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RESEARCH

A Novel Marker for Predicting Fulminant Myocarditis: Systemic Immune–Inflammation Index

Raziye Merve Yaradilmiş[1] · Muhammed Mustafa Güneylioğlu[1] · Betül Öztürk[1] · Aytaç Göktuğ[1] · Orkun Aydın[1] · Ali Güngör[1] · İlknur Bodur[1] · Özkan Kaya[2] · Utku Arman Örün[2] · Can Demir Karacan[1] · Nilden Tuygun[1]

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Abstract

In myocarditis, the search for effective and appropriate prognostic biomarkers can help clinicians identify high-risk patients in a timely manner and make better medical decisions in clinical practice. The prognostic value of systemic immune–inflammatory index (SII), an innovate biomarker of inflammation, in fulminant myocarditis in children has not been assessed. This study aims to (1) determine the effect of SII and other inflammatory markers on the prognosis of patients with myocarditis, and (2) characterize other factors affecting adverse outcomes in myocarditis. All patients aged between 1 months and 18 years who admitted to Pediatric Emergency Department between January 1, 2015 and October 1, 2021 and were diagnosed with myocarditis were retrospectively analyzed. 106 Eligible subjects were enrolled (67% male, 12.5 years (IQR 6–16). Fulminant myocarditis developed in 16 (15%) of the patients. The median SII was 1927 (1147.75–3610.25) in the fulminant myocarditis group and 351 (251.75–531.25) in the non-fulminant group ($p < 0.001$). In estimation of fulminant myocarditis, AUC was 0.87 for WBC [95% confidence interval (CI) 0.72–1.00, $p = 0.002$], 0.94 for ANC (95% CI 0.85–1.00), $p = 0.000$), 0.92 for SII (95% CI 0.82–1.00, $p = 0.000$). Spearman's correlation analysis showed a significant negative correlation between SII and LVEF ($r = 0.576$, $p < 0.001$). The highest AUC values were associated with ANC, SII, and WBC levels to predict fulminant myocarditis. SII, a readily available biomarker from routine blood parameters, allows early recognition of negative outcomes and can independently predict the prognosis of myocarditis in children.

Keywords Systemic immune–inflammatory index · Fulminant myocarditis · Prognosis · Children

✉ Raziye Merve Yaradilmiş
karaomermerve@hotmail.com

Muhammed Mustafa Güneylioğlu
drguneylioglu@gmail.com

Betül Öztürk
drbetulozaydinozturk@gmail.com

Aytaç Göktuğ
aytacyaylaci@yahoo.com

Orkun Aydın
orkunaydinmd@gmail.com

Ali Güngör
gungorali19@gmail.com

İlknur Bodur
ilknur.bodur1977@hotmail.com

Özkan Kaya
drozkankaya@gmail.com

Utku Arman Örün
utkuarman@hotmail.com

Can Demir Karacan
candecan@hotmail.com

Nilden Tuygun
nildentuygun@gmail.com

[1] Department of Pediatric Emergency Care, Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Plevne M Babur C No 41, Gunesevler, 06080 Ankara, Turkey

[2] Department of Pediatric Cardiology, Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Plevne M Babur C No 41, Gunesevler, 06080 Ankara, Turkey

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Abbreviations

SII	Systemic immune–inflammation index
PED	Pediatric Emergency Department
PICU	Pediatric intensive care unit
ECG	Electrocardiographic
Echo	Echocardiographic
WBC	White blood cell
ANC	Absolute neutrophil count
ALC	Absolute lymphocyte counts
PLT	Platelet counts
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
IG	Immature granulocytes
BNP	Pro-brain natriuretic peptide
ECMO	Extracorporeal membrane oxygenation
SD	Standard deviation
IQR	Range of quarters
ROC	Receiver operating characteristic
AUC	Area under the curve
PPV	Positive predictive values
NPV	Negative predictive values
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic diameter
OR	Odds ratio
CI	Confidence interval
MIS-C	Multisystem inflammatory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

