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ORIGINAL RESEARCH

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Effectiveness of the YEARS Algorithm Added to Classical Clinical Decision-making Rules in Suspected Pulmonary Embolism

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Abstract

Objective: Pulmonary embolism (PE) is usually non-specific in terms of symptoms and signs and needs to be confirmed by an objective test. Pulmonary computed tomography angiography (PCTA) has been widely used for diagnosis in recent years. Our aim was to evaluate the potential of the YEARS algorithm to reduce the need for PCTA compared with the classical algorithm.

Materials and Methods: This prospective observational study. Between 15.03.2018 and 15.09.2019, patients admitted to the emergency department with suspected PE who underwent PCTA according to the classical algorithm (Wells) were included in the study. YEARS criteria were reviewed according to the patients' files and general laboratory results without knowing the results of PCTA. The need for PCTA was investigated according to classical clinical decision-making rules and YEARS algorithms.

Results: The study included 300 patients. According to YEARS, 69% of patients required PCTA, whereas 31% required the YEARS PE exclusion group. According to YEARS, PE was detected in 16.4% of patients with an indication for PCTA, whereas only 2.2% of patients in the PCTA exclusion group had PE. In the patient cohort that included the "probable PE" group according to the Wells, the sensitivity according to the YEARS was 94.4%.

Conclusion: In this study, the YEARS protocol used in addition to the classical algorithm resulted in a 31% reduction in the need for PCTA. However, we also showed that the YEARS algorithm may be insufficient for the diagnosis of low rate, positive PE.

Keywords: Pulmonary embolism, YEARS algorithm, Wells criteria

Introduction

Chest pain and dyspnea comprise approximately 9% of emergency department (ED) visits, and clinicians consider these indications as potential markers of critical health issues [1,2]. In patients presenting with these symptoms, emergency physicians primarily suspect diseases with a high risk of morbidity and mortality. One of these important diagnoses is acute pulmonary embolism (PE). The signs and symptoms of PE are frequently nonspecific and require verification through an objective test [2,3]. Recently, current guidelines have recommended pulmonary computed tomography angiography (PCTA) as an initial diagnostic tool due to its high diagnostic value. The frequent use of PCTA increases the number of clinically insignificant subsegmental PE diagnoses, increases the cost, exposes patients to unneeded radiation, and results in unfavorable outcomes like contrast nephropathy [3,4]. To prevent this, the guidelines suggest using certain clinical decision rules to identify risk groups of patients and determine who should undergo PCTA, rather than performing the procedure on every patient with a preliminary diagnosis of PE. Today, the most accepted opinion in the world is to use the algorithm proposed by the European Society of Cardiology (ESC), which determines who should undergo further investigation, such as PCTA, by using the D-dimer blood test together with the determination of clinical probability using Well's and Geneva rules [5]. Although these algorithms are widely used, physicians are still searching for a diagnostic PE algorithm with higher sensitivity to reduce unnecessary PCTA scans. Thus, van der Hulle et al. [6] compared the YEARS algorithm with the classical algorithm in patients with suspected acute PE. The YEARS algorithm recommends that PE

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should be excluded if the D-dimer level is below 500 ng/mL, that PCTA scanning should be performed if the D-dimer level is above 500 ng/mL and one or more of the three criteria [PE as the most probable diagnosis, presence of clinical signs of deep vein thrombosis (DVT), hemoptysis] are present, and that PCTA scanning should be performed if the D-dimer level is above 1000 ng/mL even if no criteria are present [6]. The rationale for this prospective observational study was to evaluate the potential of the YEARS algorithm to reduce the need for PCTA scanning in our population of patients with suspected PE in the ED compared with the classical algorithm currently used and to provide preliminary information for future interventional studies.

Materials and Methods

This study was conducted at the department of emergency medicine, University of Health Sciences Türkiye, Ankara Keçiören Training and Research Hospital Clinical Research Ethics Committee (decision number: 1632, date: 28.03.2018). Between 15.03.2018 and 15.09.2019, patients with suspected PE who presented to the ED and underwent PCTA according to the classical algorithm were included. Patients were evaluated according to the currently used classic Wells algorithm, and patients who underwent PCTA scanning according to these criteria, were 18 years of age or older, and provided informed consent for the study were included in the study. After this stage, we evaluated whether PCTA would have been necessary if we had followed the YEARS protocol with only the available medical information of the patients. Patients' complaints (dyspnea, pleuritic or substernal chest pain, cough, fever, hemoptysis, syncope, unilateral leg pain), D-dimer level, vital signs, presence of DVT findings, history of previous DVT or PE, history of surgery in the last 1 month, presence of immobilization for more than 3 days, presence of hemoptysis, Wells and YEARS scores, and PCTA results were recorded and evaluated. No additional tests were requested from the patients except for tests performed for the existing conditions.

Statistical Analysis

IBM SPSS Statistics for Microsoft 20.0 (SPSS Inc, Chicago USA) program was used for statistical analysis. The Kolmogorov-Smirnov test was used to determine whether the distribution of discrete and continuous numerical variables conformed to a normal distribution. Descriptive statistics were presented as median [interquartile range (IQR) - 25-75] for discrete and continuous numerical variables and as number of cases and (%) for categorical variables. Categorical variables were evaluated using the chi-square test, and continuous variables were evaluated using the Mann-Whitney U test. The statistical significance level was determined as p-value <0.05.

Results

During the study period, 612 patients with suspected PE were evaluated. We included 300 patients who underwent PCTA according to the classical algorithm. The median age was 68 years (IQR 25-75, 52.2-79), and 58.7% were female. The most common complaints at ED admission were dyspnea (48.7%) and chest pain (33.7%), and 52% of the patients underwent a thoracic system examination within normal limits. PE was detected on PCTA in 12% of patients. Pneumonia was detected on CT scan in 14% of the patients. Demographic data and vital signs of the patients are presented in Table 1.

Wells criteria and management of the patients are given in Table 2. According to the ESC 2014 algorithm, 29.3% of patients had a high probability and 70.7% had a low-moderate probability Wells criteria and PCTA was performed because of high D-dimer levels.

According to the YEARS algorithm, 69% of patients required PCTA and 31% were in the YEARS PE exclusion group (Table 3).

According to the YEARS algorithm, PE was detected in 16.4% of patients with an indication for PCTA, whereas PE was detected in 2.2% of patients in the zero criteria group without an indication for PCTA scanning (Table 4).

According to the YEARS algorithm, the sensitivity was 94.4%, specificity was 34.7%, positive likelihood ratio was 1.44, and negative likelihood ratio was 0.16.

Discussion

The aim of this study was to investigate the effectiveness of the YEARS algorithm in the evaluation of ED patients with suspected PE and the feasibility of reducing the need for PCTA compared with the existing classical algorithms. Our results indicate that the YEARS algorithm for analyzing patients with suspected PE can be a substitute for traditional algorithms and can reduce the need for PCTA.

The signs and symptoms of PE are frequently nonspecific and require verification using an objective test. Although many diagnostic algorithms have recently been developed for patients with suspected PE, these algorithms are generally not used sufficiently in the ED or benefit certain patient populations, leading to the overuse of PCTA [7].

Gruettner et al. [8] found PE in 13% of patients in a study he conducted with 326 patients comparing the Wells and Geneva scores. In another study comparing YEARS and Wells scores, PE was found to be positive in 9.8% of patients [9]. Van der Hulle et al. [6] found PE in 13% of patients in his study. In our study, PE was observed in 12% of patients who underwent PCTA.

Table 1. Demographic data of the patients

Demographic and clinical characteristics	All patients, n=300 (%)
Age median, IQR (25-75)	68 (52.2-79)
Gender	
Male	124 (41.3)
Female	176 (58.7)
Complaints	
Dyspnea	146 (48.7)
Chest pain	101 (33.7)
Palpitation	21 (7)
General condition disorder	19 (6.3)
Syncope	9 (3)
Leg edema	3 (1)
Respiratory arrest	1 (0.3)
Blood pressure	
Hypotension	39 (13)
Normotension	205 (68.3)
Hypertension	56 (18.7)
Heart rate	
60-100	59 (19.7)
Over 100	241 (80.3)
Saturation	
92-100	129 (43)
80-91	142 (47.3)
Below 80	29 (9.7)
Body temperature	
37.5 and higher	63 (21)
37.5 below	237 (79)
Physical examination	
Normal	156 (52)
Abnormal	144 (48)
Presence of embolism in PCTA	36 (12)
Segmentary	22 (61.1)
Massive	14 (38.9)
Additional finding in PCTA without pulmonary embolism	
No	136 (45.3)
Pneumonia	42 (14)
Bronchiectasis	7 (2.3)
Consolidated mass	16 (5.3)
Emphysema	12 (4)
Atelectasis	36 (12)
Nodule	14 (4.7)
Pleural effusion	36 (12)
Aortic dissection	1 (0.3)
D-dimer level median, IQR (25-75)	1560 (852.5-3940)

IQR: Interquartile range, PCTA: Pulmonary computed tomography angiography

Table 2. Wells criteria and management algorithm according to Wells

Wells criteria	All patients, n=300 (%)
History of thromboembolism	32 (10.7)
Tachycardia	240 (80)
Surgical immobilization	57 (19)
Hemoptysis	8 (2.7)
Active cancer	19 (6.3)
DVT clinic	29 (9.7)
Possible absence of diagnosis	83 (27.7)
Management according to ESC 2014 algorithm	
High probability PE	88 (29.3)
Low-moderate PE and high D-dimer	212 (70.7)

DVT: Deep vein thrombosis, ESC: European Society of Cardiology, PE: Pulmonary embolism

Table 3. YEARS parameters and management algorithm according to YEARS

	n (%)
YEARS criteria	
DVT clinic	29 (9.7)
Hemoptysis	8 (2.7)
Most likely diagnosis	84 (28)
YEARS algorithm	
Zero criteria, D-dimer <1000	70 (23.3)
Zero criteria, D-dimer >1000	135 (45)
YEARS >1 criterion, D-dimer <500	23 (7.7)
YEARS >1 criterion, D-dimer >500	72 (24)
Management according to the YEARS algorithm	
Take PCTA scan (1 or more criteria)	207 (69)
Exclude PE (zero criteria)	93 (31)

DVT: Deep vein thrombosis, PCTA: Pulmonary computed tomography angiography, PE: Pulmonary embolism

Table 4. PCTA results of patients according to algorithms

	PE negative, n (%)	PE positive, n (%)
Management according to Wells ESC 2014 algorithm		
High Probability PE	65 (24.6)	23 (63.9)
Low-moderate PE and high D-dimer	199 (75.4)	13 (6.1)
Management according to the YEARS algorithm		
Take PCTA (1 or more criteria)	173 (83.6)	34 (16.4)
Exclude PE (zero criteria)	91 (97.8)	2 (2.2)

ESC: European Society of Cardiology, PE: Pulmonary embolism, PCTA: Pulmonary computed tomography angiography

In a study, Kearon et al. [10] reported that a D-dimer level below 1000 ng/mL was low risk for PE. In our study, the D-dimer level was found to be below 1000 ng/mL in only 5.5% of the 36 patients in whom PE was detected as a result of PCTA. It was observed that these patients had embolism only in subsegmental branches. Studies have shown that elevated D-dimer levels lead physicians to diagnose PE; therefore, many patients undergo unnecessary PCTA. We believe that the YEARS score reduces the need for PCTA because it accepts a D-dimer limit of 1000 ng/mL in the absence of any other criteria.

In a study in which Medson et al. [11] compared the Wells, YEARS, and Geneva scores, 9.3% of patients were classified as having a high clinical probability when the patients were classified as having low and high clinical probability according to the Wells criteria. In our study, 29.3% of patients were considered to have a high clinical probability. This difference may be related to the fact that the criterion of "PE as the most probable diagnosis" in Wells scoring is a subjective criterion.

In his study, van der Hulle et al. [6] compared the diagnostic efficacy of the YEARS algorithm with that of the Wells algorithm in patients with suspected PE. The primary outcome of the study was defined as the number of venous thromboembolic events occurring during 3 months of patient follow-up, and the secondary outcome was defined as a comparison of the number of PCTAs deemed necessary and performed according to the YEARS and Wells algorithms. As a result, the number of patients without the YEARS criteria was 1743, and PE was detected in 55 (3.2%) of these patients. The number of patients with one or more YEARS criteria was 1722. Four hundred one (23%) of these patients were diagnosed with PE. PE could not be excluded as the cause of death in 6 patients. At the 3-month follow-up, 18 patients were found to have PE. The results showed that the YEARS algorithm reduced the need for PCTA scans by 14% compared with classical algorithms [6]. In our study, PE was found in 2 (2.2%) of 93 patients without any YEARS criteria. PE was found in 34 (16.4%) of 207 patients with one or more YEARS criteria. In Medson et al. [11] study, PE was diagnosed in 18 (6.3%) of 286 patients in whom the YEARS algorithm excluded PE. Freund et al. [12], in a study comparing the YEARS algorithm with the classical algorithm, reported a 10% reduction in the need for PCTA scanning with the YEARS algorithm compared with the classical algorithm. In the same study, no decrease in the PE detection rate was observed at 3-month patient follow-up [12]. In another study in which the YEARS algorithm was applied to pregnant patients, it was reported that PE was safely excluded in 32-65% of patients [13]. Another multicenter study reported that the YEARS algorithm reduced the need for PCTA scanning by 14% but increased the PE miss rate by 0.5% [14].

In this study, we evaluated the potential of the YEARS algorithm to reduce the need for PCTA in patients with suspected PE compared with the classical algorithm that we currently use and found a 31% reduction in the need for PCTA compared with the standard algorithm. The difference in these rates may be related to the inclusion of a larger number of patients with high clinical probability in previous studies. We demonstrated that implementing the YEARS algorithm in risk stratification for patients with suspected PE in the ED resulted in a decreased requirement for PCTA compared with other commonly used algorithms. The study demonstrated that the YEARS algorithm was superior to the routine algorithm in excluding acute PE from patients with clinical suspicion of PE and low venous thromboembolism risk, with a sensitivity of 94.4%. However, as shown in previous studies, we found that YEARS has a low risk of PE patient omission.

Study Limitations

This study was single-centered. Because this was an observational study, patients were evaluated by different clinicians working in the ED. The criterion of "PE as the most probable diagnosis" in both the YEARS and Wells algorithms may have led to different evaluations among clinicians because it is a subjective criterion. In addition, PCTA may be performed in the clinic not only to diagnose PE and exclude diagnoses such as pneumonia from the differential diagnosis of PE. The fact that the patients were evaluated only at the time of presentation to the ED and were not followed up for PE in the long term is one of the limitations of this study.

Conclusion

The YEARS algorithm, used in the ED for risk stratification of patients with suspected PE, reduces the need for PCTA in addition to the Wells algorithm used routinely. However, we have shown that YEARS is associated with a risk of missing PE patients, albeit at a low rate. Studies have shown that patients undergo unnecessary PCTA despite the use of different clinical probability scores for PE diagnosis. There is a need to develop new scoring systems to reduce these rates.

Ethics

Ethics Committee Approval: This study was conducted at the department of emergency medicine, University of Health Sciences Türkiye, Ankara Keçiören Training and Research Hospital Clinical Research Ethics Committee (decision number: 1632, date: 28.03.2018).

Informed Consent: Patients were evaluated according to the currently used classic Wells algorithm, and patients who underwent PCTA scanning according to these criteria, were 18 years of age or older, and provided informed consent for the study were included in the study.

Authorship Contributions

Surgical and Medical Practices: H.Ö.O., Y.Ç., Concept: H.Ö.O., Ş.K.Ç., Y.Ç., Design: H.Ö.O., Ş.K.Ç., E.E., Y.Ç., Data Collection or Processing: H.Ö.O., Analysis or Interpretation: H.Ö.O., Ş.K.Ç., E.E., Literature Search: H.Ö.O., E.E., Y.Ç., Writing: H.Ö.O., E.E.

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ORIGINAL RESEARCH

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The Effect of Posterior Communicating Artery and Fetal Posterior Cerebral Artery Anomalies on Prognosis in Endovascular and Thrombolytic Therapy Patients

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Abstract

Objective: Acute reperfusion therapy is a critical intervention for stroke patients with the aim of restoring blood flow. The presence of anatomical anomalies, such as fetal posterior cerebral artery (fPCA) and posterior communicating artery (PCOM) variations, can impact treatment outcomes and patient prognosis. This study aimed to assess the potential influence of these anomalies on patients undergoing acute reperfusion therapy.

Materials and Methods: Demographic characteristics of patients who underwent acute reperfusion therapy for stroke were considered among three distinct groups: the PCOM group, fPCA group, and control group. The demographic attributes examined for each group included gender distribution, mean age, presence of comorbidities, thrombolysis in cerebral infarction, national institutes of health stroke scale (NIHSS), and European cooperative acute stroke study II (ECASS II) scores. The significance of differences in these attributes among the groups was assessed.

