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Inflammatory indexes in emergency patients with hypertensive pulmonary Oedema: A critical insight

Tutku Duman Şahan, MD *, Zeynep Karakaya, MD, Ejder Saylav Bora, MD, Mehmet Göktuğ Efgan, MD, Fatih Esad Topal, MD

Department of Emergency Medicine, Izmir Katip Çelebi University Faculty of Medicine, Izmir, Turkey

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ABSTRACT

Background: Heart failure (HF) is a prevalent and severe condition with high hospitalization and mortality rates, especially in developing countries. Inflammation plays a crucial role in its aetiology. Hypertensive pulmonary oedema, a severe form of acute decompensated heart failure (ADHF), lacks a definitive scoring system for predicting hospital admission outcomes. This study aims to evaluate the prognostic value of systemic inflammatory indexes (SII), systemic inflammation response index (SIRI), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and multi-inflammatory indexes (MII-1, MII-2, MII-3) in patients with hypertensive pulmonary oedema.

Materials and methods: We conducted a retrospective observational study at Izmir Atatürk Training and Research Hospital from March 1, 2023, to March 1, 2024. We included 150 patients aged ≥18 with hypertensive pulmonary oedema, excluding those with incomplete data or conditions affecting inflammation. Various inflammatory indices were calculated from blood parameters. We used ROC curve analysis to analyse their correlation with hospital outcomes, including discharge and mortality.

Results: Among the 150 patients (mean age 70.14 ± 11.47 years), 25 (16.7 %) experienced in-hospital mortality. Significant differences between discharged and deceased patients were found in systolic blood pressure, neutrophil count, and inflammatory indices. ROC curve analysis showed NLR, SIRI, MII-1, MII-2, and MII-3 as significant predictors of in-hospital mortality, with MII-1 having the highest AUC (0.697) and sensitivity (60.00 %).

Conclusion: SIRI, NLR, MII-1, MII-2, and MII-3 may help predict in-hospital mortality in hypertensive pulmonary oedema. Further research is needed to validate these markers and explore their utility in clinical practice.

1. Introduction

(See Figs. 1–3.) (See Tables 1–3.)

Heart failure (HF) is common all over the world, with an increasing incidence with age. It has become one of the diseases with the highest hospitalization and mortality rates in the world, especially in developing countries, bringing with it considerable medical expenditure and social burdens. Inflammation is thought to be one of the most important factors in the aetiology of HF and related morbidity and mortality [1].

Heart failure is the name given to a condition in which an abnormality in cardiac muscle function causes the heart to be unable to pump blood sufficiently to meet metabolic tissue demands. In order to maintain circulatory function against this deterioration in the short term, the body generates numerous adaptation responses in many organs. Signs and symptoms of HF result from compensatory mechanisms used by the body to correct the primary deficit in cardiac function. These responses predispose to disease progression and acute exacerbations in the future. Endogenous haemodynamic and neurohormonal mechanisms play an important role in the pathophysiology of heart failure with beneficial and detrimental interactions depending on the patient's condition. It is a complex clinical syndrome with specific symptoms and signs [2]. Heart failure (HF) frequently manifests as dyspnoea and fatigue, which reduce the capacity for exertion. In addition to these, fluid retention is also a common clinical picture. Heart failure includes a wide range of left ventricular abnormalities, from patients with a normal-sized left ventricle and preserved ejection fraction (EF) to patients with severe dilatation and low EF. In most patients, systolic and diastolic dysfunction co-exist and develop independently of EF. Heart failure (HF) is traditionally divided into HF with reduced EF (systolic HF) and HF with normal EF (diastolic HF). Both groups have reduced exercise tolerance, neurohumoral activation, abnormal left ventricular (LV) filling dynamics and impaired relaxation. Hypertensive pulmonary oedema is one of the mortal subtypes of acute decompensated heart

* Corresponding author.
E-mail address: tutkuduman75@gmail.com (T.D. Şahan).