Introduction

Myocarditis is an inflammatory disease of the myocardium [1]. Many different causes, especially viral factors, are involved in the etiology. It is rare in children and the estimated annual incidence is 1 to 2 in 100,000 children [2–4]. The clinical presentation of myocarditis is variable, patients may present with a wide clinical spectrum ranging from subclinical disease to cardiogenic shock, arrhythmias, and sudden death [5]. The search for effective and appropriate prognostic biomarkers can help clinicians identify high-risk patients in a timely manner and make better medical decisions in clinical practice. The systemic immune–inflammation index (SII) as a new inflammatory index combining lymphocyte, neutrophil, and platelet count information has recently been proposed as a strong prognostic indicator of poor outcome in some in some inflammatory diseases (such as antineutrophil cytoplasmic antibody-associated vasculitis, Henoch-Schönlein Purpura) and neoplasms (such as lung cancer, hepatocellular carcinoma) [6–9].

Studies evaluating the prognostic value of inflammatory markers in children diagnosed with acute myocarditis are limited. To our knowledge, there is no study related to this index in this field in pediatric cardiology. This study aims to (1) determine the effect of SII and other inflammatory markers on the prognosis of patients with myocarditis, and (2) characterize other factors affecting adverse outcomes in myocarditis.

Materials and Methods

Study Design and Patient Selection

All patients aged between 1 months and 18 years who admitted to our Pediatric Emergency Department (PED) between January 1, 2015 and October 1, 2021 and were diagnosed with myocarditis were retrospectively analyzed. Patients with inflammatory diseases, autoimmune diseases including systemic lupus erythematosus, cancer, leukemia or any other blood system diseases, and patients with missing file data were excluded from the study. The patients were divided into two groups as fulminant myocarditis and non-fulminant.

Data Collection

All data including demographic characteristics (age, gender), vital signs, laboratory tests, comorbidities, drug use, patient management in the PED and pediatric intensive care unit (PICU), electrocardiographic (ECG) and echocardiographic (echo) findings and complications were recorded. Laboratory indicators; white blood cell (WBC), absolute neutrophil count (ANC), absolute lymphocyte counts (ALC), platelet counts (PLT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), percentage of immature granulocytes (IG), serum troponin and pro-brain natriuretic peptide (BNP) levels were collected. The SII values of all patients in the first 6 h of admission to the PED were calculated and recorded. SII was calculated as: SII = neutrophil count × platelet count/lymphocyte count [6].

Definitions

Current criteria for diagnosis of myocarditis were defined as patients meeting signs and symptoms of acute cardiac dysfunction (e.g., dyspnea, exercise intolerance, syncope, chest pain with exertion, tachypnea, unexplained tachycardia, hepatomegaly, gallop rhythm), elevated troponin level, echo evidence of ventricular dysfunction without underlying structural heart defect, presence of prodromal disease (respiratory or gastrointestinal) within two weeks of symptom onset, ECG changes suggestive of acute myocardial injury or arrhythmia [1, 5]. The definition of the fulminant course of acute myocarditis was the presence of severe hemodynamic compromise requiring inotropic agents or ventricular assist devices such as an intraaortic balloon pump, left ventricular

assist device, or extracorporeal membrane oxygenation, ECMO [5].

Outcomes

The primary outcome is the comparison of SII of fulminant and non-fulminant myocarditis patients. Secondary outcomes are the comparison of other inflammatory markers of both groups and the determination of other factors affecting the prognosis of myocarditis.

Statistical Analysis

Statistical analysis of the data obtained in the study were made in IBM SPSS for Windows Version 28.0 package program. Descriptive statistics [percentage, mean, median, standard deviation (SD), range of quarters (IQR)] were used to define the population included in the study. In the comparison of patients with and without acute fulminant myocarditis, χ^2 or Fisher-Exact Test and *T*-Test were used for categorical and continuous variables, respectively, and Mann–Whitney *U* test was used for variables not suitable for normal distribution. Receiver operating characteristic (ROC) analysis was performed and ROC curves were plotted, and the Youden Index method was used to determine the optimal WBC, ANC, SII, ESR, and IG percent cut-off values to predict fulminant myocarditis. The area under the curve (AUC) was calculated to predict fulminant myocarditis and compare the performance of each marker. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated for the markers. Spearman's correlation was performed to analyze the correlation between SII and left ventricular ejection fraction (LVEF). To evaluate the effectiveness of SII in predicting adverse outcomes in children with myocarditis, cut-off values were determined by ROC analysis and the likelihood ratio was calculated. For all analyses, $p < 0.05$ was considered statistically significant.