Results: The study included a total of 106 patients: 42 patients in the PCOM group, 31 patients in the fPCA group, and 33 patients in the control group. No significant differences in demographic data were observed among the groups. The greatest decrease in NIHSS at the 24th hour was observed in the PCOM group, whereas the least decrease on day 7 was observed in the fPCA group. No differences were detected in the NIHSS values on the 24th hour and 7th day among the groups. When the 24th hour computed tomography scans of the groups were evaluated according to the ECASS II criteria, no significant differences were observed among the groups. Hemorrhage was not observed in 52.4% of patients in the PCOM group and 66.7% of patients in the control group.

Conclusion: The impact of fPCA and PCOM anomalies on patients undergoing acute reperfusion therapy for stroke was evaluated. Although no significant demographic differences were found among the groups, the study highlights the importance of further research to better understand their potential impact on treatment outcomes.

Keywords: Fetal PCA, acute stroke, PCOM

Introduction

Cerebrovascular disorders continue to represent a significant and increasing global health concern, necessitating the ongoing refinement of diagnostic and therapeutic approaches. Among the advancements in this field, acute reperfusion therapy has emerged as a transformative intervention with unprecedented potential for salvaging ischemic brain tissue and mitigating the devastating consequences of cerebrovascular events. As the landscape of acute reperfusion therapies evolves, it becomes increasingly critical to deepen our understanding of the intricate vascular anatomy that underlies these interventions.

Fetal posterior cerebral artery (fPCA) is a common cerebral circulation variety. Complete fPCA (cfPCA) and partial fPCA (pfPCA) are two different types of fPCA definitions. cfPCA is the

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artery that originates from the internal carotid artery and has no relationship with the basilar artery. The PCA originating from the internal carotid artery with a minor or atretic relationship with the basilar artery is referred to as pfPCA. Using autopsy or imaging techniques, such as magnetic resonance angiography, the prevalence of fPCA varies among individuals who are healthy (15-32%) and those with a history of cerebral infarction (5-36%) [1]. The posterior communicating artery (PCOM) emerges from the internal carotid artery and interacts with PCA. The vessel provides 5 to 12 branches to the thalamus, reticular nucleus, mammillothalamic tract, diencephalon, and caudate nucleus. The vessel appears unilaterally in 33% of cases, and abnormalities, such as aplasia, hypoplasia, or duplication, are visible in more than 50% of cases [2]. fPCA and PCOM are pivotal components of cerebral circulation and contribute to the intricate network that ensures optimal blood supply to the brain [3,4]. Anomalies or variations in these arterial structures can significantly impact the outcomes of acute reperfusion procedures, influencing both the safety and efficacy of these therapeutic interventions [5].

This study is positioned at the intersection of acute reperfusion therapy and cerebral vascular anatomy to investigate the potential impact of fPCA and PCOM anomalies on patients undergoing this critical intervention. By systematically assessing the presence and characteristics of these anatomical variations, we aim to contribute valuable insights into the intricate dynamics that may influence the success of acute reperfusion therapy and, consequently, the trajectory of stroke patients on their road to recovery.

Materials and Methods

Study Design

This retrospective observational study was designed to investigate the demographic characteristics of patients undergoing acute reperfusion therapy for stroke, with a specific focus on anatomical anomalies within the PCOM and fPCA. The study included three distinct groups: PCOM, fPCA, and control.

Participant Selection

Patient records from 2018-2023 were reviewed, and individuals who underwent acute reperfusion therapy for stroke were identified. Computed tomography (CT) angiography was performed for all patients. Thus, the variations in cases were determined through CT angiography. These patients were then categorized into three groups based on the presence of vascular anomalies: the PCOM group, comprising patients with PCOM anomalies; the fPCA group, comprising patients with fetal PCA anomalies; and the control group, which included patients without observed vascular anomalies.

Demographic Characteristics

Demographic attributes were systematically evaluated for each group. Gender distribution, mean age, and presence of comorbidities were assessed as baseline characteristics. Additionally, the thrombolysis in cerebral infarction (TICI) score, national institutes of health stroke scale (NIHSS), and European cooperative acute stroke study II (ECASS II) scores were recorded for each participant. The ECASS II includes hemorrhagic infarction type 1 (HI1), which is characterized by small petechiae along the infarcted margins; hemorrhagic infarction type 2 (HI2), which is characterized by confluent petechiae within the infarcted area but without a space-occupying effect; parenchymal hematoma type 1 (PH1), which involves a blood clot covering less than 30% of the infarcted area with some slight space-occupying effect; and parenchymal hematoma type 2 (PH2), which involves a blood clot covering more than 30% of the infarcted area with a significant space-occupying effect [6].

Ethical Considerations

This study adhered to the ethical guidelines and was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2021-06-10, date: 15.03.2021). Patient confidentiality was strictly maintained throughout the research process. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Statistical analysis was performed to determine the significance of differences in demographic attributes among the three groups. Descriptive statistics were used to present the baseline characteristics of each group. Continuous variables are expressed as means with standard deviations, and categorical variables are presented as percentages. To assess the significance of observed differences, appropriate statistical tests, such as t-tests or ANOVA, were employed for continuous variables, whereas chi-square tests were utilized for categorical variables.

Results

In this comprehensive examination of the dataset, comprising 106 patients distributed among three distinctive groups the PCOM group, fPCA group, and control group, detailed demographic and clinical characteristics were meticulously assessed. The PCOM, fPCA, and control groups consisted of 42, 31, and 33 patients, respectively. The initial analyses explored variables such as gender distribution, age, comorbidities, and clinical outcomes (Table 1).

Demographic Characteristics

Gender distribution exhibited minor variations among the groups, with 33.3% females in the PCOM group, 48.3% in the fPCA group, and 51.5% in the control group. Conversely, male representation was higher in the PCOM group (66.7%) than in the fPCA (51.7%) and control (48.5%) groups. The mean age,

although not statistically significant, demonstrated a slight disparity, with the fPCA group having the highest mean age (74.6 years), followed by the control (68.3 years) and PCOM (69.2 years) groups (Table 1).

The presented results compare three groups (PCOM, fPCA, and control) in the context of acute ischemic stroke. Admission NIHSS scores did not differ significantly between the groups (p=0.55). The distribution of treatment modalities (tPA, thrombectomy, tPA + thrombectomy) displayed no significant variation among the groups, with p-values of 0.83, 0.36, and 0.83, respectively. These findings provide insights into the baseline characteristics and treatment patterns of the studied groups (Table 2).

Multivariate Analysis

The multivariate analysis, considering the estimates and confidence intervals, further elucidated the influence of various factors on the study outcomes. Time exhibited a significant negative impact on NIHSS scores, emphasizing the temporal effectiveness of acute reperfusion therapy across all groups (Figure 1). Additionally, NIHSS scores at admission were positively associated with treatment effectiveness, suggesting a correlation between the severity of initial neurological impairment and the subsequent response to therapy. The group variable, which included the PCOM and fPCA groups in comparison to the control group, did not reach statistical significance, but the confidence intervals suggested a potentially greater reduction in NIHSS scores in the PCOM group (Table 3).

Clinical Outcomes and Radiological Evaluations

Detailed examination of clinical outcomes revealed intriguing patterns. TICI scores, which reflect the effectiveness of

Table 1. Demographic features of the groups

	PCOM n=42	fPCA n=31	Control n=33	p
Gender				
Female Male	14 (33.3%) 28 (66.7%)	15 (48.3%) 16 (51.7%)	17 (51.5%) 16 (48.5%)	0.24
Age	69.2 (13.9)	74.6 (12.7)	68.3 (13.4)	0.15
Comorbidities				
Absent Present	5 (11.9%) 37 (88.1%)	7 (20.7%) 24 (79.3%)	7 (21.2%) 26 (78.8%)	0.49
DM				
Absent Present	24 (57.1%) 18 (42.9%)	22 (72.4%) 9 (27.6%)	21 (63.6%) 12 (36.4%)	0.42
HT				
Absent Present	18 (42.9%) 24 (57.1%)	14 (44.8%) 17 (55.2%)	14 (42.4%) 19 (57.6%)	0.98
HL				
Absent Present	37 (88.1%) 5 (11.9%)	30 (99,1%) 1 (0.90%)	29 (87.9%) 4 (12.1%)	0.13
CAD				
Absent Present	26 (61.9%) 16 (38.1%)	25 (82.8%) 6 (17.2%)	25 (75.8%) 8 (24.2%)	0.13

DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease, PCOM: Posterior communicating artery, fPCA: Fetal posterior cerebral artery

Table 2. The distribution of treatment modalities

	PCOM n=42	fPCA n=31	Control n=33	p
Admission NIHSS	12.5 [8.00; 17.0]	12.0 [8.00; 15.0]	11.0 [8.00; 13.0]	0.55
Treatment				
tPA Thrombectomy tPA + thrombectomy	22 (52.4%) 13 (31.0%) 7 (16.7%)	13 (41.9%) 12 (38.7%) 6 (19.3%)	17 (51.5%) 12 (36.4%) 4 (12.1%)	0.83

tPA: Tissue plasminogen activator, NIHSS: National institutes of health stroke scale, PCOM: Posterior communicating artery, fPCA: Fetal posterior cerebral artery

thrombectomy, did not differ significantly among the groups. The PCOM group had a higher proportion of TICI1 scores (15.8%), whereas the fPCA group had a higher proportion of TICI2A-2B scores (73.7%). At the 24th hour, NIHSS scores exhibited variability, with no significant differences between the groups. Similarly, 24th hour CT scans based on the ECASS II criteria did not reveal significant disparities. The incidence of hemorrhage varied among the groups, with 52.4% in the PCOM group and 66.7% in the control group exhibiting no hemorrhage (Table 4).

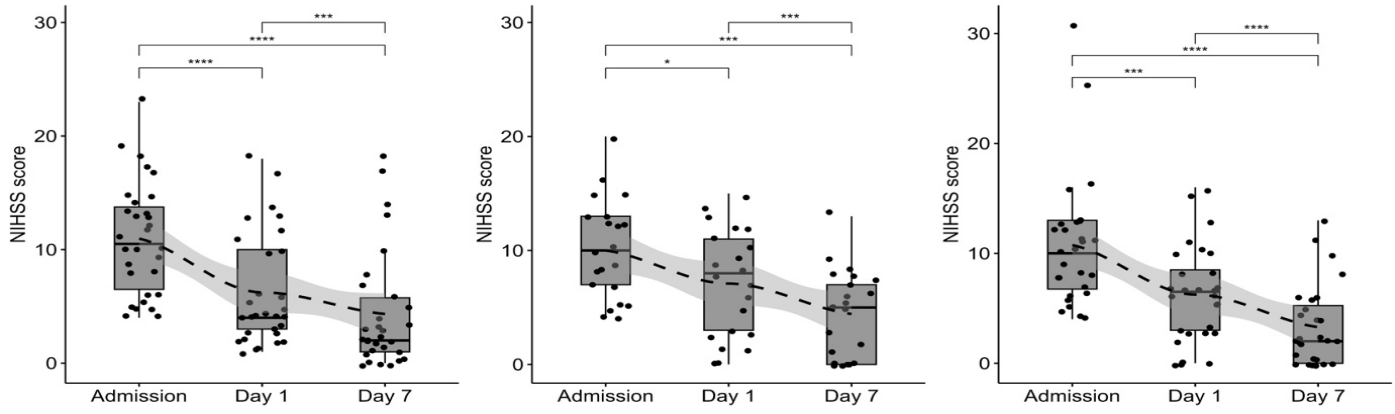

Figure 1. Relationship between NIHSS score and time (admission, day 1 and day 7)

NIHSS: National institutes of health stroke scale

Table 3. Confidence intervals and relationship between groups according to NIHSS scores

	Estimate (%95 CI)	Standard error	T value
Intercept	0.78 (-1.90, 3.47)	1.36	0.58
Time	-0.43 (-0.52, -0.33)	0.05	-9.03
Admission NIHSS	0.55 (0.36-0.73)	0.10	5.71
Group			
Control	Reference	-	-
PCOM	**1.30 (-0.98, 3.57)**	1.15	1.12
fPCA	**1.74 (-0.80, 4.27)**	1.26	1.36

CI: Confidence interval, NIHSS: National institutes of health stroke scale, PCOM: Posterior communicating artery, fPCA: Fetal posterior cerebral artery

Table 4. Clinical outcomes of the groups

	PCOM n=42	fPCA n=31	Control n=33	p
TICI score				
TICI1	3 (15.8%)	5 (26.3%)	6 (35.3%)	0.44
TICI2A-2B	16 (84.2%)	14 (73.7%)	11 (64.7%)	
24th hour NIHSS	4.00 [3.00; 11.5]	8.50 [3.00; 12.0]	7.00 [3.00; 10.0]	0.73
24th hour CT				
HI1-2	12 (28.6%)	7 (22.5%)	8 (24.2%)	0.38
PH1-2	8 (19.0%)	8 (25.8%)	3 (9.09%)	
No hemorrhage	22 (52.4%)	16 (51.6%)	22 (66.7%)	
7th day NIHSS	2.00 [1.00; 5.75]	5.50 [0.00; 7.00]	2.00 [0.00; 5.25]	0.55
7th day CT				
HI1-2	12 (30.8%)	10 (32.2%)	14 (43.8%)	0.12
PH1-2	7 (17.9%)	3 (9.6%)	0 (0.00%)	
No hemorrhage	20 (51.3%)	16 (51.6%)	18 (56.2%)	

TICI: Thrombolysis in cerebral infarction, PCOM: Posterior communicating artery, fPCA: Fetal posterior cerebral artery, NIHSS: National institutes of health stroke scale, HI: Hemorrhagic infarction, PH: Parenchymal hematoma, CT: Computed tomography

7th Day Clinical and Radiological Outcomes

On the 7th day, NIHSS scores exhibited a significant decrease across all groups, affirming the efficacy of acute reperfusion therapy. Radiological evaluations on the 7th day mirrored those at the 24th hour, with no significant differences in HI1-2 and PH1-2 and no hemorrhage observed among the groups (Table 4).

Discussion

Our investigation into the interplay of anatomical anomalies, particularly those within the PCOM and fPCA, in the context of acute reperfusion therapy for stroke has revealed intriguing patterns. The observed outcomes suggest that the treatment is effective in patients with both PCOM and fPCA; however, there appears to be a notable trend indicating potentially superior effectiveness in the PCOM group. It was observed in an article that patients with bilateral PCOM tend to have milder strokes at admission compared with those with absent/unilateral PCOM (median NIHSS score 18 versus 27 points). Additionally, these patients demonstrated better neurological improvements during discharge (quantified by the median decrease in NIHSS score) and higher rates of 3-month functional independence compared to those without good collaterals [7,8]. In support of this study, our findings indicated that individuals with PCOM had a better admission NIHSS score and more favorable neurological improvement compared to those with fPCA.

The disparity in treatment response between the PCOM and fPCA groups may be attributed to distinct characteristics inherent in these anatomical anomalies. The greater reduction in NIHSS scores within the PCOM group raises compelling considerations. One plausible explanation aligns with the anatomical location of PCOM anomalies, which may predominantly reside in the distal segments of cerebral arteries. This spatial orientation likely enhances collateral flow and provides an auxiliary blood supply route during instances of arterial blockage [9-11]. The fact that this does not result in a difference when evaluated in terms of hemorrhage status can be considered a questionable outcome in our study. Consequently, the augmented collateral flow may serve a protective role by mitigating potential brain damage and contributing to the more favorable treatment outcomes observed in the PCOM group.

Conversely, the fPCA group exhibited positive treatment responses, albeit with a lesser reduction in NIHSS scores, compared with the PCOM group. This may indicate variations in collateral capacities or regional blood supply dynamics associated with fPCA anomalies [12-14]. However, further exploration is warranted to elucidate the specific mechanisms contributing to the observed differences in treatment efficacy between the anatomical subgroups. There was no significant difference in procedural success (TICI scores) between the fPCA, PCOM, and control groups, indicating that these variations did not pose significant challenges for the interventional radiologist performing the procedure. Vascular variations did not significantly alter the procedural success of interventional radiologists. This result suggests that outcomes were more likely influenced by hemodynamic changes than procedural aspects.

Study Limitations

PCOM is the second most common aneurysm (25% of all aneurysms) and accounts for 50% of all internal carotid artery aneurysms [15,16]. Our study did not report any instances of aneurysm rupture in either the PCOM or fPCA groups, thereby limiting our ability to conclusively attribute treatment outcomes to this factor. Nevertheless, this absence underscores the importance of considering alternative explanations for observed trends. It is crucial to acknowledge the limitations of our study and the need for more extensive investigations involving larger patient cohorts and extended follow-up periods to validate and generalize our preliminary findings.