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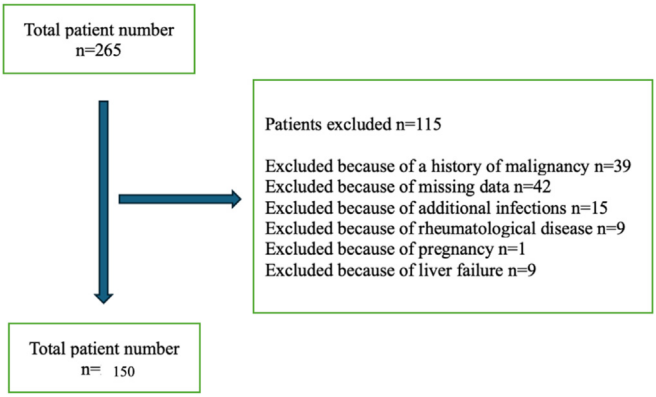

Fig. 1. Flow chart.

failure (ADHF), and there is no definitive scoring system that predicts patients' admission to the ward or intensive care unit and/or in-hospital outcome [3]. Various haematological parameters have been investigated to assess the severity and prognosis of many diseases and compared with scoring systems and acute phase reactants with proven predictive value [4-6].

Heart failure is a complex clinical syndrome with symptoms such as dyspnoea, peripheral oedema, and fatigue resulting from functional or structural cardiac damage, which impairs the ability of the heart to perform its pumping function [7] effectively. The body reflexively generates numerous organ adaptation responses to maintain circulatory function [8]. Signs and symptoms of HF result from compensatory mechanisms used by the body to correct the primary deficit in cardiac function. These responses predispose to disease progression and acute exacerbations [9]. Endogenous hemodynamic and neurohormonal mechanisms play an important role in the pathophysiology of heart failure, with beneficial and detrimental interactions depending on the patient's condition [10].

Inflammation is an immunological response triggered by events such as infection and tissue injury. This response forms the basis of physiological and pathological processes. There is ample evidence that inflammation plays a role in the development of diseases such as cancer, diabetes, cardiovascular diseases, neurodegenerative diseases and inflammatory bowel diseases. In order to develop more effective

