs, so we should be more careful when using NOACs in people who have used multidrugs (6,8). For this reason, it is imperative that multicenter studies with strict follow-up be increased, rather than a few cases where physician control of the most important discussion topic on NOACs-Emboli Protection and Effective Dose-is weak.

Rather than giving us an approach on this subject, these cases will guide us to start further studies on this subject.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parent for publication of the case report and the accompanying images.

Authorship Contributions

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

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Case Report

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Anesthesia Management in Tracheobronchial Anomaly Case Detected During Tracheotomy: A Case Report

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Abstract

Tracheobronchial anomalies (TBA) are abnormal airway pathologies that originate from the primary branching site of the tracheobronchial tree, and their prevalence is 0.1-0.2%. The tracheal bronchus and accessory cardiac bronchus are among the most common TBAs. Although these anomalies are usually asymptomatic, they manifest as respiratory tract infections, hemoptysis, atelectasis, and respiratory distress. Appropriate identification and detection of these anomalies are vital in anesthesia management. Accidental canulation of a tracheal bronchus with an anomaly can prevent ventilation of all other bronchopulmonary segments, and due to potential hyperinflation, pneumothorax secondary to alveolar rupture may develop. In this case presentation, we shared our anesthesia method applied to a child with a tracheobronchial anomaly that was coincidentally detected during a tracheotomy.

Keywords: Tracheotomy, tracheobronchial anomaly, anesthesia management, rare case

Introduction

Tracheobronchial anomalies (TBA) are abnormal airway pathologies that originate from the primary branching site of the tracheobronchial tree, and their prevalence is 0.1-0.2% (1-3).They are more frequently seen in children with anomalies such as Down syndrome, congenital cardiomyopathy, or lung malformations (4). Although these anomalies are usually asymptomatic, they manifest as respiratory tract infections, hemoptysis, atelectasis, and respiratory distress (5,6). Most patients are treated without surgery, but if they have permanent or recurring upper lobe pneumonia or atelectasis, the relevant segment must be removed surgically (2). Appropriate identification and detection of these anomalies are vital in anesthesia management (7-9). If you accidentally cannulate a tracheal bronchus that has a problem, it can stop all the other bronchopulmonary segments from breathing. This can lead to hyperinflation, which can cause an alveolar rupture and a pneumothorax. An intubation tube can plug the lumen of the tracheal bronchus and lead to postoperative hypoxemia and weaning difficulties (2-4,7-9). In this case presentation, we shared our anesthesia method applied to a child with a tracheobronchial anomaly that was coincidentally detected during a tracheotomy.

Case Report

Family consent was obtained for the case presentation. The patient with intrauterine growth retardation was born spontaneously vaginally without complications due to oligohydramnios weighing 3.010 g at 39 weeks of gestation.

The patient, who did not stay in the incubator and was noticed not being able to hold her head in routine controls made when she was 2-3 months old, was evaluated by pediatric neurology, and although its etiology was not fully clarified, it was learned that she could have cerebral palsy (CP) secondary to asphyxia. The patient started to turn purple while crying and had seizures afterwards, developing aspiration pneumonia. She was hospitalized in the intensive care unit (ICU) for follow-up and treatment. In her

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follow-up in the ICU, an increase was observed in her already existing stridor, and a tracheotomy was planned because of CP-related muscle hypotonia and laryngomalacia. In the pre-operative physical examination of the patient, who was 9 months old and weighed 6 kg with no specific family history, retrognathia, distinct premaxilla, long philtrum, hypertonic extremities, and deep palmar lines were observed. The preoperative values of the patient were normal.

The patient was breathing spontaneously, and standard anesthesia monitoring was applied. Her blood pressure was 120/80 mmHg, her pulse was 120/min, and her SpO_2 in the room ambiance was 98%. After preoxygenation, anesthesia induction (20 mg propofol, 5 mg lidocaine, 10 mcg fentanyl, and 3 mg rocuronium) was performed, and intubation with Macintosh blade no. II was planned. The laryngoscope was quickly replaced with a C-MAC® videolaryngoscope in a patient with Cormack-Lehane grade 3. The patient was intubated with a number 3.5 endotracheal tube (ETT) on the first attempt without complications. By confirming the tube site through bilateral lung sounds and end-tidal carbon monoxide pressures, the tube was fixed. Anesthesia maintenance was provided with 2.5-3% sevoflurane, a 50%: O_2/air mixture, and a remifentanil infusion.

After an incision was made between the 2nd-3rd tracheal cartilages and tracheotomy cannula number 4 was placed smoothly, the patient could not be ventilated. The patient was intubated again with the same ETT. The hemodynamic parameters of the patient followed a stable course throughout anesthesia, and a small tracheotomy canula numbered 0.5 was placed. However, the patient was re-intubated because ventilation could not be provided. An intraoperative flexible endoscopy was performed on the patient, who was stable in terms of ventilation after intubation but could not be ventilated through the tracheotomy cannula. Endoscopy revealed a third pathway (tracheal bronchus/blind sac?) above the carina line (Figure 1). Because of intraoperative consultations with pediatric and chest surgery clinics, it was thought that the canula may have entered this pathway due to the tracheal anomaly in the case and therefore could not be ventilated. The stoma of the patient was closed, and she was transferred to the pediatric ICU as an intubated patient to be evaluated by an advanced center.