This study was approved by the Ethics Committee of our hospital (E-21/11-242).

Results

A total of 106 patients with myocarditis were included in the study (Fig. 1). The median age was 12.5 (IQR 6–16) years, and 67% of the patients were male. All characteristics of the total cohort, patients with fulminant myocarditis and non-fulminant myocarditis, including demographical data, laboratory findings, management, and outcomes are given in Table 1. Fulminant myocarditis was diagnosed in 16 (15%) of the patients.

ECG and Echo Findings

Common ECG findings in the study population and comparison between groups are presented in Table 2. In addition, in the fulminant myocarditis group, two patients had long QT syndrome, one patient had ventricular tachycardia, one patient had complete atrioventricular block, one patient had wide QRS and low voltage, one patient had supraventricular tachycardia, one patient had atrial tachycardia attacks, and one patient had supraventricular extrasystolic beats. No ECG findings were detected in 29 (27.3%) patients in the non-fulminant group.

The median value of LVEF was 66.5% (IQR 51.75–72.0) in the whole cohort, 41.2% (IQR 35.0–50.5) in the fulminant group, and 65.0% (IQR 60.75–70.0) in the non-fulminant group ($p < 0.001$). Left ventricular end-diastolic diameters (LVEDD) were calculated as the body surface area of the patients and recorded as normal or increased. LVEDD values were normal in all non-fulminant group and normal in

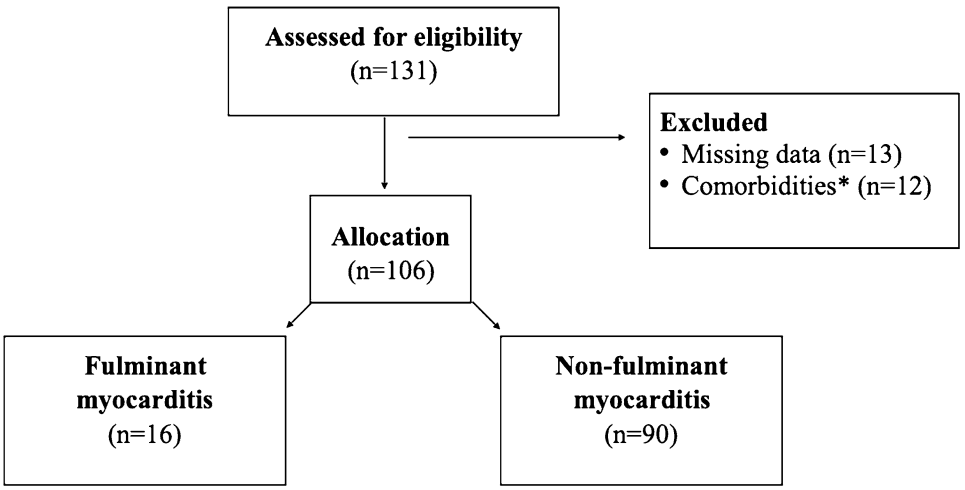

Fig. 1 Flow chart of patients. *Patients with inflammatory diseases, autoimmune disease including systemic lupus erythematosus, cancer, leukemia, or any other blood system disease