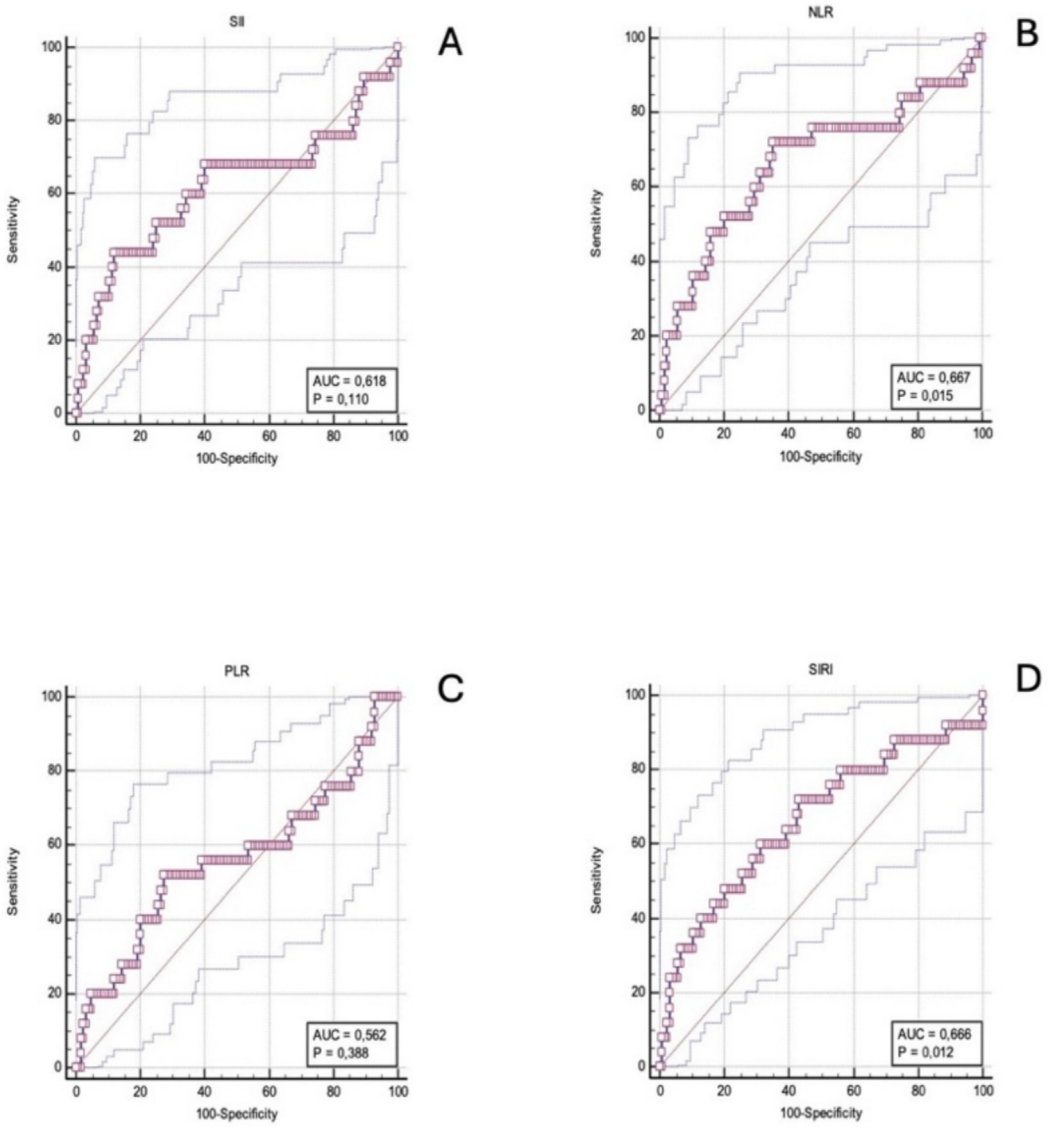

Fig. 2. ROC curve analysis of SII (A), NLR (B), PLR (C), and SIRI (D) variables for predicting in-hospital mortality.

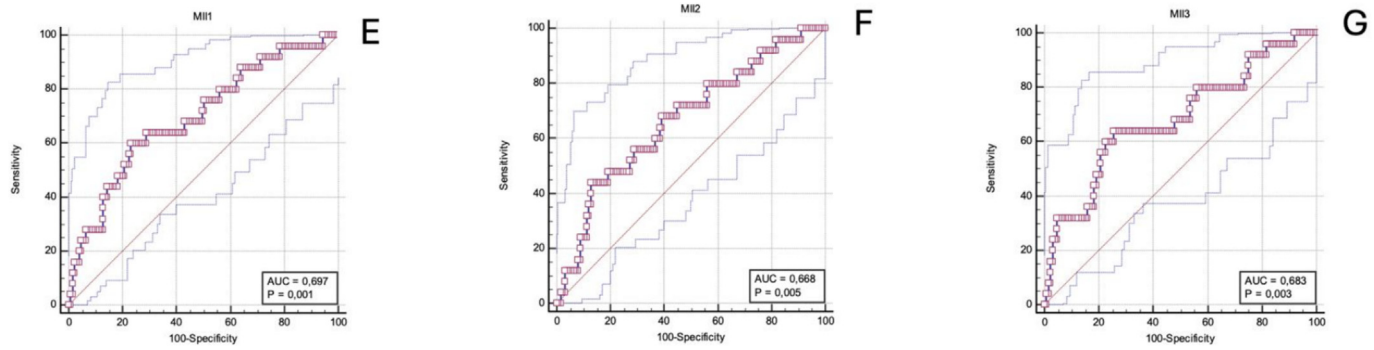

Fig. 3. ROC curve analysis of MII-1 (E), MII-2 (F), and MII-3 (G) variables for predicting in-hospital mortality.

treatments for these diseases, research on the cascades that initiate inflammation and cause its progression is ongoing. Many recent studies have investigated the use of systemic inflammatory indexes (SII) as a parameter to determine the prognostic value of various diseases. Although SII (neutrophil x lymphocyte/platelet) is predicted as a general marker of systemic inflammation, SII is associated with mortality and morbidity in some systemic diseases. In cardiovascular diseases, SII has been studied mainly in coronary artery disease and heart failure with low ejection fraction and has been reported to be significantly associated with disease prognosis and some specific parameters [11-13].

It has been thought that the levels of many haematological parameters, such as haemostasis elements such as platelets, neutrophils, and lymphocytes, and red cell distribution width, which vary in peripheral blood, may be associated with the severity of various diseases [14]. These haematological parameters have recently come to the fore as Systemic Immune Inflammatory Index (SII), Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), Multi-Inflammatory Index (MII), and Systemic Inflammation Response Index (SIRI).

Our study aimed to investigate the predictive value of SII, SIRI, NLR, PLR, and MII 1–2-3 parameters for hospitalization and in-hospital outcomes in patients admitted to the emergency department with hypertensive pulmonary oedema.