Conclusion

In conclusion, acute reperfusion is effective and safe for patients with fPCA or PCOM anomalies. These anatomical variations may not only pose minimal impediments to the therapeutic procedure but also act as potential collateral pathways. The observed trends suggest a reduced risk of bleeding during the procedure and propose a positive prognosis for patients with such anomalies. However, the generalizability of these findings requires validation in more comprehensive studies with larger sample sizes and longer follow-up durations.

Ethics

Ethics Committee Approval: This study adhered to the ethical guidelines and was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2021-06-10, date: 15.03.2021).

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

Authorship Contributions

Surgical and Medical Practices: H.A.E., Ö.Y., Concept: İ.A., V.Y., Design: H.A.E., İ.A., Z.E.K., Data Collection or Processing: H.A.E., İ.A., Analysis or Interpretation: H.A.E., Ö.Y., Literature Search: H.A.E., İ.A., Ö.Y., Writing: H.A.E., İ.A.

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ORIGINAL RESEARCH

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Comparison of Oral Anticoagulant Users with Non-users Admission Laboratory Parameters, Length of Hospital Stay and Outcomes in COVID-19 Infection

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Abstract

Objective: We aimed to investigate the effect of oral anticoagulant (OA) use during coronavirus disease-2019 (COVID-19) on early admission laboratory parameters and/or length of hospital stay in patients receiving chronic OA medication.

Materials and Methods: This retrospective study included two groups; group 1 (n=62) consisted of OA users, and group 2 (n=75) of age and sex-matched OA non-users at the time of COVID-19 diagnosis. Early admission laboratory measures, numbers of comorbidities, length of hospital stay, and outcomes of patients were recorded and analyzed.

Results: Despite higher comorbidities in group 1, serum C-reactive protein (CRP) and D-dimer levels were significantly lower than group 2 ($p<0.05$, all). The mortality rate was higher in group 2 but did not reach statistical significance ($p>0.05$). Regression analysis showed that OA users (compared to OA non-users) had 0.980 and 0.520 times lower serum CRP and D-dimer levels, respectively.

Conclusion: This study showed a beneficial effect of OA use on early admission serum CRP, and D-dimer levels, which are important prognostic predictors of COVID-19. Additionally, OA use is associated with fewer hospital stays for COVID-19 patients. These beneficial effects of OA use might help improve the management of this infection after further studies in this field.

Keywords: Anticoagulant, COVID-19, C-reactive protein, D-dimer, length of hospital stay, outcome

Introduction

Coronavirus disease-2019 (COVID-19) has a high morbidity and/or mortality rate. Coagulopathy is one of the main determinants of outcomes. In general, these patients have an increased risk of both venous and arterial thrombotic events [1]. These may be presented as micro or macro thrombotic events [2,3]. The presence of cardiac valvular diseases and/or atrial fibrillation (AF) increases the risk of thromboembolism in COVID-19-infected patients [4-6]. Therefore, elevated serum D-dimer level is regarded as a bad prognostic marker [3,6-8]. Therefore, most local and international guidelines recommend anticoagulation treatment with heparins among hospitalized patients with COVID-19 [9]. Despite this, thromboembolic complications are still not preventable even with high doses of heparin therapy protocols [2,10,11]. As active managing physicians in pandemic clinics at our hospitals, we encounter thromboembolic complications in patients with COVID-19 who are managed with optimal doses of low-molecular-weight (LMWH) or unfractionated heparins (UH) [9]. In light of the high burden of microvascular thrombosis and immunothrombosis in this disease, some researchers recommend the use of

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antiplatelet therapies (as aspirin) in hospitalized patients with COVID-19 [12]. As known, oral anticoagulants (OAs) are used in the treatment or prevention of thrombotic events in high-risk individuals. These drugs are vitamin K antagonists (warfarin or acenocoumarol) or direct OAs (dabigatran, apixaban, rivaroxaban, and edoxaban). To our knowledge, these drugs are not indicated for preventing or treating COVID-19-related thromboembolic events. Additionally, at the time of the development of COVID-19 in anticoagulated patients, researchers advise switching to heparin treatment. The rationale for this is the difficulty in monitoring the effects and/or side effects of OAs [13-15]. The most notable outcome is the controversial results of their impact on the outcomes of COVID-19 infection [13,14,16-20]. Our national guidelines recommend switching to LMWH or standard UH at the time of COVID-19 diagnosis in patients already on OA treatment [9]. During our daily practice, we manage such patients in our COVID-19 inpatient clinics. Due to their special clinical status, we were obligated to continue treatment in some patients with OA successfully. These positive observations encouraged us to collect retrospective data on OA users newly diagnosed with COVID-19 and compare it with those of their peers who are OA non-users. Therefore, in this study, we aimed to compare early admission laboratory parameters, hospital stay length, and outcomes of OA users newly diagnosed with COVID-19 who were already on OA use with those who were not.

Materials and Methods

This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2020-24-12, date: 07.12.2020). Informed consent form was obtained from all patients. Data of COVID-19 patients admitted to the pandemic medical departments of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital and University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital from November 1, 2020, to January 1, 2021. The 1st group consisted of patients using OA at the time of diagnosis of COVID-19 (n=62). The second group consisted of age- and sex-matched COVID-19 patients who did not use any OA at the time of COVID-19 diagnosis (n=75). For admission criteria, and management of these patients, the Turkish Ministry of Health's guidelines were followed. According to Turkish guidelines, all COVID-19-diagnosed outpatients and inpatients are given antiviral treatment favipiravir as soon as possible [9]. The main symptoms of these patients were shortness of breath, fever, myalgia, and cough. These patients were selected according to the following inclusion and exclusion criteria;

Inclusion criteria: (1) confirmed COVID-19 diagnosis (by real-time reverse transcription-polymerase chain reaction test) (both groups), (2) age ≥60 years old (both groups), 3) using of OA on the day of diagnosis of COVID-19 (at least >1 month) (group 1 only).

Exclusion criteria: (1) using any OA at the time of diagnosis of COVID-19 (group 2 only), (2) incomplete hospital laboratory and/or follow-up records (both groups).

Complete hospital admission clinical and laboratory data were recorded. The number of comorbidities, length of hospital stay, and outcomes were also recorded. A total of 155 patient records were screened, and 18 were excluded (3 of them from group 1, and 15 from group 2). The exclusion criteria were incomplete hospital records for group 1 patients. For group 2; age (<60 years old), suspicious diagnosis of COVID-19, and incomplete hospital records were the causes of patient exclusion. Thus, the final analysis was performed with a total of 137 patients [group 1 (n=62), and group 2 (n=75)]. Seventeen of the group 1 patients used warfarin, and the remainder 45 patients were using new OAs; apixaban (n=17), rivaroxaban (n=15), edoxaban (n=9), and dabigatran (n=3) (see Figure 1).

Data Availability

All necessary data are presented in the manuscript. Nevertheless, for reasonable requests, the corresponding author can be reached by e-mail.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package for Windows. The distribution of variables was evaluated using the Kolmogorov-Smirnov test. The data were not distributed normally. Therefore, the description of the data was expressed as median (minimum-maximum). The Mann-Whitney U test was used to compare variables. The effect size was estimated using the rank-biserial correlation coefficient [$r^{r\text{-}b}$]. Chi-square analysis was used to compare categorical variables between groups. The Spearman test was used to evaluate the correlation between quantitative variables. Logistic regression (model: forward logistic regression) [adjusting od ratio at 95% confidence interval (CI)] analysis was applied to find the simplest model that could predict the outcome. A p-value <0.05 was accepted as significant [21].

Results

A total of 137 patients were included in this study. The comparison of the study parameters of group 1 with group 2 is shown in Table 1. The ratio of female (F)/male (M), and mean ± standard deviation [median (minimum-maximum)] age of group 1 (n=62) and group 2 (n=75) was 25 F/37 M, and 71.30±8.89 [69.00 (60.00-94.00)] years versus 37 F/38 M, and 70.30±6.48 [70 (60.00-88.00)] years, respectively (p>0.05, both). The timing of hospital admission (i.e., duration of disease's symptom(s) at the time of admission) did not differ between the

2 study groups (p>0.05). The median number of comorbidities was significantly higher in group 1 patients, but the median serum CRP and D-dimer levels were significantly lower in the same group (in comparison to group 2 patients) (p<0.05, all). The median mortality rate was higher in group 2 patients but did not reach statistical significance (p>0.05) (see Table 1).

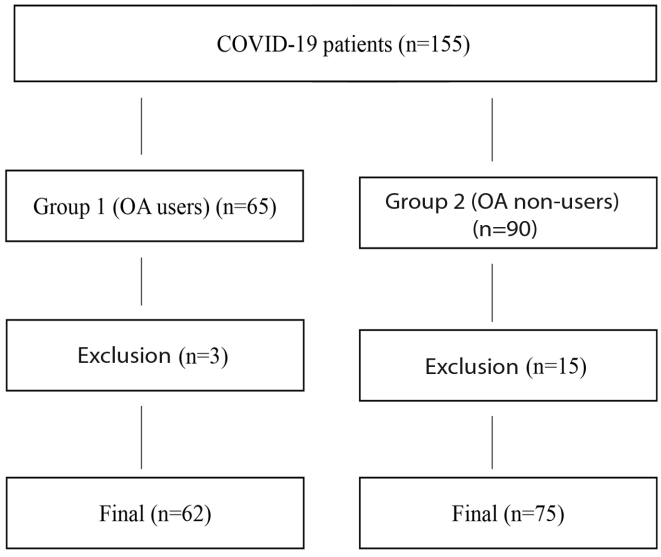

Figure 1. The study groups and study flow diagram

OA: Oral anticoagulant, COVID-19: Coronavirus disease-2019

A comparison of patients who survived with those who died is presented in Table 2. The median serum CRP level was higher, but the median lymphocyte and platelet counts were significantly lower in patients who died (see Table 2 for medians, p-values, and effect sizes).

Spearman's rank correlation analysis identified a negative correlation between the use of OA and serum CRP, D-dimer, and length of hospital stay (correlation coefficient r were -0.377, -0.260, and -0.207, and p-values were <0.001, 0.002, and 0.015, respectively).

Regression analysis showed that OA users (in comparison to OA non-users) had 0.980 and 0.520 times lower serum CRP and D-dimer levels, respectively (95% CI) were 0.982-0.995, and 0.280-0.991, respectively).

Discussion

The median number of comorbidities was significantly higher in group 1 than in group 2 patients ($r^{r\text{-}b}$=0.423, and p<0.001). It is well known that comorbidities are among the important determinants of mortality in COVID-19 infection.

Table 1. Comparison of oral anticoagulant users (group 1) with non-users (group 2) COVID-19 patients' data

Order	Parameter	Group 1 (n=62)	Group 2 (n=75)	p	Effect size*
1	**Age (years)** Median (min-max)	69.00 (60.00-94.00)*+	70.00 (60.00-88.00)	NS	-
2	**Gender** Female/male	25/37	37/38	NS	-
3	**Duration of symptom(s) at hospital admission (days)**	5 (1-10)*+	3 (1-12)	NS	-
4	**Hospital's stay days** Median (min-max)	10.00 (2.00-42.00)*+	12.00 (3.00-31.00)	0.016	0.239
5	**Number of comorbidities** Median (min-max)	3.00 (1.00-7.00)*+	2.00 (0.00-7.00)	<0.001	0.429
6	**Leucocyte count (x10^3/uL)** Median (min-max)	7.30 (1.87-25.10)*+	7.18 (0.82-21.67)	NS	-
7	**Lymphocyte (x10^3/uL)** Median (min-max)	1.02 (0.30-3.24)*+	1.07 (0.20-3.32)	NS	-
8	**Platelet (x10^3/uL)** Median (min-max)	199.50 (52.00-495.00)*+	205.00 (77.00-822.00)	NS	-
9	**CRP (mg/L)** Median (min-max)	41.65 (1.30-248.00)	118.00 (1.60-418.00)	<0.001	0.437
10	**D-dimer (µg FEU/mL)** Median (min-max)	0.25 (0.02-1.96)*+	0.45 (0.07-3.90)	0.002	0.301
11	**Mortality rate** n (%)	9 (14.75)	12 (16.00)	NS	-

NS: Not significant

*Rank-biserial correlation

*+Non-normal distribution

COVID-19: Coronavirus disease-2019, min: Minimum, max: Maximum, CRP: C-reactive protein

Table 2. Comparison of COVID-19 patients that survived with those that not survived

Order	Parameter	Survivors (n=115)	Non-survivors (n=21)	p	Effect size*
1	**Age (years)** Median (min-max)	70.00 (60.00-90.00)*+	68.00 (61.00-89.00)*+	NS	-
2	**Gender** Female/male	54/64	7/14	NS	-
3	**Hospital's stay days** Median (min-max)	10.00 (2.00-42.00)*+	12.00 (3.00-31.00)*+	NS	-
4	**Number of comorbidities** Median (min-max)	2.00 (0.00-7.00)*+	2.00 (0.00-5.00)*+	NS	-
5	**Leucocyte count (x10^3/uL)** Median (min-max)	7.42 (0.82-25.10)*+	7.13 (2.74-12.76)*+	NS	-
6	**Lymphocyte (x10^3/uL)** Median (min-max)	1.10 (0.20-3.20)*+	0.73 (0.37-2.77)*+	0.019	0.323
7	**Platelet (x10^3/uL)** Median (min-max)	211.00 (52.00-822.00)*+	158.00 (71.00-272.00)*+	0.002	0.427
8	**CRP (mg/L)** Median (min-max)	79.80 (1.30-340.00)*+	128.00 (25.00-418.00)*+	0.007	0.371
9	**D-dimer (µg FEU/mL)** Median (min-max)	0.37 (0.02-3.90)*+	0.26 (0.02-3.90)*+	NS	-

NS: Not significant

*Rank-biserialcorrelation

*+Non- normal distribution

COVID-19: Coronavirus disease-2019, min: Minimum, max: Maximum, CRP: C-reactive protein

Cardiovascular disease and AF are the leading determinants of mortality in these patients [22,23]. As expected, our group 1 of OA users with COVID-19 had significantly higher rates of these comorbidities. Although not statistically significant, the mortality rate of group 1 COVID-19 patients was lower than that of group 2 COVID-19 patients (see Table 1 for the rates). One of the important prognostic factors of COVID-19 is serum CRP levels [23]. Our study results showed significantly higher early admission median (minimum-maximum) serum CRP levels in patients who died (n=21) than in those who survived (n=115) [128.00 (25.00-41800) versus 79.80 (1.30-340.00) mg/dL, r=0.371, p=0.007] (Table 2). Our study group 1 (OA users) had lower serum CRP levels than the 2 (OA non-users) patients (r^{r-b}=0.437, p<0.001) (see Table 1). As is well known, longer hospital stay increases mortality, healthcare-associated infection, and economic burden as well [24]. The median length of hospital stay days was significantly lower for OA users than for OA non-users (10 versus 12 days, r^{r-b}=0.240, and p=0.016). In other words, there was a significant negative correlation between OA use and length of hospital stay (correlation coefficient r=-0.207, p<0.05). Age, presence of comorbidities, serum CRP, and D-dimer levels are some of the predictors of length of hospital stay in COVID-19 infection [25]. The number of comorbidities was significantly higher in OA users (in comparison to OA non-users) (p<0.05). Serum CRP and D-dime levels were significantly lower in COVID-19 patients with OA. They showed a significant negative correlation with OA use (correlation coefficient r were -0.377, and -0.260, respectively, p<0.05, both). Therefore, it seems that lower serum CRP and D-dimer levels in OA users are good prognostic factors [7,8]. OA treatment has a lowering effect on serum CRP and D-dimer levels [26]. Additionally, in patients that OA has been discontinued, the elevation of serum CRP and D-dimer levels may predict venous thromboembolism recurrence [27]. Heparin has no effect on serum CRP levels but a lowering effect on D-dimer levels in COVID-19 [28]. OA therapy is not routinely used in the management of COVID-19. Some guidelines recommend the D-dimer levels-based approach (the international medical prevention registry on venous thromboembolism-D-dimer score), whereas others do not [13,14]. Also, some studies showed that OA positively affects the outcome of COVID-19, whereas other studies showed no benefit. Can these different results be population-related? However, the most important point is that none of the studies showed harmful effects of OA use in COVID-19 [16-19]. The main characteristic of our study is the inclusion of a different population (i.e., Turkish population). We should mention that the aforementioned studies evaluated the effect of OA use on the mortality and outcomes of COVID-19. As far as we know, our study is the 1st that studies the effect of chronic OA use on

the CRP and D-dimers levels in early COVID-19 infection, and most importantly, its relationship with hospital stay length. Herd immunity is one of the main goals of decision-makers and researchers worldwide [29-31]. Reaching herd immunity with available vaccination and prevention strategies in the near future appears difficult (if not impossible) [31]. Complete and/or great shutdowns have major economic sequences that make most countries' decision-makers escape from them and prefer less strict policies in this issue [32,33]. Whether using the beneficial early effects of OA use with vaccination and maximum-tolerated shutdown policies could help reach herd immunity easier and as early as possible needs to be considered. At least, as shown in previous studies and in our COVID-19 patients, there were no major adverse outcomes. One may find this nonsense. However, as Jean Piaget (9th August 1896-16th September 1980) stated: "intelligence is what you use when you don't know what to do: when neither innateness nor learning has prepared you for the particular situation." [34].