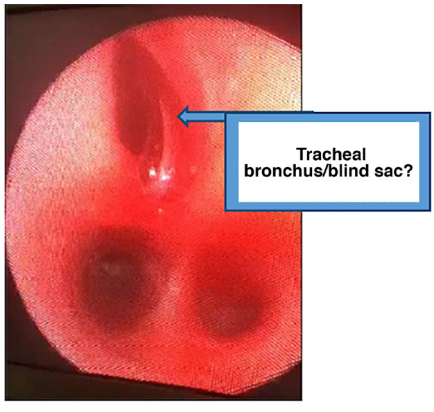

Figure 1. A third pathway (tracheal bronchus?/blind sac?) on the carina

Discussion

The respiratory system starts to develop in the third week of gestation, and the development of the tracheobronchial tree from its main branches to the terminal bronchioles is completed in the 16th week of intrauterine life. Tracheobronchial anomalies occur during this period. The tracheal bronchus and accessory cardiac bronchus are among the most common TBAs. Tracheal bronchi are anomalies that originate from the trachea and main bronchi (1,10). The prevalence of tracheal bronchus is 0.1-2% on the right and 0.3-1% on the left (1). A few anatomical types of tracheal bronchus have been described: if the upper lobe bronchus does not have a branch and there is an aberrant bronchus in the middle, it is called "displaced bronchus"; if it is concurrent with a normal upper lobe bronchus, it is called "supernumerary bronchus" (1).

The majority of TBAs in adults are asymptomatic, and only by chance are they detected through bronchoscopy or radiological imaging (2). On the other hand, in pediatric patients, they are associated with airway diseases such as recurring pneumonia and hemoptysis. Therefore, they are detected in children earlier and more frequently than in adults (4). Anomalies in the tracheobronchi can lead to respiratory problems like atelectasis, hemoptysis, recurrent or permanent lower respiratory tract infections, focal emphysema (especially in the upper lobe), bronchiectasis, and cystic malformation (5,6), even though they don't usually cause any symptoms. Stridor at birth should suggest congenital anomalies, whereas stridor that starts in the 4-6th week should indicate laryngomalacia and tracheomalacia (5). Bronchoscopy is recommended for all patients who present with recurrent lung infection and stridor without a known cause (2,11). Bronchoscopy is useful preoperatively because it will provide a clear image of TBAs. However, because the origin of TB may be similar to the tracheal bifurcation in the carina, the diagnosis of TB may be overlooked. Computed tomography (CT) is useful for understanding the structure of TBAs and their relationship with surrounding tissues. Magnetic resonance imaging has some disadvantages, such as a longer imaging time than CT, creating motion-related artifacts, and requiring long-term sedation (1-4,12). Congenital anomalies and the association of early-onset stridor with

laryngomalacia should have been considered. In our case, for which the cause of the stridor was not investigated before surgery, an intraoperative flexible endoscopy was performed because of the problems, and a right TB was detected 2-3 cm above the carina. Because the right upper lobe was not examined in detail during the intraoperative period, we believe that the tracheotomy cannula was placed in this stump, disrupting ventilation, and that it may be a supernumerary bronchus.

Tracheobronchial anomalies can lead to severe complications in airway management (7-9). An endotracheal tube cuff can plug TB and prevent ventilation of the right upper lobe. A TB can be accidentally canulated, in which case the remaining lobes of the right and left lungs cannot be ventilated. In both cases, perioperative hypoxemia and atelectasis can develop. Therefore, TB, albeit rarely, should be considered in the differential diagnosis of desaturation cases related to endotracheal intubation (2-6). To prevent complications, it is recommended to use a short ETT (to prevent TB obstruction) or to fix the tube by performing the intubation procedure using fiberoptic bronchoscopy (7). Conacher (13) suggested that in cases where desaturation develops due to the obstruction of TB with ETT, ETT should be carefully withdrawn by performing right upper lobe auscultation and waiting for the improvement in SpO_2. In our case, in which ventilation was provided after intubation but ventilation could not be ensured despite the placement of a smaller tracheotomy canula for the second time, it was thought that the intubation tube and cuff provided ventilation by staying over the region with TBA and that the tracheotomy canula disrupted ventilation by entering TB. In our case, who was brought to the operating room with spontaneous respiration, to ensure the safety of the procedure to be applied in case of respiration distress that may develop postoperatively and to eliminate the possibility of an accidental TB canulation, the stoma of the patient was closed and transferred to the intensive care unit as intubated.

Conclusion

It should be kept in mind that various bronchial anomalies can develop in pediatric patients who have congenital anomalies and stridors. In these situations, a thorough preoperative evaluation should include fiberoptic bronchoscopy and a radiological examination like computed tomography for safe anesthesia management. This will show any TBAs and help with planning airway management strategies and reducing complications.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parent for publication of the case report and the accompanying images.

Authorship Contributions

Concept: G.K., Z.G., S.A., Design: G.K., Z.G., Data Collection or Processing: Z.G., S.A., D.E., Literature Search: G.K., Z.G., R.D.O., Writing: G.K., Z.G., R.D.O., Critical Review: R.D.O., S.A.

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