2. Material and method

2.1. Type of study

This study was designed as a retrospective observational study. Before starting the study, approval was obtained from the local ethics committee.

2.2. Place and time of the study

The study covers patients who applied to the Emergency Department of Izmir Atatürk Training and Research Hospital between 01.03.2023 and 01.03.2024.

2.3. Population and sample of the study

Patients aged 18 years and older who presented to the Emergency Department of Izmir Atatürk Training and Research Hospital with a diagnosis of hypertensive pulmonary oedema were included in the study. Among these patients, patients with incomplete data whose outcome could not be followed (referred patients or patients who refused treatment) were excluded from the study. In addition, patients with a history of cancer, autoimmunity, allergy, inflammatory or infectious disease in the last three months, pregnant or breastfeeding women, and patients with a diagnosis of liver failure were excluded.

2.4. Variables of the study

Calculations were performed using the hemogram results obtained for each case. N: Neutrophil, P: Platelet, L: Lymphocyte, M: Monocyte values. SII, SIRI, NLR, PLR, MII-1, MII-2, and MII-3 values were calculated using the following formulae.

-SII: (N x P)/L.
-SIR: (N x M)/L.
-NLR: N/L.
-PLR: P/L.
-MII-1: NLR x CRP.
-MII-2: PLR x CRP.
-MII-3: SII x CRP.

2.5. Data collection tools

Patient records were accessed through the hospital information management system to determine which patients should be included in the study. In order to identify patients diagnosed with hypertensive pulmonary oedema in the emergency department within the specified date range, ICD10 diagnosis codes 'J81: Pulmonary oedema' were searched in the hospital's information management system, and the results were confirmed by scanning the patient files. A total of 265 patients were identified. Included and excluded patients are indicated in the flow chart below.

For the patients included in the study, clinical information (hypertensive pulmonary oedema, SII score, blood gas analysis, GCS score, systolic and diastolic blood pressure, pulse rate, respiratory rate) were collected from the hospital information management system and patient files and noted on the data recording form. It was analysed whether the calculated SII, SIRI, NLR, PLR, MII-1, MII-2, and MII-3 values could be used as prognosis indicators in all patients with hypertensive pulmonary oedema.

2.6. Primary outcome of the research

The primary outcome of the study was to evaluate the importance of inflammatory indices in assessing the mortality of patients presenting to the emergency department with hypertensive pulmonary oedema.

2.7. Sample size

A sample of 50 from the positive group and 50 from the negative group achieve 82 % power to detect a difference of 0,1600 between the area under the ROC curve (AUC) under the null hypothesis of 0,5600 and an AUC under the alternative hypothesis of 0,7200 using a two-sided z-test at a significance level of 0,05000. The data are discrete (rating scale) responses. The AUC is computed between false positive rates of 0,000 and 1000. The ratio of the standard deviation of the

Table 1
Descriptive statistics.

	Statistics
Age	70.14 ± 11.47
Gender	
Female	74 (%49.3)
Male	76 (%50.7)
The need for diuretic treatment	
No	59 (%39.3)
Yes	90 (%60.0)
The use of Beta Blockers	
No	7 (%48.0)
Yes	77 (%51.3)
The use of Calcium Channel Blockers	
No	98 (%65.3)
Yes	51 (%34.0)
The use of ACE inhibitors	
No	111 (%74.0)
Yes	38 (%25.3)
The use of ARBs	
No	141 (%94.0)
Yes	8 (%5.3)
Need for non-invasive mechanical ventilation	
No	36 (%24.0)
Yes	114 (%76.0)
Emergency Department outcome	
Discharged	52 (%34.7)
Ward Admission	34 (%22.7)
Intensive care hospitalization	64 (%42.7)
In-hospital outcome	
Discharged	125 (%83.3)
Ex	25 (%16.7)
Systolic blood pressure	179.43 ± 40.62
Diastolic blood pressure	94.90 ± 25.68
Heart rate	103.92 ± 21.81
Respiratory rate	31.44 ± 12.30
GCS	14.25 ± 2.28
CRP	18.20 ± 40.29
BUN	28.20 ± 16.14
Creatinine	1.68 ± 1.14
Leukocyte	13.75 ± 5.46
Neutrophile	9.11 ± 4.45
Lymphocyte	3.42 ± 2.42
Platelet	292.81 ± 123.98
Monocyte	0.89 ± 0.42
Eosinophil	0.22 ± 0.34
AST	37.43 ± 48.80
ALT	26.30 ± 25.56
pH	7.37 ± 0.60
PaO_2	80.05 ± 41.15
$PaCO_2$	44.74 ± 13.53
Lactate	2.66 ± 2.22
HCO_3	21.35 ± 4.72
EF	47.36 ± 12.00
SII	1344.76 ± 1483.67
SIRI	4.05 ± 4.78
NLR	4.79 ± 5.38
PLR	140.52 ± 136.45
MII-1	117.37 ± 457.72
MII-2	2840.92 ± 10,273.81
MII-3	33,286 ± 143,495.43