Study Limitations

The main limitation of this study is that it did not include young patients with COVID-19. If included, the results would be expected to be more useful. We could continue the OA use in only one of our COVID-19 patients. If we were able to continue OA use after diagnosing COVID-19 infection in more patients, the results might be more comprehensive. Nevertheless, its early use effect on the progress and outcome of COVID-19 infection is promising.

Conclusion

Our pilot study results showed that OA use at the early stage of COVID-19 infection was beneficial. It was associated with lower serum CRP and D-dimer levels at early admission. In addition, these patients had a shorter hospital stay length (in comparison to age and sex-matched OA non-user COVID-19 patients). The beneficial effects of OA use in patients with COVID-19 might help decision makers in the challenging war with this pandemic. However, further dedicated studies are required in this field.

Acknowledgement

We would like to confirm that all authors fulfilled the authorship criteria.

Ethics

Ethics Committee Approval: This retrospective study was approved by University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision number: 2020-24-12, date: 07.12.2020).

Informed Consent: Informed consent form was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: F.K., E.E., E.B., B.E., H.K., R.K., Concept: F.K., M.H., Z.K., K.K.Y., Design: F.K., M.H., Z.K., Data Collection or Processing: F.K., M.H., E.E., E.B., Z.K., B.E., H.K., R.K., Analysis or Interpretation: M.H., H.İ., K.K.Y., Literature Search: F.K., M.H., Writing: F.K., M.H.

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ORIGINAL RESEARCH

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The Diagnostic Role of Immature Granulocyte in Differentiating Acute Calculous Cholecystitis From Biliary Colic

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Abstract

Objective: Acute biliary cholecystitis (ABC) is a significant cause of abdominal pain in emergency department. In this study, we investigated the role of immature granulocytes (Ig) as markers of inflammatory response in distinguishing between biliary colic and ABC.

Materials and Methods: This retrospective study included 150 patients who presented with abdominal pain and were found to have or were diagnosed with gallstones. Patients were divided into biliary colic and ABC groups. Laboratory values of the patients, such as age, white blood cell count (WBC), hemoglobin, platelet, mean platelet volume, red cell distribution width, neutrophil (Neu), lymphocyte, Ig%, Ig number, and C-reactive protein (CRP) were recorded in the study form. Receiver operating characteristic and regression analysis were performed for the diagnosis of ABC.

Results: We found that the WBC, Neu, and Ig counts were statistically significantly higher in patients with ABC than in those with biliary colic. However, in the regression analysis, only the Murphy's sign and CRP value were found to be significant in the diagnosis of ABC [p<0.001, odds ratio (OR): 0.119 [95% confidence interval (CI): 0.053-0.268], p=0.002, OR: 1.007 (95% CI: 1.002-1.011), respectively].

Conclusion: Although the Ig number was statistically significant in distinguishing between ABC and biliary colic, we believe that the CRP value and Murphy's sign are superior parameters.

Keywords: Acute biliary cholecystitis, biliary colic, gallstones, immature granulocytes, abdominal pain

Introduction

Acute cholecystitis is the inflammation of the gallbladder caused by infection and is a common cause of patients presenting to the emergency department. This condition can lead to severe complications and requires rapid diagnosis and effective treatment [1,2]. It is crucial to ascertain whether patients presenting with abdominal pain alongside gallstones are experiencing an attack of cholecystitis because this has significant implications for the individual's clinical management and subsequent follow-up [3].

The discovery of new diagnostic methods and markers can aid in the early diagnosis and management of this disease. Some laboratory parameters, such as white blood cell count (WBC), neutrophil (Neu), Neu/lymphocyte ratio (NLR), C-reactive protein (CRP), and the CRP/albumin ratio play a significant role in determining whether patients will be admitted for observation [4-6]. Additionally, clinical signs, such as Murphy's sign, assist in developing diagnostic and treatment strategies [7]. However, there are still uncertainties in the current literature regarding the specificity and sensitivity of these markers and signs.

Immature granulocytes (Ig) are forms of Neus in the blood circulation that has not yet fully matured. We observed that they are produced in increased amounts when the body experiences infections, inflammation, or certain malignancies. An increase in Ig levels typically reflects bone marrow activation in response to active infection or other pathological conditions.

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In recent years, there has been a growing interest in using the percentage of Ig as a potential marker, especially in the early diagnosis and prognosis evaluation of infected patients [8-14].

This study aimed to investigate the potential role of Ig number and Ig% in the differential diagnosis of acute biliary cholecystitis (ABC) and biliary colic patients and in determining the need for inpatient follow-up while treating patients in line with the literature.

Materials and Methods

This retrospective single-center study was designed after receiving approval from our University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital's Ethics Committee (approval number: KAEK/2022.04.81, date: 07.04.2022). Between January 1, 2021, and January 1, 2022, all patients presenting to the emergency department with abdominal pain and detected gallstones had their WBC, platelet, Neu, hemoglobin, mean platelet volume, red cell distribution width, Ig number and percentage, and CRP results recorded from the hospital information management system. Because all data were obtained retrospectively from the hospital automation system, informed consent was not required.

After examining discharge reports, patients without available background information, those with a history of hematological diseases, malignancies, those under 18 years of age, pregnant, or using anti-inflammatory or immunosuppressive drugs were excluded from the study. After excluding 31 patients with abdominal pain and gallstones who received a diagnosis other than biliary colic and ABC, the study was conducted with a total of 150 patients. The examination and test results were evaluated according to the Tokyo 2018 criteria, and a distinction was made between ABC and biliary colic [2]. In total, 52 patients were included in the ABC group, and 98 were included in the biliary colic group.

Statistical Analysis

Categorical data are expressed as numbers and percentages. Normality analysis of continuous variables was performed using the Kolmogorov-Smirnov and Shapiro-Wilk tests and skewness and kurtosis values. The t-test was used for the analysis of data with a normal distribution, and the Mann-Whitney U test was used for non-normally distributed data, and data were shown as mean ± standard deviation and median (minimum-maximum), respectively. Receiver operating characteristic (ROC) analysis was performed for independent variables that were found to be significant between groups to determine the cut-off values. Sensitivity and specificity values were calculated for these cut-off values. Logistic regression analysis was performed to determine the role of independent variables in the diagnosis of ABC. Statistical significance was defined as $p<0.05$ and 95% confidence interval. The data obtained were analyzed using SPSS 26.0 Statistics (IBM Corporation, Armonk, New York, USA).

Results

Of the 98 patients (65.3%) included in the study, they were discharged with a diagnosis of biliary colic, while 52 patients (34.7%) were hospitalized with a diagnosis of ABC. We found no statistically significant differences between the groups regarding the age or gender of the patients. When laboratory values were compared, WBC, Neu, Ig, and CRP values were significantly higher in the ABC group than in the biliary colic group. We found a statistically significant relationship between the presenting complaints of the patients and the presence of Murphy's sign; however, this relationship was only evident in patients with ABC and those who showed positivity for Murphy's sign (Table 1).

Independent variables that created a statistically significant difference between the biliary colic and ABC groups had cut-off values calculated using ROC analysis for the diagnosis of ABC (Figure 1). Sensitivity and specificity values were calculated for the determined cut-off values (Table 2). Logistic regression analysis of significant variables was performed to demonstrate their effect on the diagnosis of ABC (Table 3).

Discussion

In this study, the diagnostic role of markers such as Ig count and Ig percentage in distinguishing patients with ABC from those with biliary colic was examined, revealing that they do not have a significant relationship.

Karakulak et al. [15] elucidated the crucial correlation between elevated Ig percentage levels and severity, as well as the in-hospital mortality rates, in acute pancreatitis cases. This pivotal study underscores the significant role of Ig% as both a diagnostic and prognostic marker in the context of acute pancreatitis, offering valuable insights into patient outcomes [15]. In the study of Ünsal et al. [16] in 2022 investigated the predictive value of Ig count and delta Neu index (DNI) in the diagnosis of complicated acute cholecystitis. The findings indicate that both the Ig count and DNI have high diagnostic value in acute complicated cholecystitis. In particular, in the ROC analysis, a sensitivity of 68.8% and specificity of 86.9% were found for the Ig count, and 49.3% sensitivity and 96.2% specificity were found for DNI. These results suggest that Ig may play a significant role in assessing the risk of complications in acute cholecystitis [16]. In our study, although the Ig count was significantly higher in patients with ABC, its sensitivity was determined as 65.4% and specificity as 60.2%. Although there was statistical significance in group comparison, we determined that the Ig value did not play a role in distinguishing between

Table 1. Distribution of patient characteristics according to clinical follow-up

	Biliary colic (98)	Acute biliary cholecyctitis (52)	p
Age	54.91±17.90	55.17±16.87	0.930
WBC, 10^3/µL	10.29 (3.67-27.21)	12.99 (4.12-27.73)	**0.001***
Hemoglobin, g/dL	12.98±1.66	13.25±1.96	0.380
Platelet, 10^3/µL	251.41±76.69	259.33±71.85	0.540
MPV, fL	9.74±1.11	9.58±0.90	0.385
RDW, %	13.60 (11.90-17.80)	13.75 (12.00-18.70)	0.991*
Neutrophile, 10^3/µL	8.06±3.98	10.05±3.86	**0.004**
Lymphocyte, 10^3/µL	1.75 (0.20-4.50)	1.60 (0.40-14.90)	0.674*
Ig, %	0.00 (0.0-0.40)	0.00 (0.0-0.10)	0.158*
Ig count, 10^3/µL	0.01 (0.00-0.19)	0.02 (0.00-0.30)	**0.009***
CRP, mg/L	9.15 (0.46-343.12)	32.58 (1.17-386.79)	**<0.001***
	n (%)	**n (%)**	
Gender, female	59 (60.2)	26 (50)	0.230[a]
Nausea	11 (11.2)	9 (17.3)	0.297[a]
Vomitting	9 (9.2)	6 (11.5)	0.647[a]
Murphy (+)	17 (17.3)	33 (63.5)	**<0.001[a]**
Abdominal pain	93 (94.9)	51 (98.1)	0.321[b]
Constipation	92 (93.9)	51 (98.1)	0.233[b]

Student t-test, *: Mann-Whitney U test, [a]: Pearson's chi-square test, [b]: Fisher's exact test

WBC: White blood cells, MPV: Mean platelet volume, RDW: Red cell distribution width, CRP: C-reactive protein, Ig: Immature granulocytes

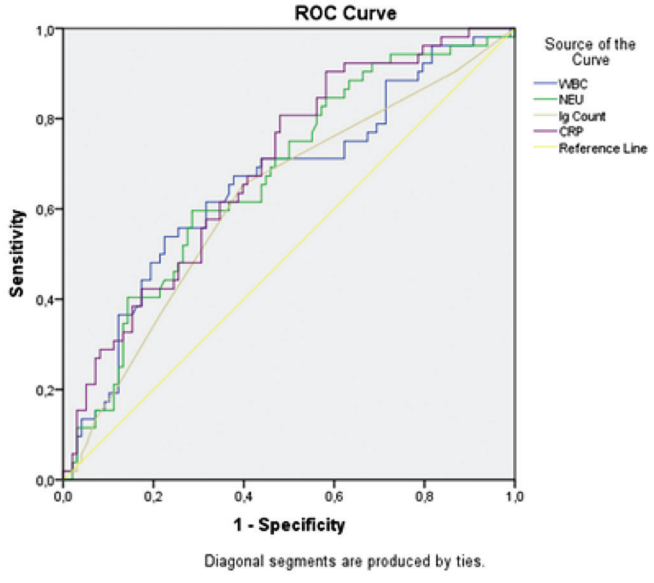

Figure 1. ROC curve of significant independent variables

ROC: Receiver operating characteristic, WBC: White blood cells, Neu: Neutrophil, Ig: Immature granulocytes, CRP: C-reactive protein

biliary colic and ABC in the regression analysis. It would not be appropriate to mention statistical significance and differences from the literature because many studies in the literature did not perform regression analysis.

A study conducted by Mahmood et al. [5] stated that the clinical diagnosis of distinguishing between complicated acute cholecystitis and simple acute cholecystitis is challenging. In this study, the potential use of inflammatory markers like CRP and NLR, to differentiate these two conditions was assessed. In this study, in which 176 patients were treated with emergency laparoscopic cholecystectomy, it was found that patients' age [odds ratio (OR): 1.047; p=0.003], high CRP (OR: 1.005; p=0.012), and NLR (OR: 1.094; p=0.047) values were independently associated with the severity of cholecystitis. The ROC analysis for CRP showed an area under the ROC curve value of 0.773 and indicated that a value above 55 mg/L for CRP is associated with predicting complicated cholecystitis with a sensitivity of 73.9% and specificity of 73.1%. These results suggest that CRP and NLR could be useful markers to predict the risk of complicated acute cholecystitis during emergency admission [5]. In our study, we found that CRP levels above 9.88 mg/L for ABC had a sensitivity of 80.8% and specificity of 52%. This is similar to the literature; however, we believe the difference in specificity may be due to the fact that all patients had gallstones and presented with abdominal pain.

A pivotal study exploring the correlation between gallbladder wall thickness and the CRP/albumin ratio identified the latter as a potentially valuable biomarker for detecting gallbladder inflammation [6]. Further emphasizing the utility of CRP in gallbladder pathologies, another investigation identified CRP levels exceeding 200 mg/dL as critical for reliably predicting

Table 2. ROC analysis, sensitivity, and specificity values of variables for ABC

Variables	Area	Sensitivite	Spesifite	p	95% confidence interval	
					Lower bound	Upper bound
WBC, ≥10.785 10^3/µl	0.658	71.2	56.1	**0.001**	0.565	0.752
Neutrophile, ≥9.105 10^3/µl	0.671	59.6	71.4	**0.001**	0.581	0.760
Ig count, ≥0.015 10^3/µl	0.624	65.4	60.2	**0.012**	0.529	0.719
CRP, ≥9.88 mg/L	0.694	80.8	52.0	**0.000**	0.608	0.780

ABC: Acute biliary cholecystitis, WBC: White blood cells, CRP: C-reactive protein, ROC: Receiver operating characteristic, Ig: Immature granulocytes

Table 3. Results of regression analysis for ABC

	Univariate		Multivariate	
	p	OR (95% CI)	p	OR (95% CI)
WBC	0.008	1.120 (1.030-1.219)	0.912	0.980 (0.684-1.404)
Neutrophile	0.006	1.132 (1.037-1.236)	0.576	1.113 (0.765-1.621)
Ig count	0.196	744.617 (0.033-16684194.55)		
CRP	0.002	1.007 (1.002-1.011)	0.044	1.005 (1.000-1.010)
Murphy (+)	<0.001	0.121 (0.056-0.261)	<0.001	0.119 (0.053-0.268)

ABC: Acute biliary cholecystitis, WBC: White blood cells, CRP: C-reactive protein, OR: Odds ratio, CI: Confidence Interval, Ig: Immature granulocytes

the onset of gangrenous cholecystitis, marking a significant advancement in early diagnostic capabilities [17]. In our study, we observed a statistically significant increase in all inflammatory markers in the ABC group compared with the biliary colic group. These results are consistent with the literature.

The iconic Murphy's sign, steeped in clinical lore, maintains its pivotal stance in the diagnosis of gallbladder diseases. Our findings reaffirm the high-risk association between a positive Murphy's sign and acute cholecystitis, thus advocating for its undisminished value in tandem with modern diagnostic approaches [18]. In our study, we also identified that this sign plays a central role in patient management. These findings emphasize the importance of using clinical examination as a complementary tool to modern diagnostic methods.

Study Limitations

Our study has several limitations that should be acknowledged. First, the study is retrospective in nature, which implies that the data obtained were inherently limited, affecting the comprehensiveness of the analysis. Second, the small number of cases and the confinement of the analysis to a single center may limit the generalizability of our findings. Furthermore, we were unable to evaluate the time from the onset of symptoms to hospital admission, which might have an impact on the values of inflammatory markers.

Conclusion

This study highlights the synergistic utility of biomarkers, such as Ig, CRP, WBC count, and the clinical signs of Murphy's in the diagnosis and management of ABC. The integrated application of these markers may enhance the precision of diagnostic processes and improve patient management. Our findings suggest the potential for a more efficient triage of patients presenting with abdominal pain in emergency settings, potentially expediting appropriate treatment decisions.

Although the results are promising, they should be interpreted with an understanding that they stem from a single-center study with a limited sample size. Confirmation of these findings in larger, multicentric studies is essential to solidify their place in clinical practice.