Table 1 Demographic, laboratory characteristics, and managements of the patients

	Total	Fulminant myocarditis	Non-fulminant myocarditis	*p* value
Patients [*n* (%)]	106	16 (15)	90 (84,9)	
Age, median (years)	12.5 (6–16)	4.5 (2–10)	14 (8–16)	**< 0.001**
Gender [*n* (%)]				0.032
Male	71 (67)	7 (43.7)	64 (71)	
Female	35 (33)	9 (56)	26 (28.8)	
Chronic disease [*n* (%)]	23 (21.6)	5 (31.2)	18 (20)	0.314
Drug use [*n* (%)]	16 (15)	3 (18.7)	13 (14.4)	0.658
Laboratory, median (IQR)				
WBC ($\times 10^9$/L)	8.00 (6.20–9.91)	14.32 (9.80–19.25)	7.40 (5.95–9.20)	**< 0.001**
ANC ($\times 10^9$/L)	3.90 (3.19–5.45)	11.80 (7.32–15.35)	3.80 (2.80–4.42)	**< 0.001**
ALC ($\times 10^9$/L)	2.49 (1.85–3.50)	1.42 (0.87–2.80)	2.52 (2.00–3.57)	**< 0.001**
PLT ($\times 10^9$/L)	250 (196–340)	364 (151–437)	239 (199–290)	0.230
SII ($\times 10^9$/L)	398.50 (267.75–828.75)	1927 (1147.75–3610.25)	351 (251.75–531.25)	**< 0.001**
CRP (mg/L)	16.0 (2.65–51.0)	33.5 (2.47–148.5)	16.0 (2.65–48.0)	0.219
ESR (mm/h)	26 (15–45)	42.5 (23–68.5)	22 (10.5–42.5)	**0.021**
IG %	0.2 (0.1–0.6)	1.15 (0.62–2.25)	0.2 (0.1–0.3)	**< 0.001**
Troponin (ng/mL)	0.9 (0.2–5.22)	0.9 (0.18–23.7)	0.9 (0.2–59.2)	0.528
Pro-BNP (pg/mL)	6412 (764–20,745)	12,831 (1400–31,783)	4758 (515–14,209)	0.316
PICU admission [*n* (%)]	20 (18.8)	16 (100)	4 (4.4)	**< 0.001**
Length of stay in PICU, > 48 h [*n* (%)]	17 (16)	15 (93.7)	2 (2.2)	**0.028**
Management [*n* (%)]				
Mechanical ventilator	9 (8.4)	8 (50)	1 (1.1)	**< 0.001**
Inotropes	16 (15)	16 (100)	0	**< 0.001**
ACEi/ARB	15 (14.1)	9 (56.2)	6 (6.6)	**< 0.001**
Diuretic	17 (16)	13 (81.2)	4 (4.4)	**< 0.001**
Intravenous immunoglobulin	17 (16)	11 (68.7)	6 (6.6)	**< 0.001**
Antiarrhythmic	6 (5.6)	1 (6.2)	5 (5.5)	0.912
Pacemaker	2 (1.8)	2 (12.5)	0	–
Dialysis	2 (1.8)	2 (12.5)	0	–
Complication[a] [*n* (%)]	10 (9.4)	8 (50)	2 (2.2)	**< 0.001**
Death [*n* (%)]	2 (1.8)	2 (12.5)	0	–

WBC white blood cell count, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *PLT* platelet count, *SII* systemic immune-inflammation index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IG* immature granulocytes, *BNP* brain natriuretic peptide, *PICU* pediatric intensive care unit, *ACEi* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers

Value in bold font indicates statistically significant

[a]Renal failure, liver failure, left ventricular hypertrophy, fibrotic changes in the left ventricle, dilated cardiomyopathy

7 (43.7%) patients in fulminant group. LVEDD was high in 9 (56.2%) patients in the fulminant group, with a mean value was 49 mm (SD ± 1). Valve regurgitation and velocities of all patients are given in Table 2. Mitral regurgitation was detected in 36 patients in total, and the median value of mitral annular velocity was measured as 3.2 m/s (IQR 2.8–3.77). The median value of mitral annular velocity was 3.3 m/s (IQR 2.7–3.9) in the fulminant group, and 3.2 m/s (IQR 2.6–3.8) in the non-fulminant group. There was no significant difference between the groups ($p = 0.870$). Pulmonary hypertension was detected in 3 (18.7%) patients in the fulminant myocarditis group, and pulmonary hypertension was not detected in any patient in the non-fulminant group.