responses in the negative group to the standard deviation of the responses in the positive group is 1000.

2.8. Statistical analysis

For discrete and continuous variables, descriptive statistics (mean, standard deviation, median, minimum value, maximum value, and percentile) were given. In addition, the homogeneity of the variances, which is one of the prerequisites of parametric tests, was checked through Levene's test. The assumption of normality was tested via the Shapiro-Wilk test. To compare the differences between the two groups, the Student's *t*-test was used when the parametric test prerequisites were fulfilled, and the Mann Whitney–*U* test was used when such prerequisites were not fulfilled. To compare the differences between three and more groups, one-way analysis of variance was used when the parametric test prerequisites were fulfilled, and the Kruskal Wallis test was used when such prerequisites were not fulfilled. The Bonferroni correction method, which is a multiple comparison test, was used to evaluate the significant results concerning three and more groups. Chi-square test was used for determining the relationships between two discrete variables. When the expected sources were less than 20 %, values were determined through the Monte Carlo Simulation Method in order to include such sources in analysis. Also age and BMI variables were determined as covariance (to be excluded) and groups were compared with covariance analysis.

The performance of a test can be defined by the diagnostic ability of the test or by its ability to accurately divide events into subgroups (exitus/ discharged). The cut-off points of the parameters were evaluated by ROC analysis. AUC Value, Sensitivity, Selectivity values were calculated. The data were evaluated via SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). $p < 0.05$ were taken as significance levels.

3. Results

A total of 150 patients were included in the study, and the mean age was 70.14 ± 11.47 years. Of all patients, 74 were female and 76 were male. Of the patients, 52 (34.7 %) were discharged from the emergency department, 34 (22.7 %) were hospitalized in the ward, and 64 (42.7 %) were hospitalized in the intensive care unit. In-hospital mortality was 25 (16.7 %).

Patients were divided into four groups according to the outcome of the emergency department. These groups were discharged, ward hospitalization, intensive care unit hospitalization, and exitus. There were no patients who ended with exitus in the emergency department. All variables were compared between the remaining three groups. Accordingly, statistically significant differences were found between the groups in systolic blood pressure, diastolic blood pressure, respiratory rate, GCS, lymphocyte, lactate, EF, need for non-invasive mechanical ventilation, SII, NLR, PLR, SIRI, MII-1, MII-2, MII-3.

Patients were divided into two groups according to in-hospital outcomes. These groups were discharge and exitus groups. All variables were compared between these two groups. Accordingly, there were statistically significant differences between systolic blood pressure, neutrophil, lymphocyte, eosinophil, CRP, BUN, creatinine, NLR, SIRI, MII-1, MII-2, and MII-3 variables.

4. Discussion

Besides the discovery of new therapies, the development of new prognostic markers to determine patients' risk is also of great value in improving patients' prognosis.

Natriuretic peptide is synthesised from the myocardium as pro-BNP in response to increased pressure or volume stimulation of the ventricle. It is then split into BNP and the biologically inert NT-proBNP, and these biochemical markers can be measured by laboratory tests. Both biomarkers are associated with short- and long-term mortality according to the New York Heart Association (NYHA) heart failure classification. NT-proBNP, a widely used marker of heart failure, has a good value in prognostic assessment but has some disadvantages for risk assessment [15]. The first of these is that there may be more than one cause of dyspnoea in patients. From this perspective, high plasma BNP or NT-proBNP concentration does not exclude the presence of other diseases. Another limitation is that plasma BNP or NT-proBNP levels are not diagnostic in some patients with acute decompensated HF. Therefore,

Table 2
Parameters found to be statistically significant in the comparison of all variables according to in-hospital outcome groups.