Future research expanding and refining these preliminary observations could pave the way for identifying the optimal combination of biomarkers and clinical signs for the diagnosis and treatment of gallbladder diseases. Adopting a more holistic and multifaceted approach in clinical practice is likely to enhance success rates in the management of biliary disorders and improve patient outcomes.

Ethics

Ethics Committee Approval: This retrospective single-center study was designed after receiving approval from our University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital's Ethics Committee (approval number: KAEK/2022.04.81, date: 07.04.2022).

Informed Consent: Informed consent was not required, because all data were obtained retrospectively from the hospital automation system.

Authorship Contributions

Surgical and Medical Practices: R.Y., M.U., T.Ö., Consenp: R.Y., B.Y., M.K.A., S.D., Design: R.Y., M.U., T.Ö., A.F.B.K., S.D., Data Collection or Processing: R.Y., B.Y., M.U., T.Ö., M.K.A., Analysis

or Interpretation: R.Y., M.U., M.K.A., S.D., Literature Search: R.Y., B.Y., A.F.B.K., Writing: R.Y., B.Y., A.F.B.K., S.D.

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ORIGINAL RESEARCH

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The Prognostic Role of Systemic Inflammatory Parameters and Severity Scores in Patients with Acute Pancreatitis

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Abstract

Objective: To investigate the predictive power of the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/eosinophil ratio (MER), and C-reactive protein (CRP) levels, as well as the harmless acute pancreatitis score (HAPS) and modified computed tomography severity index (mCTSI) score, in patients with acute pancreatitis (AP).

Materials and Methods: This retrospective study included adult patients hospitalized for AP. Patients were classified according to disease severity using HAPS and mCTSI. Systemic inflammatory parameters and demographic data were compared among patients to identify factors associated with disease severity.

Results: A total of 442 patients, 199 males (45%) and 243 females (55%), were enrolled in the study. Patients with severe disease had significantly higher mean NLR, PLR, MER, and CRP values than those with mild or moderate disease according to HAPS and mCTSI classifications. Positive correlations were observed between serum NLR, PLR, MER, CRP, and mCTSI. HAPS was correlated with NLR, MER, and CRP. Elevated NLR, MER, and CRP levels were independent predictors of disease severity in patients with AP according to HAPS and mCTSI.

Conclusion: NLR, MER, and CRP levels, but not PLR, in conjunction with HAPS or mCTSI may be useful for clinical decision-making regarding AP severity.

Keywords: Acute pancreatitis, systemic inflammatory parameters, harmless acute pancreatitis score, modified CT severity index

Introduction

Immediate pancreatic tissue inflammation is referred to as acute pancreatitis (AP). The condition can cause significant morbidity and mortality in severe cases, especially when accompanied by pancreatic necrosis [1]. Rapid evaluation and determination of disease severity in patients presenting to the emergency department (ED) with AP are crucial for improving prognosis and treatment success [2].

Numerous biological markers and inflammatory mediators can be used to diagnose and assess the severity of AP. During the initial examination, amylase and lipase levels, complete blood count, metabolic panel (levels of urea, creatinine, glucose, calcium, etc.), triglyceride level, urinalysis, and arterial blood gas are diagnostically valuable [3]. Moreover, scoring systems such as the Ranson's criteria, Glasgow-Imrie criteria, acute physiology and chronic health evaluation II scale, computed tomography severity index (CTSI), harmless acute pancreatitis score (HAPS), and prognostic nutritional index can be used to assess AP severity [4]. However, most scoring systems used to evaluate AP severity require at least 48 hours of patient monitoring. As a result, scoring systems have limited utility in patients with AP [5].

HAPS facilitates an early diagnosis of mild, non-intensive care unit (ICU) AP cases [6]. HAPS can be assessed during the first 30

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minutes of a patient's visit to the clinic based on the absence of rebound pain or guarding, normal hematocrit levels, and normal serum creatinine levels [7]. HAPS accurately predicted benign prognosis in 98% of 394 patients [6]. The CTSI, as defined by Balthazar et al. [8], revealed a highly significant association of mortality and morbidity with the presence of necrosis >30% of the pancreatic gland on abdominal CT. In addition, a retrospective analysis of 268 patients with AP showed that individuals with a CTSI >5 had an eightfold increased mortality rate [9].

The systemic inflammatory indicators neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/eosinophil (MER) ratio, and C-reactive protein (CRP) level are associated with disease severity and clinical outcomes in critical illness [10]. Azab et al. [11] showed that an elevated NLR in patients with AP was associated with an increased rate of ICU admission and length of stay. In the same study, the NLR was significantly higher in deceased patients than in survivors [11]. Larvin [12] found that CRP levels >15 mg/dL within the first 48 hours could distinguish severe and moderate AP. A study of 168 patients with AP showed the utility of systemic inflammatory parameters such as leukocyte count, CRP level, and NLR in addition to other diagnostic and prognostic tools [13].

We evaluated the ability of the NLR, PLR, MER, and CRP levels, as well as the HAPS and CTSI, to predict the severity of AP during clinical follow-up.

Materials and Methods

Ethics Committee Approval and Patient Consent

This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital's Ethics Committee (decision number: 127-2021, date: 09.02.2022). The institutional review board did not require patient consent to access the medical records because there were no potentially identifiable markers or patient identifiers in the photographs or text.

Study Design and Setting

This retrospective, cross-sectional, observational, single-center study included 442 consecutive adult patients aged ≥18 years diagnosed with pancreatitis in the ED and hospitalized between January 1, 2016 and January 1, 2021.

Data were collected by searching for the K85 and K86 international classification of disease codes in the hospital's record systems and archives. We assessed the patients' demographics (age and sex), laboratory parameters [leukocyte (normal level [N]: 4.5-10.0 10^3/μL), neutrophil (N: 1.5-8.0 10^3/μL), lymphocyte (N: 0.8-5.0 10^3/μL), eosinophil (N: 0.01-0.40 10^3/μL), and platelet counts (N: 150-450 10^3/μL) and monocyte (N: 4.2-11.8%), neutrophil (N: 42.9-74.3%), eosinophil (N: 0.2-5.3%), and lymphocyte (N: 18.3-45.7%) percentages, NLR, PLR, MER, and CRP (N: <5 mg/dL)] values measured on admission, and radiological findings.

Initially, patients were divided into two groups based on clinical outcome (ward vs. ICU admission). The groups were compared according to age, sex, etiology, HAPS, CTSI, modified CTSI (mCTSI), NLR, PLR, MER, and CRP. Patients were separated into three groups based on AP severity defined by the HAPS: mild, moderate, and severe AP. Finally, the CTSI and mCTSI were used to categorize AP as mild, moderate, or severe. We investigated differences in age, sex, and inflammatory parameters among the groups.

Scoring Systems for Severity in AP

The HAPS is a clinical scoring system that identifies patients with their first episode of AP who do not require intensive care. HAPS is generally determined within 30 minutes of admission and is based on a lack of rebound tenderness or guarding, normal hematocrit level, and normal serum creatinine level [6].

The CTSI was created by Balthazar et al. [8] to assess the severity of AP. The grades of pancreatitis (normal pancreas: 0; pancreatic enlargement: 1; inflammatory changes in the pancreas and peripancreatic fat: 2; poorly defined single peripancreatic fluid collection: 3; two or more poorly defined peripancreatic fluid collections: 4) and the extent of pancreatic necrosis (none: 0; ≤30%: 2; >30-50%: 4; >50%: 6) are components of the CTSI. The maximum score was 10 [14].

The mCTSI has a stronger relationship with patient outcomes, including hospitalization duration and the incidence of organ failure. The score (maximum 10) was based on estimated pancreatic inflammation and necrosis. Three factors were considered in the mCTSI: pancreatic inflammation (normal pancreas: 0, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat: 2, pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis: 4), pancreatic necrosis (none: 0; ≤30%: 2; >30%: 4), and extra-pancreatic consequences (one or more pleural effusions, ascites, vascular complications, parenchymal complications, and/or gastrointestinal involvement: 2) [15].

Study Population and Sampling

To reduce selection bias, all patients meeting the eligibility criteria during the study period were included. We enrolled 2,360 consecutive adult patients diagnosed with AP in the ED who were hospitalized during the study period. Of these patients, the following were excluded: 220 due to unavailable data, 4 due to pregnancy, 1,152 due to a diagnosis of chronic pancreatitis, 150 due to a history of hematological disease,

and 392 due to an additional inflammatory disease, other than pancreatitis, including cholangitis, or a history of medication usage (anti-inflammatory drugs, antibiotics, statins, etc.) during the previous week, which can affect the serum NLR, PLR, MER, and CRP levels. Finally, 442 patients were included in the analysis.

Statistical Analysis

Before data collection, the sample size was determined by power analysis using data from previous studies. With a power of 95% and alpha error of 5%, it was anticipated that at least 334 patients would be required to detect significant differences in disease severity among groups.

Data analysis was conducted using SPSS statistical software (version 15.0 for Windows; SPSS Inc., Chicago, IL). Categorical variables (sex and age) are expressed as numbers of patients (n) expressed as percentages (%). Numerical data are expressed as means with standard deviations. Intergroup comparisons were conducted using the Mann-Whitney U test for non-normally distributed data (e.g., NLR, PLR, MER, CRP, HAPS, CTSI, and mCTSI). One-Way ANOVA was used to compare numerical variables among more than two groups for normally distributed variables (e.g., age and sex), and the Kruskal-Wallis test was used for non-normally distributed variables (e.g., NLR, PLR, MER, CRP, HAPS, CTSI, and mCTSI). Non-parametric subgroup analyses were conducted using the Mann-Whitney U test and interpreted using Bonferroni correction. Spearman's correlation analysis was used to analyze the relationship between numerical variables when the parametric test condition was not satisfied. Independent variables were analyzed using multivariate logistic regression analysis. All potential predictor variables were included in the initial model using the enter method. Significance assessments via the likelihood ratio test led to the retention of statistically significant variables in the final model. Non-significant variables were removed to achieve a more parsimonious model. The alpha significance level was set to $p<0.05$.

Results

The study included 442 patients, including 199 (45.0%) males and 243 (55.0%) females. The mean age of the patients was 54.5±18.2 years (minimum 18, maximum 97 years). Biliary pancreatitis accounted for 50.7% (n=224) and nonbiliary pancreatitis for 49.3% (n=218) of the cases. Regarding clinical outcomes, 419 patients (94.8%) were followed up in the ward, whereas 23 (5.2%) were followed up in the ICU. There were no fatalities.

There were no significant differences in age or sex between the ward and ICU patients (p=0.110 and p=0.149, respectively). When the participants were categorized according to HAPS, a significant difference was observed between the ward and ICU patients (p<0.001). In addition, the CTSI and mCTSI were significantly higher in the ICU than ward patients (p<0.001, for both comparisons). There were significant differences in the NLR and MER between the ward and ICU patients (p=0.002 and p<0.001, respectively). However, the PLR and CRP levels did not differ between the two groups (p=0.232 and p=0.064, respectively) (Table 1).

Table 1. Clinical outcomes

		ICU	Ward	p*
Age (years), mean ± SD		60.20±18.20	54.20±18.10	0.110
Sex, n (%)	Male Female	7 (30.4%) 16 (69.6%)	192 (45.8%) 227 (54.2%)	0.149
Etiology, n (%)	Biliary Nonbiliary	11 (47.8%) 12 (52.2%)	213(50.8%) 206 (49.2%)	0.779
HAPS	Mild Moderate Severe	0 (0.0%) 8 (34.8%) 15 (65.2%)	281 (67.1%) 108 (25.8%) 30 (7.2%)	<0.001
		Mean ± SD	**Mean ± SD**	
CTSI		4.20±1.30	1.80±1.40	<0.001
Modified CTSI		6.00±1.90	2.10±1.90	<0.001
NLR		12.79±10.16	7.71±8.43	0.002
PLR		246.10±216.6	191.70±159.30	0.232
MER		59.00±37.40	28.30±27.60	<0.001
CRP		82.80±71.30	55.8±6.69	0.064

Data are expressed as numbers (n) and percentages (%), means, and standard deviations (SD)

*Intragroup analyses (ICU vs. ward) were conducted using chi-squared and the Mann-Whitney U tests, as appropriate

ICU: Intensive care unit, HAPS: Harmless acute pancreatitis score, CTSI: Computed tomography severity index, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MER: Monocyte/eosinophil ratio, CRP: C-reactive protein

Age was positively correlated with NLR (rho =0.227 and p<0.001), PLR (rho =0.113 and p=0.017), and CRP level (rho =0.166 and p<0.001). However, no significant correlation was observed between age and MER (p=0.512). HAPS was positively correlated with NLR (rho =0.165 and p<0.001), MER (rho =0.190 and p<0.001), and CRP level (rho =0.196). Similarly, the CTSI and mCTSI were positively correlated with NLR, PLR, MER, and CRP levels (Table 2).

Based on HAPS, 281 (63.6%) patients were classified as mild AP, 116 (26.2%) as moderate AP, and 45 (10.2%) as severe AP. Neither age nor sex was significantly different according to AP severity (p=0.187 and p=0.086, respectively). However, the NLR, PLR, MER, and CRP levels differed significantly according to HAPS (p=0.001 for all comparisons) (Table 3). Multivariate logistic regression analysis identified MER [odds ratio (OR): 1.014, confidence interval (CI): 1.006-1.021; p<0.001], CRP level (OR: 1.005, 95% CI: 1.002-1.008; p=0.002), and NLR (OR: 1.046, 95% CI: 1.002-1.089; p=0.031) as independent predictors of severe AP according to HAPS (Table 4).

For identifying severe AP according to the HAPS, a MER ≥21.2 had 57.1% sensitivity and 56.6% specificity [area under the curve (AUC): 0.604, 95% CI: 0.548-0.660, p<0.001]. A CRP level ≥29.5 mg/L indicated severe AP with 57.8% sensitivity and 56.3% specificity (AUC: 0.599, 95% CI: 0.544-0.655, p=0.001).

Table 2. Correlations of the mean serum NLR, PLR, MER, and CRP level with demographic and clinical characteristics

	NLR		PLR		MER		CRP	
Characteristic	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Age	0.227	<0.001	0.113	0.017	0.031	0.512	0.166	<0.001
HAPS	0.165	<0.001	0.013	0.790	0.190	<0.001	0.196	<0.001
Length of stay in hospital	0.155	0.001	0.067	0.159	0.043	0.364	0.297	<0.001
ICU length of stay	0.146	0.002	0.057	0.228	0.190	<0.001	0.086	0.070
CTSI	0.248	<0.001	0.133	0.005	0.348	<0.001	0.258	<0.001
Modified CTSI	0.259	<0.001	0.144	0.002	0.365	<0.001	0.281	<0.001

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MER: Monocyte/eosinophil ratio, CRP: C-reactive protein, HAPS: Harmless acute pancreatitis score, CTSI: Computed tomography severity index, ICU: Intensive care unit

Table 3. Demographic characteristics and systemic inflammatory parameters according to AP severity based on severity scores

		Mild mean ± SD	**Moderate mean ± SD**	**Severe mean ± SD**	**p***
HAPS	NLR	7.30±8.60	7.60±6.20	13.10±11.70	<0.001
	PLR	193.80±161.50	161.50±100.40	284.40±250.30	0.001
	MER	25.30±25.40	34.10±30.70	47.60±36.30	<0.001
	CRP	47.00±54.90	61.10±70.50	111.00±98.00	<0.001
		Non-severe mean ± SD		**Severe mean ± SD**	**p***
CTSI	NLR	7.90±8.50		14.10±12.70	0.131
	PLR	192.80±162.90		279.30±145.40	0.449
	MER	29.60±28.70		44.00±37.60	0.265
	CRP	56.50±67.10		88.90±74.30	0.585
		Mild mean ± SD	**Moderate mean ± SD**	**Severe mean ± SD**	**p***
Modified CTSI	NLR	6.70±6.20	9.90±11.60	15.80±11.90	<0.001
	PLR	175.00±117.40	225.20±218.00	302.40±264.50	0.031
	MER	21.20±22.30	46.20±31.40	56.60±40.70	<0.001
	CRP	43.70±51.60	81.60±85.00	107.10±86.00	<0.001

Data are expressed as numbers (n) and percentages (%), means, and standard deviations (SD)

*Intragroup analyses (eg, non-severe or severe) were conducted using chi-squared, One-Way ANOVA test (eg, mild, moderate, or severe), and the Kruskal-Wallis tests, as appropriate

AP: Acute pancreatitis, HAPS: Harmless acute pancreatitis score, CTSI: Computed tomography severity index, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MER: Monocyte/eosinophil ratio, CRP: C-reactive protein

Finally, an NLR ≥5.59 was identified as the cut-off value for detecting severe AP, with 58.4% sensitivity and 57.7% specificity (AUC: 0.583, 95% CI: 0.527-0.638, p=0.004) (Figure 1).