	Hospital Outcome		Test Statistics	
	Discharged	Ex	Test value	*p* value
Systol	184.31 ± 36.14	155.04 ± 52.44	$z = 2.477$	**0.013**
$\bar{x}\pm ss$	184 (100–280)	160 (50–240)		
M (*min*-max)				
Netrophil	8.70 ± 4.12	11.19 ± 5.46	$z = 2.128$	**0.033**
$\bar{x}\pm ss$	7.55 (2.80–23.10)	8.73 (1.44–19.00)		
M (*min-max*)				
Lymphocyte	3.57 ± 2.40	2.66 ± 2.39	$z = 2.037$	**0.042**
$\bar{x}\pm ss$	3.01 (0.24–10.00)	1.83 (0.28–11.15)		
M (*min-max*)				
Eosinophil	0.22 ± 0.25	0.20 ± 0.62	$z = 3.789$	**0.001**
$\bar{x}\pm ss$	0.16 (0.00–1.67)	0.02 (0.00–3.13)		
M (*min-max*)				
CRP	16.77 ± 40.32	25.35 ± 40.18	$z = 2.408$	**0.016**
$\bar{x}\pm ss$	5.80 (0.02–345.80)	13.94 (0.08–195.38)		
M (*min-max*)				
BUN	26.70 ± 15.74	35.64 ± 16.73	$z = 3.030$	**0.002**
$\bar{x}\pm ss$	21 (9–81)	30 (12–82)		
M (*min-max*)				
Creatinine	1.57 ± 1.04	2.23 ± 1.47	$z = 2.812$	**0.005**
$\bar{x}\pm ss$	1.31 (0,54-7,13)	1.67 (0.71–6.64)		
M (*min-max*)				
NLR	4.14 ± 4.56	8.04 ± 7.70	$z = 2.625$	**0.009**
$\bar{x}\pm ss$	2.60 (0.62–32.29)	5.37 (0.62–30.50)		
M (*min-max*)				
SIRI	3.46 ± 4.08	7.02 ± 6.72	$z = 2.610$	**0.009**
$\bar{x}\pm ss$	2.05 (0.39–27.16)	4.09 (0.22–22.39)		
M (*min-max*)				
MII1	93.46 ± 420.03	236.92 ± 609.33	$z = 3.104$	**0.002**
$\bar{x}\pm ss$	15.91 (0.01–4319.36)	64.28 (0.33–3092.94)		
M (*min-max*)				
MII2	2587.94 ± 10,613.27	4105.83 ± 8444.89	$z = 2.655$	**0.008**
$\bar{x}\pm ss$	579.63 (0.63–108,769.82)	1670 (16.14–42,913.82)		
M (*min-max*)				
MII3	28,120.56 ± 142,255.00	59,114.91 ± 149,821.04	$z = 2.877$	**0.004**
$\bar{x}\pm ss$	4328.09 (3.01–1.49)	19,849 (114.44–760,862.05)		
M (*min-max*)				

searching for more useful biomarkers has attracted increasing attention from researchers and clinicians. In line with this need and based on the effect of inflammation in the pathogenesis of heart failure, this study demonstrates the prognostic value of SII, SIRI, NLR, PLR, and MII-1,2,3 parameters in patients admitted to the emergency department with hypertensive pulmonary oedema.

Hypertensive pulmonary oedema, in other words, acute cardiogenic pulmonary oedema, results from fluid passage through the alveolocapillary membrane, and its relationship with inflammation has been reported in previous studies [16]. In the present pathological picture, increased oedema decreased pulmonary permeability, and impaired oxygen transport have been reported as factors triggering the inflammation process. It is also known that the existing inflammation changes capillary wall permeability and increases oedema. Similarly, it has been demonstrated in previous studies that long-term alveolocapillary barrier damage and pulmonary parenchymal inflammation increase the vulnerability of the lung to recurrent pulmonary fluid accumulation [17].

When intramyocardial inflammation occurs, the limited replication ability of the heart often causes irreparable damage, leading to HF, which may be why the heart has mechanisms to limit inflammation [18]. Likewise, an increase in inflammation-related cytokines indicates inflammation activation and is also considered an indicator of poor prognosis [19]. Based on this, in this study, we emphasized that SII, SIRI, NLR, PLR, and MII-1,2,3 parameters, which are used as markers of systemic immune inflammation, may have a prognostic significance, especially in hypertensive pulmonary oedema, a clinical picture in which this inflammation reaches its maximum. Previous studies support that these inflammatory parameters can be a potential biomarker for cardiovascular diseases with similar pathophysiology [20,21]. Apart from

Table 3
Cutoff Scores, AUC Value, Sensitivity, Selectivity, and Statistical Significance of SII, NLR, PLR, SIRI, MII-1, MII-2, and MII-3 variables for predicting in-hospital mortality.

Variables	*Youden Index*	*Cutoff*	*AUC*	*SE*	*p**	Asymptotic 95 % Confidence Interval		*Sensitivity*	*Specificity*
						L.Bound	U. Bound		
SII	0.320	>2114	0.618	0.073	**0.320**	0.535	0.696	44.00	88.00
NLR	0.368	>3.33	0.667	0.068	**0.014**	0.585	0.741	72.00	64.80
PLR	0.248	>155.24	0.562	0.071	**0.388**	0.478	0.642	52.00	72.80
SIRI	0.288	>2.36	0.666	0.066	**0.012**	0.584	0.740	72.00	56.80
MII-1	0.368	>59.10	0.697	0.059	**0.001**	0.617	0.769	60.00	76.80
MII-2	0.312	>2731	0.668	0.059	**0.004**	0.587	0.743	44.00	87.20
MII-3	0.384	>14,168	0.683	0.062	**0.003**	0.602	0.756	64.00	74.40

AUC: Area under the curve, *CI*: Confidence interval, *se*: Standard error, *: ROC Curve Analysis.

cardiovascular diseases, it has been reported that these markers can be used as prognosis indicators in pathologies that progress with inflammation, such as malignancies and infections [22].

The systemic immune inflammation index is an inflammatory parameter that combines three important immune cells, including neutrophils, lymphocytes, and platelets and is considered an excellent indicator of local immune response and systemic inflammation [23]. Neutrophils, platelets, and the cytokines they produce are associated with non-specific immune responses, whereas lymphocytes are associated with specific immune pathways [24]. Compared to the absolute number of immune cells alone, SII has a very good representation of the body's inflammatory state with better stability. SII has previously been confirmed to be closely associated with poor prognosis of various cardiovascular diseases such as coronary artery disease [25], aortic stenosis [26], and infective endocarditis [27]. Yang Y.L. et al. investigated the usefulness of SII value as a prognostic indicator in coronary artery disease and found the cutoff value of SII to be 694.3. It was reported that major cardiovascular events occurred more frequently in patients above this value [25]. Tosu AR et al. investigated the usefulness of the SII value as a prognosis indicator in major adverse cardiac events. They found that the limit value of >1056 could be used, but it was observed that major adverse cardiac events were more common in patients with this value and above [26]. Agus HZ et al. evaluated the usefulness of SII value at admission in predicting in-hospital mortality in patients with infective endocarditis. They concluded that it can be used with a cutoff value 2314 [27]. In this study, the SII cutoff value for predicting in-hospital mortality was 2114, but its use was not statistically significant ($p = 0.063$). In light of this information, the cutoff value is higher in pathologies with higher predicted inflammation, such as infective endocarditis, and lower in pathologies with lower predicted inflammation, such as coronary artery disease. The close relationship between the intensity of inflammation and the SII value may explain this. PLR value was previously reported to be associated with mortality in patients with acute cardiogenic pulmonary oedema [28]. The use of PLR value in a meta-analysis investigating the prognostic value of PLR value in cardiovascular diseases was found to be significant [29]. In this study, the use of PLR value for in-hospital mortality prediction in patients admitted with hypertensive pulmonary oedema was statistically insignificant ($p = 0.332$). The possible reason why SII and PLR values could not be used in the prediction of in-hospital mortality in the study may be that one of their components is platelets. Platelets are known to have anti-inflammatory properties. It is known thatplatelets interact with regulatory T cells and strengthen their responses, which leads to an increase in IL-10 levels [30]. Furthermore, previous studies have shown that activated platelets modulate macrophages towards an anti-inflammatory phenotype with increased IL-10 release and decreased TNF-a secretion [31,32]. For these reasons, platelets are also thought to represent the regeneration of inflammation [33]. This explains why values such as SII, for which platelet value is available in the calculation, cannot be used to predict in-hospital mortality.