Based on the CTSI, 433 patients (97.9%) had non-severe AP and 9 severe AP. There were no significant differences in age or sex (p=0.195 and p=0.840, respectively) between the non-severe and severe AP groups. Moreover, the NLR, PLR, MER, and CRP values did not differ between the groups (p=0.131, p=0.449, p=0.265, and p=0.585, respectively) (Table 3).

There were 296 (67%) individuals with mild AP, 129 (29.2%) with moderate AP, and 17 (3.8%) with severe AP based on the mCTSI. Age and sex did not differ significantly according to AP severity (p=0.090 and p=0.168, respectively). However, the NLR, PLR, MER, and CRP levels differed significantly according to AP severity (p<0.001, p=0.031, p<0.001, and p<0.001, respectively) (Table 3). Multivariate logistic regression analysis identified NLR (OR: 1.046, 95% CI: 1.014-1.079; p=0.005), MER (OR: 1.034, 95% CI: 1.026-1.043; p<0.001), and CRP level (OR: 1.008, 95% CI: 1.004-1.011; p<0.001) as independent predictors of severe AP according to the mCTSI (Table 4).

An MER ≥23.45 was identified as the cut-off value for detecting severe AP according to the mCTSI, with 68.5% sensitivity and 67.3% specificity (AUC: 0.731, 95% CI: 0.678-0.784, p<0.001). A CRP level ≥35.5 mg/dL had 61.6% sensitivity and 62.9% specificity for the detection of severe AP (AUC: 0.654, 95% CI: 0.598-0.709, p<0.001). An NLR ≥5.93 was identified as the cut-off value for predicting severe AP, with a sensitivity of 60.3% and specificity of 60.9% (AUC: 0.621, 95% CI: 0.564-0.678, p<0.001). Finally, a PLR ≥152.1 was identified as the cut-off value for detecting severe AP, with 55.5% sensitivity and 55.4% specificity (AUC: 0.570, 95% CI: 0.511-0.628, p=0.017) (Figure 2).

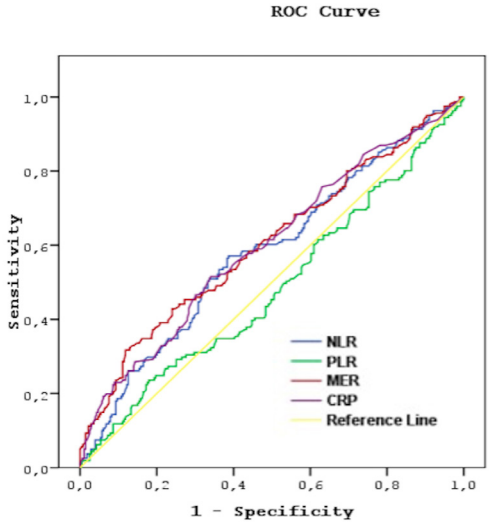

Figure 1. Specificity and sensitivity of the NLR, PLR, MER, and CRP level for determining the severity of AP according to the HAPS using ROC curves

ROC: Receiver operating characteristics, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MER: Monocyte/eosinophil ratio, CRP: C-reactive protein

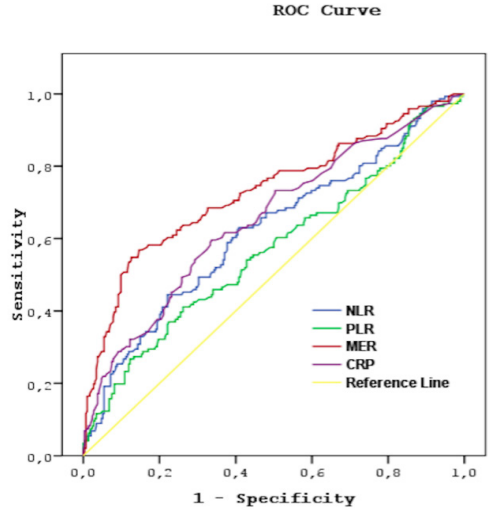

Figure 2. Specificity and sensitivity of the NLR, PLR, MER, and CRP level for determining the severity of AP according to the modified CTSI using ROC curves

ROC: Receiver operating characteristics, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MER: Monocyte/eosinophil ratio, CRP: C-reactive protein

Table 4. Multivariate logistic regression analysis to determine disease severity

		p	OR	95% CI	
HAPS	NLR	0.031	1.046	1.004	1.089
	PLR	0.050	0.998	0.996	1.000
	MER	<0.001	1.014	1.006	1.021
	CRP	0.002	1.005	1.002	1.008
Modified CTSI	NLR	0.005	1.046	1.014	1.079
	MER	<0.001	1.034	1.026	1.043
	CRP	<0.001	1.008	1.004	1.011

OR: Odds ratio, CI: Confidence interval, HAPS: Harmless acute pancreatitis score, CTSI: Computed tomography severity index, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MER: Monocyte/eosinophil ratio, CRP: C-reactive protein

Discussion

The clinical manifestations of AP range from transient abdominal discomfort to death [16]. Given the significant mortality and morbidity rates, early assessment of clinical characteristics and treatment initiation are crucial. We assessed the predictive power of systemic inflammatory markers and HAPS and mCTSI in patients with AP.

The key findings are as follows. The HAPS, CTSI, and mCTSI were significantly higher in the ICU than ward patients. Additionally, NLR and MER differed significantly between the groups. HAPS was significantly and positively correlated with NLR, MER, and CRP levels. The CTSI and mCTSI were positively correlated with NLR, PLR, MER, and CRP levels. Patients with severe AP, according to the HAPS, had significantly higher NLR, PLR, and CRP values than those with mild and moderate AP patients. According to the mCTSI, patients with severe AP had increased NLR, PLR, MER, and CRP values. Moreover, NLR, MER, and CRP levels were independent predictors of severe AP based on HAPS and mCTSI. According to HAPS, an MER ≥21.2, CRP level ≥29.5 mg/dL, and NLR ≥5.59 were identified as the cut-offs for predicting severe AP. Based on the mCTSI, an MER ≥23.45, CRP level ≥35.5 mg/dL, NLR ≥5.93, and PLR ≥152.1 predicted severe AP.

None of the AP scoring systems are completely reliable [17,18]. Typically, scoring systems require 48 hours to obtain results, which may not be feasible in the ED. The HAPS can be calculated quickly using only three simple parameters [6]. In a cohort trial involving 394 patients, Lankisch et al. [6] reported that HAPS reliably identified mild AP. In a study of 322 patients with AP, Gülen et al. [19] found that HAPS was not predictive of poor prognosis. In the same study, logistic regression analysis of the CTSI, HAPS, red blood cell distribution width, NLR, age, diabetes mellitus, and systolic blood pressure revealed that only the CTSI was independently associated with mortality. We found that HAPS and CTSI were significantly higher in ICU patients than in hospitalized adults. Furthermore, the NLR, PLR, and CRP levels were positively correlated with HAPS. Moreover, the CTSI was significantly and positively correlated with the NLR, PLR, MER, and CRP levels.

Systemic inflammatory parameters such as NLR, PLR, MER, and CRP levels are indicative of disease severity and poor clinical outcomes in various conditions [20-22]. NLR and CRP levels are inexpensive, reproducible, rapid, and easily accessible markers of inflammatory status. Song et al. [23] showed that initial NLR was associated with the prognosis of infection-related diseases. Additionally, Jeon and Park [10] reported that NLR was associated with organ failure and disease severity in patients with AP. Larvin [12] showed that CRP >15 mg/dL within the first 48 hours differentiated severe from moderate AP. Similarly, Stirling et al. [24] revealed that a CRP level of >190 mg/dL indicates severe AP. Yarkaç et al. [13] found a statistically significant difference between mild and severe AP in terms of hospitalization duration, CRP level, leukocyte count, and NLR among 168 patients with AP. In a comparison of the predictive values of inflammatory markers for AP severity and mortality, NLR had the greatest predictive power, regardless of age [25]. Kaya et al. [26] reported that the PLR could predict AP severity early. In this study, ICU patients had higher NLR and MER values than ward patients. However, PLR and CRP levels did not significantly differ between the groups. According to the HAPS, patients with severe AP had higher NLR, PLR, and CRP values than those with mild or moderate AP patients. Regression analysis showed that MER, CRP level, and NLR were predictive of severe AP.

Ward and ICU AP patients had significantly different CTSI values. However, the NLR, PLR, MER, and CRP levels did not differ between severe and non-severe AP patients according to the CTSI. The NLR, PLR, MER, and CRP levels significantly differed among patients with mild, moderate, and severe AP, as defined by the mCTSI. In addition, NLR, MER, and CRP levels were independent predictors of severe AP. No previous study has compared the CTSI and mCTSI. Our results showed that the mCTSI was more predictive of morbidity than the CTSI. HAPS and mCTSI were positively correlated with NLR, PLR, MER, and CRP levels. In patients presenting to the ED with AP, HAPS or mCTSI in conjunction with inflammatory markers can potentially differentiate serious diseases in patients with AP.

Azab et al. [11] recommended an NLR >4.7 as a predictor of severe AP. Suppiah et al. [27] reported that the optimal cut-off value determined from a receiver operating characteristic curve was >4.8, with 90.9% sensitivity and 22.5% specificity. In this study, NLR values ≥5.59 and ≥5.93 were considered predictive of severe AP based on HAPS and mCTSI, respectively. Furthermore, HAPS defines severe AP as an MER ≥21.2 and CRP level ≥29.5 mg/dL. Finally, an MER ≥23.45, CRP level ≥35.5 mg/dL, and PLR ≥152.1 were identified as cut-offs for detecting severe AP according to the mCTSI.

Study Limitations

This study had several limitations, most of which were its retrospective, single-center design and inclusion of only 442 patients. The rate of unavailable data was quite high, potentially affecting our results. Missing data can introduce bias and reduce study precision. In addition, single measurements of serum NLR, PLR, MER, and CRP levels were performed upon admission to the ED. Hence, these parameters, which can affect long-term outcomes, were not assessed in the AP patients following hospitalization. These issues should be considered in future studies.

Conclusion

Our findings revealed that systemic inflammatory parameters, including the mean serum NLR, MER, and CRP levels, but not the PLR, upon admission to the ED when evaluated in combination with HAPS or mCTSI, may be useful biomarkers

for predicting disease severity in patients with AP. However, randomized controlled studies with more cases are needed to validate the use of NLR, MER, and CRP as biomarkers and for clinical decision-making regarding AP severity.

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Ethics

Ethics Committee Approval: This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital's Ethics Committee (decision number: 127-2021, date: 09.02.2022).

Informed Consent: The institutional review board did not require patient consent to access the medical records because there were no potentially identifiable markers or patient identifiers in the photographs or text.

Authorship Contributions

Concept: T.A., A.A., Ö.S., Design: T.A., Ö.S., T.A., Data Collection or Processing: T.A., T.A., T.S.C., Analysis or Interpretation: T.A., T.S.C., Literature Search: T.A., A.A., Writing: T.A., A.A., Ö.S.

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ORIGINAL RESEARCH

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Prognostic Value of Systemic Immune-inflammation Index in Patients with Pediatric Blunt Abdominal Trauma

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Abstract

Objective: Trauma is a leading cause of morbidity and mortality in children. One in every four patients with trauma has abdominal trauma. Abdominal trauma is the third leading cause of death associated with trauma. Mortality increases in patients with inflammation because of the body's reaction to trauma. The systemic immune-inflammation index (SIII) is a test indicative of body inflammation based on complete blood count alone. Index value may indicate prognosis of pediatric patients with blunt abdominal trauma.

Materials and Methods: The present study was designed as a retrospective, single-center research. The study included pediatric patients with isolated blunt abdominal trauma who were admitted to the emergency department between June 01, 2021 and June 01, 2022 and met the inclusion criteria. Patient demographic data; medical history; leukocytes, platelet, and neutrophil count; SIII; and outcome status were captured in the case form.

Results: The study included 103 patients, of whom 64.1% were male and the mean age was 7.32±5.12 years. Mortality was noted in 6.8% of the patients included in the study. The sensitivity and specificity for a cut-off value of 890.47×10^3/L SIII were 95.7% and 62.5%, respectively (area under the curve: 0.832; 95% confidence interval: 0.820-0.944, $p<0.003$), in pediatric patients with blunt abdominal trauma.

Conclusion: High SIII scores, a rapid, inexpensive, reliable, and radiation-free test, could be used as a predictor of mortality in pediatric patients admitted to the emergency department with blunt abdominal trauma.

Keywords: Systemic immune-inflammation index, blunt abdominal trauma, pediatric patient, mortality

Introduction

Trauma is one of the leading causes of morbidity and mortality in >1-year-old children [1]. Data from the USA indicates that more than 10 million children present to emergency departments each year because of injuries associated with trauma [2]. Approximately 25% of pediatric patients experience abdominal trauma [3]. More than 90% of these injuries are due to blunt trauma [1]. Blunt abdominal trauma is the third most prevalent cause of mortality associated with trauma in children following head and chest injuries [4].

According to World Health Organization data, trauma is responsible for approximately 950,000 deaths annually among children and young people <18 years [5]. The challenges associated with detecting intra-abdominal injuries in children with multiple injuries account for the higher mortality rate [6]. In this patient group, physical examination may provide limited data. Thus, focused assessment with sonography in trauma (FAST) is used in children with blunt abdominal trauma, yet the sensitivity of the FAST test is quite low [7]. Computed tomography (CT) scan is considered the gold standard in these patients; nevertheless, radiation exposure in pediatric patients is associated with an increased risk of malignancy [8]. Patient selection for advanced imaging procedures is crucial. Therefore, clinicians tend to use easier, cheaper, faster, and radiation-free laboratory tests subsequent to physical examination to detect intra-abdominal injury in children [9].

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The inflammation process is induced by biomolecular activation following trauma. Inflammation starts with the activation of various cells due to the release of purinergic receptors and ATP during trauma. Among these cells, neutrophils are one of the first to respond to inflammation, causing tissue damage [10]. Platelets adhere to damaged vessel walls and release platelet granules, inducing thrombus formation. Platelets are also involved in local inflammation. Neutrophils, lymphocytes, and platelets included in the complete blood count parameters play a role in the inflammatory process [11]. The systemic immune-inflammation index (SIII) is a novel inflammatory biomarker used as both a diagnostic and prognostic marker in several internal and surgical conditions [12]. SIII may reflect systemic inflammation in the body [13] and is a biomarker of platelet, neutrophil, and lymphocyte counts [14]. SIII is an easily assessable, inexpensive, and objective parameter composed only of hemogram parameters. Therefore, SIII may be a prognostic indicator in pediatric patients with blunt abdominal trauma.

Materials and Methods

This retrospective single-center study was performed in the emergency department of a training and research hospital upon approval of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (approval number: KAEK/2022.06.212, date: 23.06.2022). The study included pediatric patients who were admitted to the emergency department because of isolated blunt abdominal trauma between June 01, 2021 and June 01, 2022, and who met the inclusion criteria. Patient data were retrieved from the hospital information management system (HIMS). Informed consent was obtained from the patients included in the study.

The study included <18-year-old patients with isolated abdominal trauma, abdominal CT imaging, complete blood count, mortality or discharge status, and complete data in the HIMS. Patients aged >18 years, those with trauma other than abdominal trauma, incomplete data, pregnant women, those with a history of malignancy, those with hematologic or bone marrow pathology, and those with suspected infection were excluded.

Patients' demographic data; medical history; leukocytes, platelet, and neutrophil count; SIII; and mortality or discharge status were retrieved from the HIMS and captured on the case form. Patients were divided into two groups according to mortality status. The study included 133 patients admitted to the emergency department because of isolated abdominal trauma. Of the patients, 17 were excluded because of incomplete data, 5 because of hematologic or bone marrow pathology, 4 because of malignancy, and 4 because of suspected infection. The study was conducted on the remaining 103 patients (Figure 1).

The hemogram results for each patient were used in the calculations. The platelet, neutrophil, and lymphocyte counts were expressed as P, N, and L, respectively. The neutrophil-to-lymphocyte ratio (NLR) (N/L ratio) and SIII [(P×N)/L] were calculated based on these values [12].

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Software (Version 26.0) was used for data analyses. Number, percentage, mean, standard deviation (SD), median, minimum, and maximum values were used for the presentation of descriptive data. The Kolmogorov-Smirnov test was used to test the normality of the data. In the univariate analysis, continuous variables with normal distribution were expressed as mean±SD and compared using the t-test. The Pearson chi-square test was used to analyze the categorical variables. Fisher's exact test was used when there were less than five categorical variables. The independent samples t-test was used to compare two independent numerical datasets. Diagnostic accuracy was assessed using receiver operating characteristic (ROC) curve analysis. Appropriate cut-off values were determined, and sensitivity and specificity values were calculated for parameters with an area under the curve (AUC) >0.600. A p-level <0.05 was considered statistically significant.