The systemic immune response index is an inflammatory parameter that combines three important immune cells, including neutrophils, lymphocytes, and monocytes, and its association with mortality, especially in cardiovascular events, has been proven in previous articles [34,35]. Yildiz G et al. investigated the usefulness of SIRI value in showing thrombus localization in patients with acute pulmonary embolism. They reported that SIRI values of 4.12 and above were associated with thrombus formation in the main pulmonary artery [36]. Yun S. et al. investigated the usability of SIRI value to predict the prognosis of patients with aneurysmal subarachnoid haemorrhage and found that it can be used to predict patients with aneurysmal haemorrhage with a limit value of 3.2 [37]. Han K et al. investigated the prognostic significance of SIRI value in patients with acute coronary syndrome undergoing percutaneous coronary intervention. They reported that it was associated with major cardiac events [38]. In this study, the SIRI value was found to help predict in-hospital mortality with a cutoff value of 2.36 ($p = 0.012$). Since it is a pathology associated with inflammation, using the SIRI value created using inflammation markers such as SIRI for in-hospital mortality prediction in hypertensive pulmonary oedema is an appropriate approach.

The neutrophil/lymphocyte ratio has been used for years as an important biomarker using two important laboratory values related to inflammation. Samad G et al. investigated the usefulness of NLR in predicting in-hospital mortality and complications after STEMI and reported that high NLR values had a predictive role [39]. In a meta-analysis by Wang X et al., it was suggested that NLR value could predict all-cause mortality and cardiovascular events in patients undergoing angiography or cardiac revascularisation [40]. Xue J et al. investigated the prognostic value of NLR in acute ischaemic stroke. They found that the optimal cutoff value of NLR for predicting the primary adverse outcome was 2.39 [41]. This study's cutoff value for predicting in-hospital mortality in patients with hypertensive pulmonary oedema was 3.33. According to the existing literature, it is statistically significant ($p = 0.014$) to use in predicting in-hospital mortality in the patient group of this study, as well as predicting other mortal outcomes. As we mentioned before, NLR value is a good reflection of the inflammatory process, which is effective in the current pathophysiology of pulmonary oedema and can be used as a marker for in-hospital mortality prediction.

MII-1, MII-2, and MII-3 are markers formed by multiplying SII, NLR, and PLR values, respectively, with CRP, another significant laboratory value indicating inflammation. It is known that CRP is an acute phase reactant that increases in response to infections, malignancy, sepsis, and other acute inflammatory conditions. Therefore, its use in calculations is accepted to increase the power of existing markers. In a previous study by Gardini et al. investigating the use of MII values as a prognostic indicator in patients with metastatic colorectal cancer, it was found that MII values were higher in the poor outcome group [42]. Boyuk F reported in his study that MII values can be used to differentiate massive and non-massive patients [43]. Doganay B et al. investigated the usefulness of MII values as an indicator of stent thrombosis and in-hospital mortality in patients with acute coronary syndrome. They concluded that all 3 MII values were associated with mortality [44]. In the present study, the use of MII1, MII-2, and MII-3 values in predicting in-hospital mortality with cutoff values of 59.10 ($p = 0.001$), 2731 ($p = 0.004$) and 14,168 ($p = 0.003$), respectively, was found to be statistically significant. While SII and PLR values cannot be used for this purpose, the addition of CRP, an acute phase reactant, as a multiplier strengthens predictability by ensuring their usability. The fact that CRP is a biomarker that increases significantly in acute conditions shows the importance of evaluations with CRP multiplier in the emergency department. It gives hope for the use of these biomarkers in the emergency department.

5. Limitations

First, the single-centre and retrospective design was considered to be the most important limitation of this study. In addition, our current patient groups were not grouped and analysed according to EF status. Therefore, the relationship and correlation between EF and inflammatory markers are unknown. These issues can be analysed in future studies.

6. Conclusion

Hypertensive pulmonary oedema requires biomarkers that can be easily calculated and give rapid results in the emergency department and clinical practice. Based on this, SIRI, NLR, MII-1, MII-2, and MII-3 values may be the parameters that should be used to predict in-hospital mortality. Further studies and meta-analyses will elucidate this issue.

CRediT authorship contribution statement

Tutku Duman Şahan: Writing – original draft. **Ejder Saylav Bora**: Investigation. **Zeynep Karakaya**: Visualization. **Mehmet Göktuğ Efgan**: Writing – review & editing. **Fatih Esad Topal**: Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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