Results

The present study included 103 patients, of whom 64.1% were male, and the mean age was 7.32±5.12 years. Among the included patients, 41.7% were discharged, 24.3% were admitted to the intensive care unit (ICU), and the remaining 34% were admitted to the ward. The length of hospital stay was an average of 3.80±5.99 days. Mortality was observed in

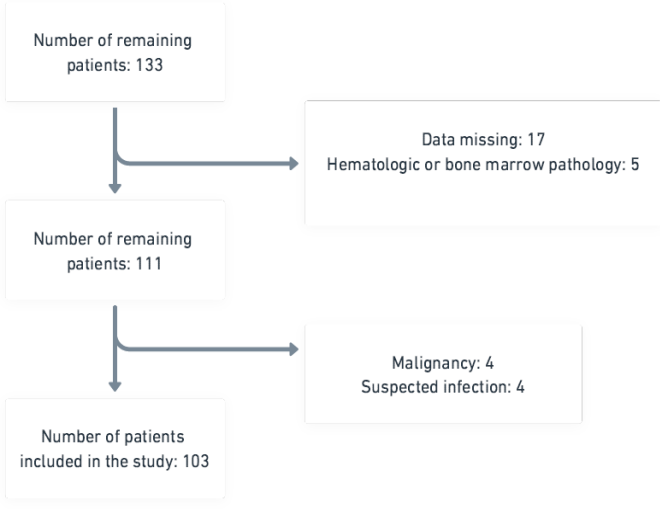

Figure 1. Flowchart of the cases included in the study

6.8% of cases. The mean values for vital signs and laboratory results are presented in Table 1. Accordingly, the mean NLR value and the mean SIII value were 4.25±4.36 and 1217.59×10³±1396.50×10³), respectively (Table 1).

Patients' demographic and clinical data were compared according to mortality status. There were no significant differences between mortality and mean age and sex. Systolic blood pressure, diastolic blood pressure, and saturation were lower in patients who died, whereas the pulse rate was significantly higher in these patients. All patients who died were admitted to the ICU (Table 2).

Laboratory data analysis showed significantly lower hemoglobin levels, whereas platelet, C-reactive protein, alanine transaminase (ALT), aspartate transaminase (AST), amylase, and lipase levels were significantly higher in patients who died than in those who survived. Furthermore, NLR as calculated based on laboratory data was not significant in predicting mortality, whereas the SIII index was significant

Table 1. Assessment of demographic and clinical data of the patients

Parameter		n (%)/mean ± SD
Age (years)		7.32±5.12
Sex	Male	66 (64.1)
	Female	37 (35.9)
Vital signs	SBP (mmHg)	106.20±13.15
	DBP (mmHg)	68.23±14.54
	Pulse rate (beats/min)	108.29±24.80
	Saturation (%)	97.18±6.72
Hospitalization status	None/discharged	43 (41.7)
	Ward admission	35 (34.0)
	ICU admission	25 (24.3)
Length of hospitalization (days)		3.80±5.99
Mortality	Yes	7 (6.8)
	No	96 (93.2)
Laboratory data	WBC (×10³/mm³)	15.78±8.67
	HGB (mg/dL)	11.74±2.09
	PLT (×10³/mm³)	277.88±97.33
	NEU (×10³/mm³)	10.68±7.83
	LEN (×10³/mm³)	4.15±3.68
	ALT (IU)	115.60±224.99
	AST (IU)	190.23±368.00
	Amylase (IU)	70.19±66.62
	Lipase (IU)	53.36±101.94
Indexes	NLR	4.25±4.36
	SIII (×10³)	1217.59±1396.50

SD: Standard deviation; ICU: Intensive care unit, WBC: Leukocytes, HGB: Hemoglobin, PLT: Platelet, NEU: Neutrophils, LEN: Lymphocyte, ALT: Alanine transaminase, AST: Aspartate transaminase, NLR: Neutrophil/lymphocyte ratio, SIII: Systemic immune-inflammation index, min: Minute, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2. Demographic and clinical data of the patients by mortality status

Parameter		Survivor n (%)/mean ± SD	Excitus n (%)/mean ± SD	p
Age		7.43±5.13	5.86±5.30	0.437
Sex		63 (65.6)	3 (42.9)	0.247
Vital signs	SBP (mmHg)	107.26±12.93	91.71±5.44	0.002
	DBP (mmHg)	69.73±13.58	47.71±12.11	**<0.001**
	Pulse rate (beats/min)	106.48±23.05	133.14±35.63	0.005
Hospitalization status	None/discharged	43 (44.8)	0 (0.0)	0.040
	Ward admission	35 (36.4)	0 (0.0)	
	ICU admission	18 (18.8)	7 (100.0)	
Length of hospitalization (days)		3.50±5.57	7.86±9.96	0.063

Table 2. Continued

Parameter		Survivor n (%)/mean ± SD	Excitus n (%)/mean ± SD	p
Laboratory data	WBC ($\times10^3/mm^3$)	15.61±8.77	18.13±7.34	0.461
	HGB (mg/dL)	11.89±1.93	9.73±3.20	0.008
	PLT ($\times10^3/mm^3$)	262.60±80.67	487.43±55.10	**<0.001**
	NEU ($\times10^3/mm^3$)	10.48±7.95	13.42±5.76	0.340
	LEN ($\times10^3/mm^3$)	4.26±3.78	2.70±1.00	0.280
	ALT (IU)	92.13±200.39	437.57±308.12	**<0.001**
	AST (IU)	157.31±330.74	641.71±561.35	0.001
	Amylase (IU)	65.50±61.03	134.57±106.22	0.007
	Lipase (IU)	40.99±68.94	223.00±255.69	**<0.001**
Indexes	NLR	4.10±4.30	6.22±4.98	0.215
	SIII ($\times10^3$)	1086.69±1215.38	3012.76±2394.08	<0.001

SD: Standard deviation, ICU: Intensive care unit, WBC: Leukocytes, HGB: Hemoglobin, PLT: Platelet, NEU: Neutrophils, LEN: Lymphocyte, ALT: Alanine transaminase, AST: Aspartate transaminase, NLR: Neutrophil/lymphocyte ratio, SIII: Systemic immune-inflammatory index, min: Minute, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

in predicting mortality and was significantly higher in mortal cases than in survivors (Table 2).

ROC analyses were conducted to determine the sensitivity and specificity of NLR and SIII according to cut-off values for predicting mortality in pediatric patients with blunt abdominal trauma. The sensitivity and specificity for a cut-off value of 890.47×10^3/L SIII were 95.7% and 62.5%, respectively [AUC: 0.832; 95% confidence interval (CI): 0.820-0.944, p<0.003], in pediatric patients with blunt abdominal trauma. There were no significant differences between the mean NLRs for predicting mortality in pediatric patients with trauma. SIII was a successful index for predicting mortality in pediatric patients with trauma (Figure 2 and Table 3).

Discussion

Trauma is a leading cause of mortality, particularly in pediatric patients. Although it is a social problem affecting all age groups, abdominal trauma can cause death in this patient group. Thus, several parameters have been used as prognostic markers, particularly in pediatric patients with blunt abdominal trauma. The present study investigated the SIII, an inexpensive, fast, easy, and radiation-free test, as a prognostic parameter in this patient group. In particular, SIII could be an indicator of mortality in pediatric patients with blunt abdominal trauma because of its cut-off value of 890.47×10^3/L, sensitivity of 95.7%, and specificity of 62.5%.

Several previous studies have suggested that NLR is a good predictor of mortality associated with abdominal trauma [15-17]. Nevertheless, to the best of our knowledge, no study has compared NLR and SIII in pediatric patients with blunt abdominal trauma. The present study showed that SIII was a marker of mortality associated with intra-abdominal injury in pediatric patients admitted to the emergency department because of blunt abdominal trauma. SIII had higher sensitivity and specificity and was statistically significant in predicting mortality in pediatric patients with blunt abdominal trauma compared with NLR.

In a study by Spijkerman et al. [18], the mean age of patients admitted because of pediatric blunt abdominal injury was 12 years, and the proportion of male patients was 68%. In another study, the mean age was 8 years, and the proportion of male patients was 66.7% [19]. In the present study, both the average age and male ratio were consistent with those reported in the literature. This is attributed to the fact that intra-abdominal injuries are more prevalent in children in this age group owing to the proportionally larger size of the organs than the body. Furthermore, the fact that boys were more active in this age group might have contributed to the higher prevalence rates.

A cohort study of patients with blunt abdominal trauma reported that intra-abdominal organ injury in hemodynamically unstable patients (hypotensive patients) resulted in mortality [20]. In addition, another study showed that patients with stable hemodynamic status survived even when not admitted to the ICU [21]. Consistent with previous studies, mortal patients were hemodynamically unstable in the present study. This may be attributed to the fact that unstable patients can rapidly progress to multiorgan failure due to impaired perfusion.

Elevated ALT and AST levels indicate intra-abdominal organ injury, particularly in pediatric patients with blunt abdominal trauma [22]. Furthermore, previous studies reported that the levels of ALT and AST were higher in mortal patients [16]. Pancreatic enzymes (amylase and lipase) are increased in patients with blunt abdominal trauma, both in cases of mortality and intra-abdominal organ injury [6,23]. Similarly, in the present study, both liver function tests and pancreatic enzyme levels were elevated in mortal patients. The severity of the injury, which increased the severity of the trauma and led to larger solid organ injuries in the early period, might have accounted for the above outcome.

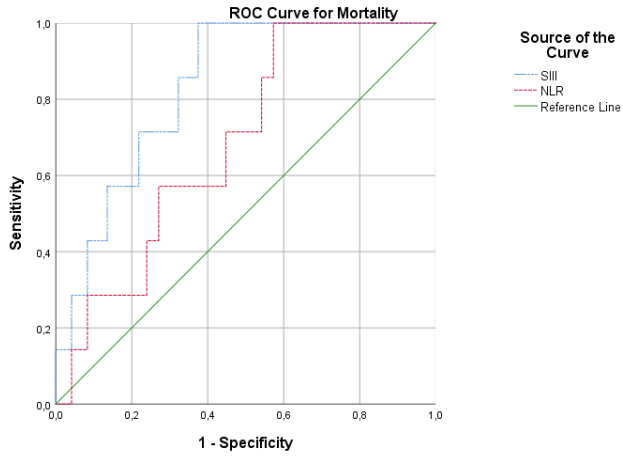

Figure 2. ROC analysis for determining the mortality of the cases

SIII: Systemic immune-inflammatory index, NLR: Neutrophil/lymphocyte ratio, ROC: Receiver operating characteristic

Table 3. ROC analysis results for determining the mortality of the cases

Parameter	Cut-off value	Sensitivity	Specificity	Area under the curve	95% CI		p
					Lower bound	Upper bound	
NLR	2.09	93.2	42.7	0.686	0.525	0.847	0.101
SIII ($\times 10^3$/L)	890.47	95.7	62.5	0.832	0.820	0.944	0.003

NLR: Neutrophil/lymphocyte ratio, SIII: Systemic immune-inflammatory index, CI: Confidence interval, ROC: Receiver operating characteristic

A previous study involving patients with trauma reported that NLR was increased in cases of severe trauma [15]. Another study found that the NLR value calculated at the time of initial presentation predicted 30-day survival in patients with trauma [15]. In a study by Dilektasli et al. [24], the sensitivity and specificity of NLR for predicting mortality in patients with trauma were 70.8% and 61.9%, respectively. The cut-off value of NLR for pediatric patients with trauma was 2.77, and the sensitivity and specificity as indicators of mortality were 70% and 77%, respectively [16]. Unlike in previous studies, although the cut-off value of the NLR was 2.09 with a sensitivity and specificity of 93.2% and 42.7%, respectively, the NLR was not significant as an indicator of mortality in the present study. This might be attributed to the fact that the patients included in previous studies had a more severe inflammatory response due to multi-trauma.

There are no previous studies on the use of SIII as a prognostic marker in pediatric patients with blunt abdominal trauma. Nevertheless, it was reported that SIII was useful in demonstrating brain damage, particularly in patients with head trauma [25]. Another study suggested that SIII was a useful indicator of traumatic brain injury [26]. The present study indicated that SIII could be used as a mortality indicator in pediatric patients with blunt abdominal trauma with a cut-off value of 890.47×10^3/L, sensitivity of 95.7%, and specificity of 62.5%. Therefore, it will be possible to determine prognosis based only on whole blood count results and to start early follow-up and treatment of pediatric patients admitted to the emergency department due to trauma.

Study Limitations

The fact that this was a retrospective study is the most important limitation of this study. The other limitations include the single-center nature of the study and comparatively lower number of cases. The present study determines the short-term mortality outcomes of the included patients. Therefore, it does not provide information about long-term complications. The inclusion criteria were those with hematological or bone marrow pathology, a history of malignancy, and suspected infection and the exclusion of pregnant women, resulting in a relatively small sample size for the study. A larger sample size would provide more robust and reliable results, especially when assessing the predictive value of biomarkers such as the SIII. Future prospective studies with larger sample sizes are required to confirm the predictive values of the parameters investigated in the present study.

Conclusion

The mortality rate of pediatric patients with blunt abdominal trauma is extremely high. Therefore, the survival rate of patients may vary according to the extent of the inflammatory process induced by abdominal trauma. The results of the present study suggest that a higher SIII value at initial presentation in pediatric patients with abdominal trauma can be used to

predict patient mortality. However, this hypothesis needs to be supported by future prospective multicenter studies with larger sample sizes.

Ethics

Ethics Committee Approval: This retrospective single-center study was performed in the emergency department of a training and research hospital upon approval of the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (approval number: KAEK/2022.06.212, date: 23.06.2022).

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

Authorship Contributions

Surgical and Medical Practices: E.A., R.G., Concept: E.A., İ.A., A.Ç., R.G., Design: E.A., S.K., Data Collection or Processing: E.A., İ.A., K.Ş., S.K., Analysis or Interpretation: E.A., İA., A.Ç., K.Ş., R.G., Literature Search: E.A., İ.A., A.Ç., Writing: E.A., A.Ç., K.Ş., S.K., R.G.

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ORIGINAL RESEARCH

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Prognostic Value of Systemic Immune-inflammatory Index in Pulmonary Embolism

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Abstract

Objective: This study aimed to investigate the extent to which the systemic immune-inflammatory index (SII) is associated with patients with acute pulmonary embolism (PE), compare the SII with other commonly used biomarkers and scoring systems, and evaluate its suitability for routine use in PE risk classification.

Materials and Methods: Patients with acute PE admitted in 2021 were retrospectively reviewed. A cut-off value for the SII was obtained to examine the predictive value of the SII for 30-day mortality as the primary outcome. The secondary outcome of the study was to compare the SII with other predictors of 30-day mortality in patients with acute PE.

Results: A total of 139 patients with a mean age of 68.33±14.58 years were included in the study. The cut-off value for 30-day mortality was an SII of ≥0.904 (sensitivity: 88.5%; specificity: 58.4%; area under the curve: 0.803; p<0.001). Lactate, age, right ventricular dysfunction (RVD), and SII ≥0.904 were independent risk factors for 30-day mortality in PE (p<0.05). The SII has a strong correlation with lactate and the presence of RVD (p<0.001).

Conclusion: The SII was found to be strongly associated with RVD, age, and lactate in patients with acute PE. Prospective studies may prove that the SII can fill the gap of inexpensive, rapid, and accessible prognostic biomarkers in rural emergency departments where echocardiography is not accessible.

Keywords: Neutrophil, lymphocyte, pulmonary embolism, pulmonary embolism severity index, systemic immune-inflammation index, Wells

Introduction

Pulmonary embolism (PE) is defined as the occlusion of the pulmonary artery and/or its distal branches. It is the third leading cause of cardiovascular death, with a short-term 30-day mortality rate of 16% [1]. The symptoms and clinical signs of acute PE are non-specific, but generally include chest pain, dyspnea, presyncope, and hemoptysis [2]. Only 5% of patients with acute PE have symptoms of shock or right ventricular dysfunction (RVD) [3]. Predicting prognosis and mortality is a critical step in PE management. Clinicians routinely use risk scoring systems such as Wells, pulmonary embolism severity index (PESI), and modified Geneva scores to identify high- and low-risk patients. In addition, the 2019 European Society of Cardiology PE guidelines recommend the use of markers such as lactate, troponin, interleukin-6, and brain natriuretic peptide for risk classification [4-6]. Despite these recommendations, there is a lack of biomarkers suitable for routine use, inexpensive enough, and accessible in all emergency departments (EDs).

The systemic immune-inflammatory index (SII) is a new parameter based on neutrophil, lymphocyte, and platelet counts. It can be used to simultaneously assess the inflammatory and immune status of patients. Recent studies have reported that higher SII levels are associated with poor prognosis and high mortality rates in malignancies, intracranial hemorrhage, chronic heart failure, coronary artery disease,

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and even coronovirus disease-2019 (COVID-19) patients [7-12]. Begieneman et al. [13] reported the presence of massive inflammatory cell accumulation in the myocardium of patients with PE who died within 48 h. Although inflammation is known to play an important role in atherosclerosis and thrombosis, the relationship between the SII and clinical outcomes in patients with PE remains unclear.

The aim of this study was to determine the extent to which the SII is associated with acute PE, compare the SII with other commonly used biomarkers and scoring systems, and evaluate its suitability for routine use in acute PE risk stratification.

Materials and Methods

This cross-sectional retrospective study was conducted between January 2021 and December 2021 in the ED of a regional academic hospital providing tertiary healthcare services. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Aksaray University Clinical Research Ethics Committee (decision number: 2022/13-03, date: 21.07.2022). Informed consent was not obtained from patients due to the retrospective nature of the study.

Patient Selection

Patients admitted to the ED in 2021 were retrospectively reviewed. The inclusion criteria were positive computed tomographic pulmonary angiography for acute PE and age older than 18 years. Patients were excluded if: 1) aged <18 years, 2) had missing data (the lack of echocardiographic examination data and the lack of SII values data), 3) with pregnancy, 4) with a hematologic disease that may affect the results of the complete blood count, and 5) had a cardiac arrest before arrival to the ED were excluded from the study.

Study Design

Patient demographics (age and sex), heart rate (beats per minute), blood pressure (mmHg), shock index (pulse/systolic blood pressure), medical history (presence of diabetes mellitus, hypertension, chronic obstructive pulmonary disease, deep vein thrombosis), laboratory values [complete blood count, D-dimer (mg/L), troponin (ng/mL), venous blood gas for lactate (mmol/L, before oxygenation)], SII (calculated as neutrophil/lymphocyte ratio x platelet), echocardiographic findings performed <12 hours after diagnosis, clinical risk classification scores (Wells and PESI), length of hospital stay (days), and 30-day mortality were retrospectively recorded. PESI class I-II patients were classified as low risk and those with PESI class III-V patients were classified as high risk. Patients with a Wells score ≤4 were considered unlikely to have PE, whereas those with a score >4 were considered likely to have PE [4].

Echocardiography

In our hospital, all patients diagnosed with acute PE undergo echocardiography within 12 hours. A Philips EPIQ 7c diagnostic echocardiography device (Philips Ultrasound, Bothell WA, USA) is used in the cardiology echocardiography unit. A right ventricle/left ventricle ratio of ≥1 on the end-diastolic apical four-chamber view was accepted as RVD [14,15]. The ejection fraction and pulmonary artery pressure (PAP) were also recorded from the examination results.

Statistical Analysis

The primary endpoint of the study was 30-day mortality. The predictive value of the SII for 30-day mortality was evaluated using receiver operating characteristic (ROC) curves. The cut-off value was determined using the Youden index. Factors influencing mortality were compared using the chi-squared or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous and sequential variables. Multivariable logistic regression analysis with a backward stepwise model was performed to identify factors predicting 30-day mortality in patients with acute PE. Age, shock index, D-dimer level, SII, lactate level, PESI, PAP level, and RVD were included in the regression model.

The secondary endpoint of the study was to evaluate the suitability of the SII for routine use in risk stratification. Spearman's correlation tests were performed to evaluate the association between the clinical parameters of SII, RVD, PAP, shock index, and lactate. Data were analyzed using MedCalc software version 20.110, and a p-value of <0.05 was considered statistically significant.

Results

There were 151 patients diagnosed with acute PE in the ED during the study period. Three patients were excluded due to hematologic malignancy, 6 due to echocardiography time >12 h, and 3 due to missing data. Finally, 139 patients with a mean age of 68.33±14.58 years were included in the study. Fifty-four (38.8%) patients were male and 85 (61.2%) were female. The median (interquartile range) SII was 907.04 (1339), and 36 (25.9%) patients had RVD. The median length of hospital stay was 9.61±5.64 days. The 30-day mortality rate was 18.7% (n=26). Table 1 summarizes the clinical, laboratory, and demographic characteristics of the study population.

There was a significant difference in age ($p<0.001$), diastolic blood pressure ($p<0.05$), shock index ($p<0.001$), lactate ($p<0.001$), D-dimer ($p<0.05$), SII ($p<0.001$), PESI score ($p<0.001$), and presence of RVD ($p<0.05$) between patients who died and those who survived. On the other hand, there were no significant differences in sex, chronic diseases, presence of deep vein thrombosis, troponin level, ejection fraction, or Wells score ($p>0.05$). The comparison between patients who died and those who survived is summarized in Table 2.

The ROC analysis showed that the cut-off value for 30-day mortality was an SII of >903.66 [sensitivity: 88.5%; specificity: 58.4%; +likelihood ratio (LR), 2.13; -LR, 0.2; area under the curve: 0.803; 95% confidence interval (CI), 0.727-0.865; p<0.001; Figure 1].

Multivariate logistic regression analysis revealed that lactate, age, RVD, and SII ≥904 were independent risk factors for 30-day mortality in PE (p<0.05). Table 3 presents the details of the regression analysis.

Spearman's analysis showed that SII was moderately correlated with shock index and PAP and strongly correlated with lactate and the presence of RVD (p<0.001) (Table 4).

Discussion

In this retrospective study, we investigated the extent to which SII was associated with 30-day mortality among patients with acute PE diagnosed in the ED. In patients in whom the SII calculated at the time of ED admission is >904, there is an increased likelihood of short-term 30-day mortality [+LR 2.13 (95% CI 1.64-2.76)].

Acute PE is a leading cause of nontraumatic death, accounting for more than 100,000 deaths per year in the United States [16]. It has a wide spectrum, ranging from low-risk patients who can be treated in outpatient clinics and then discharged to high-risk patients who may present with a severe clinical presentation of shock leading to mortality. This risk stratification is important to avoid unnecessary costs and to identify candidates for thrombolytic treatment. Although scoring systems and echocardiographic findings are useful, there is a need for inexpensive, rapid, and accessible biomarkers to predict mortality in patients with acute PE, especially in rural EDs where echocardiography is not accessible.

The SII includes three peripheral blood parameters that comprehensively summarize the immune and inflammatory status of patients. As expected, it has already been reported as a prognostic biomarker in patients with sepsis [17]. In a recent study, Fois et al. [18] reported that patients with higher SII values had significantly worse PaO_2/FiO_2 ratio and chest computed tomography severity scores among patients with COVID-19. They mentioned that the SII may specifically reflect lung damage in patients with COVID-19 rather than a general impairment of their clinical conditions. In addition, the SII has been shown to be associated with worse prognosis in some malignancies, coronary artery disease, and intracerebral hemorrhage [7,10,19-21].

In coronary artery disease, atherosclerosis is strongly associated with an ongoing inflammatory response [22]. NLR is an independent predictor of cardiovascular events and

Table 1. Demographics and laboratory findings of the study population

Age, y, mean ± SD	68.33±14.58
Male sex, n (%)	54 (38.8)
Chronic obstructive pulmonary disease, n (%)	60 (43.2)
Diabetes mellitus, n (%)	39 (28.1)
Hypertension, n (%)	65 (46.8)
Malignancy, n (%)	5 (3.6)
Deep vein thrombosis, n (%)	75 (54)
Systolic blood pressure, mmHg, mean ± SD	109.04±26.21
Diastolic blood pressure, mmHg, mean ± SD	68.06±13.19
Heart rate, beats per min, mean ± SD	104.7±16.55
Shock index, mean ± SD	0.95±0.22
Troponin, ng/mL, median (IQR)	0.05 (0.25)
Lactate, mmol/L, median (IQR)	1.9 (1.23)
D-dimer, mg/L, median (IQR)	5.9 (7.4)
Systemic immune-inflammatory index, median (IQR)	907.04 (1339)
Ejection fraction, %, mean ± SD	56.77±6.11
Pulmonary artery pressure, mmHg, mean ± SD	47.97±13.89
Right ventricle dysfunction, n (%)	36 (25.9)
Wells score, mean ± SD Pulmonary embolism unlikely, n (%) Pulmonary embolism likely, n (%)	6.64±2.2 17 (12.2) 122 (87.8)
Pulmonary embolism severity index score, mean ± SD Low-risk, n (%) High-risk, n (%)	116.45±34.96 26 (18.7) 113 (81.3)
Length of stay in the hospital, d, mean ± SD	9.61±5.64
30-day mortality, n (%)	26 (18.7)

SD: Standard deviation, min: Minute, IQR: Interquartile range, y: Years, d: Days

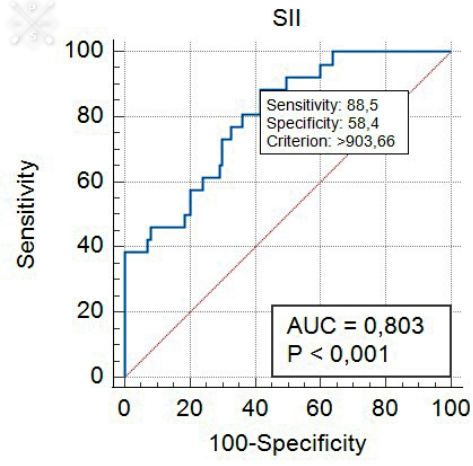

Figure 1. ROC curve of the systemic immune-inflammatory index in predicting 30-day mortality

SII: Systemic immune-inflammatory index, AUC: Area under the curve

mortality in ST-segment elevation myocardial infarction [23]. In addition to NLR, platelets have been considered biomarkers of coronary artery disease by predicting prothrombotic potential and blood vulnerability [24]. Platelet-lymphocyte ratio has been reported to be an effective predictor of severe atherosclerosis [25]. Yang et al. [9] reported that a higher SII was independently associated with a higher future risk of cardiac death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure in patients with coronary artery disease after coronary intervention. They mentioned that the index could be used as a simple and practical indicator to identify high-risk patients with coronary artery disease after percutaneous coronary intervention.

In patients with acute PE, the primary causes of death are thought to be myocardial injury and acute RVD resulting from an acute increase in intraventricular pressure [4]. Increased

Table 2. Comparison of survivor and death patients

	Alive (n=113, 81.3%)	Death (n=26, 18.7%)	p
Age, y, mean ± SD	66.13±14.59	77.88±10.16	**<0.001**
Male sex, n (%)	45 (39.8)	9 (34.6)	0.623
Chronic obstructive pulmonary disease, n (%)	50 (44.2)	10 (38.5)	0.591
Diabetes mellitus, n (%)	31 (27.4)	8 (30.8)	0.733
Hypertension, n (%)	50 (44.2)	15 (57.7)	0.215
Malignancy, n (%)	3 (2.7)	2 (7.7)	0.235
Deep vein trombosis, n (%)	59 (52.2)	16 (61.5)	0.390
Systolic blood pressure, mmHg, mean ± SD	112.09±26.8	103.46±23.37	0.225
Diastolic blood pressure, mmHg, mean ± SD	69.56±12.69	61.54±13.6	**0.005**
Heart rate, beats per min, mean ± SD	102.6±14.19	110.46±24.09	0.065
Shock index, mean ± SD	0.92±0.19	1.1±0.3	**<0.001**
Troponin, ng/mL, median (IQR)	0.04 (0.25)	0.06 (0.41)	0.501
Lactate, mmol/L, median (IQR)	1.75 (1.13)	3.29 (6.13)	**<0.001**
D-dimer, mg/L, median (IQR)	5.2 (6.1)	8.7 (23.8)	**0.023**
SII, median (IQR)	716 (1034)	1750 (5600)	**<0.001**
Ejection fraction, %, mean ± SD	56.87±6.22	56.35±5.73	0.683
Pulmonary artery pressure, mmHg, mean ± SD	46.89±13.47	52.65±14.98	0.056
Right ventricle dysfunction, n (%)	24 (21.2)	12 (46.2)	**0.009**
Wells score, mean ± SD	6.59±2.21	6.86±2.21	0.581
Pulmonary embolism unlikely, n (%)	15 (13.3)	2 (7.7)	0.433
Pulmonary embolism likely, n (%)	98 (86.7)	24 (92.3)	
PESI score, mean ± SD	108.64±30.89	150.38±31.6	**<0.001**
Low-risk, n (%)	25 (22.1)	1 (3.8)	**0.047**
High-risk, n (%)	88 (77.9)	25 (96.2)	

SD: Standard deviation, min: Minute, IQR: Interquartile range, PESI: Pulmonary embolism severity index, SII: Systemic immune-inflammatory index, y: Years

Table 3. Multivariate logistic regression analysis for 30-day mortality predictors

	Wald	p	Odds ratio	95% Confidence interval
Age	6.456	**0.011**	1.078	1.017-1.143
PAP	1.686	0.194	1.032	0.984-1.083
Shock index	2.817	0.093	7.439	0.714-77.505
D-dimer	0.261	0.610	1.018	0.950-1.091
Lactate	4.866	**0.027**	1.267	1.027-1.563
PESI, high-risk	0.062	0.803	0.743	0.072-7.656
SII ≥0.904	9.476	**0.002**	9.728	2.285-41.410
RVD	8.000	**0.005**	7.112	1.826-27.694

PAP: Pulmonary artery pressure, PESI: Pulmonary embolism severity index, RVD: Right ventricle dysfunction, SII: Systemic immune-inflammatory index

Table 4. Correlations between SII and PAP, shock index, lactate and RVD		
	Correlation coefficient	p
SII - PAP	0.396	**<0.001**
SII - shock index	0.488	**<0.001**
SII - lactate	0.655	**<0.001**
SII - RVD	0.793	**<0.001**
PAP: Pulmonary artery pressure, RVD: Right ventricle dysfunction, SII: Systemic immune-inflammatory index		

pulmonary vascular resistance causes RV dilatation, inotropic and chronotropic stimulation, and systemic vasoconstriction, followed by RV ischemia. RV contractility, RV output, and left ventricular preload decreases [4]. Decreased left ventricular filling and decreased cardiac output lead to platelet activation [26]. In addition, impaired hepatic and renal perfusion contributes to increased platelet activation [27]. It is known that there is a massive accumulation of inflammatory cells in the myocardium of patients of acute PE who died within 48 hours [13]. Previous studies, including those on neutrophils and lymphocytes, have shown that NLR can be used as a prognostic factor in PE [28,29]. A recent study by Gok and Kurtul [30] reported that SII was a strong independent predictor of massive acute PE, with an optimal cut-off value of >1161. The SII may be a useful, novel biomarker for predicting the severity of acute PE in addition to older inflammatory and prognostic biomarkers, such as C-reactive protein and troponin. Our results contribute to these findings. Considering that the potential prognostic value of the SII is similar to that of RVD, with a strong correlation (correlation coefficient: 0.793, $p<0.001$) and increases as a result of RVD and associated immune response, the SII may help clinicians to predict RVD and associated short-term 30-day mortality in acute PE cases.

According to our results, the SII, which is a combination of NLR and platelets, was an independent predictor of 30-day mortality in patients with acute PE, with a sensitivity of 88.5% and specificity of 58.4%. Access to echocardiography is limited in most rural EDs, especially during night shifts. Even when echocardiography is accessible, obtaining images to assess RVD can be difficult in patients with dyspnea who are receiving mechanical ventilation support or who cannot lie in the supine position. Complete blood counts are easy to perform, are inexpensive, provide information on several cell types, and can be used to risk stratify patients diagnosed with acute PE.

Study Limitations

The study has potential weaknesses due to its retrospective nature and several limitations. 1) The number of patients included was small, especially missing data on echocardiographic findings, which led us to exclude some potentially eligible patients, 2) the other prognostic cardiac indicators, such as brain natriuretic peptide, were not compared with the SII because they are not routinely checked in our hospital in patients with acute PE, 3) treatment information, including thrombolysis, which may affect short-term 30-day mortality, could not be verified, 4) there was no significant difference in the Wells score, a widely used scoring system in acute PE, between patients who died and those who survived. Therefore, the Wells score was not included in the regression analysis. We believe that this is due to the fact that our hospital serves a local area, and the patient population does not have sufficient heterogeneity due to the relatively small number of patients.

Conclusion

In conclusion, SII ≥904 can be used as a practical prognostic factor together with RVD, age, and lactate in patients with acute PE. Prospective studies may prove that the SII can fill the gap of inexpensive, rapid, and accessible prognostic biomarkers in rural EDs where echocardiography is not accessible. Large-scale and prospective studies are needed to obtain better results on the association between the SII and mortality in acute PE.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Aksaray University Clinical Research Ethics Committee (decision number: 2022/13-03, date: 21.07.2022).

Informed Consent: Informed consent was not obtained from patients due to the retrospective nature of the study.

Authorship Contributions

Surgical and Medical Practices: İ.K., A.Ç., Concept: M.M., A.Ç., Design: M.M., İ.K., A.Ç., Data Collection or Processing: İ.K., A.Ç., Analysis or Interpretation: A.Ç., Literature Search: M.M., A.Ç., Writing: M.M., İ.K., A.Ç.

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

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