Biomarkers

The median SII was 1927 (1147.75–3610.25) in the fulminant myocarditis group and 351 (251.75–531.25) in the non-fulminant group, and there was a significant difference between the groups ($p < 0.001$, Table 1). Median WBC, ANC, ESR values, and IG percentage were higher, and the median ALC value was lower in the fulminant

Table 2 Comparison of ECG and Echo findings

	Total	Fulminant myocarditis	Non-fulminant myocarditis	*p* value
Patients [*n* (%)]	106	16	90	
ECG [*n* (%)]				
No findings	29 (27.3)	0	29 (32.2)	–
Sinus tachycardia	33 (31.1)	6 (37.5)	27 (30)	0.904
ST elevation	20 (18.8)	2 (12.5)	18 (20)	0.675
ST depression	6 (5.6)	2 (12.5)	4 (4.4)	0.054
Supraventricular tachycardia	3 (2.8)	1 (6.2)	2 (2.2)	–
Echo				
Mitral regurgitation [*n* (%)]	36 (33.9)	15 (93.7)	21 (23.3)	0.287
First-degree	24 (22.6)	8 (50)	16 (17.7)	
Second-degree	8 (7.5)	4 (25)	4 (4.4)	
Third-degree	2 (1.8)	1 (6.2)	1 (1.1)	
Fourth-degree	2 (1.8)	2 (12.5)	0	
Mitral annular velocity, m/s, median (IQR)	3.2 (2.8–3.77)	3.3 (2.7–3.9)	3.2 (2.6–3.8)	0.870
Tricuspid regurgitation [*n* (%)]	100 (94.3)	16 (100)	84 (93.3)	0.05
First-degree	92 (86.7)	11 (68.7)	81 (90)	
Second-degree	6 (5.6)	3 (18.7)	3 (3.3)	
Third-degree	2 (1.8)	2 (12.5)	0	
Tricuspid annular velocity, m/s, median (IQR)	2.0 (2.0–2.25)	2.0 (2.4–2.8)	2.0 (2.1–2.2)	0.055
Pulmonary regurgitation [*n* (%)]	11 (10.3)	7 (43.7)	4 (4.4)	0.237
First-degree	9 (8.4)	5 (31.2)	4 (4.4)	
Second-degree	2 (1.8)	2 (12.5)	0	
Pulmonary annular velocity, m/s, median (IQR)	1.8 (1.5–2.0)	2.0 (1.7–2.5)	1.5 (1.2–1.8)	0.071
Aortic regurgitation [*n* (%)]	4 (3.7)	2 (12.5)	2 (2.2)	–
Aortic annular velocity, m/s, median (IQR)	3.5 (3.0–4.4)	3.8 (2.9–)	3.5	–

ECG electrocardiography, *Echo* echocardiography

$p < 0.05$ significant

myocarditis group (p, respectively, < 0.001, < 0.001, 0.021, < 0.001, < 0.001, Table 1).

ROC Analysis

In estimation of fulminant myocarditis, AUC was 0.87 for WBC [95% confidence interval (CI) 0.72–1.00, $p = 0.002$], 0.94 for ANC (95% CI 0.85–1.00, $p = 0.000$), 0.92 for SII (95% CI 0.82–1.00, $p = 0.000$), 0.73 (95% CI 0.53–0.93, $p = 0.052$) for ESR, and 0.79 (95% CI 0.59–0.98, $p = 0.016$) for IG. The ROC curves of the markers for the prediction of fulminant myocarditis are shown in Fig. 2. Sensitivity, specificity, PPV, NPV, AUC, and odds ratio (OR) values for each marker are given in Table 3. When the markers were analyzed according to the most appropriate cut-off values in the prediction of fulminant myocarditis, the best markers were determined as ANC, SII, and WBC.

The Correlation Between SII and LVEF

Spearman's correlation analysis showed a significant negative correlation between SII and LVEF ($r = 0.576$, $p < 0.001$).

Efficiency of High SII in Predicting Adverse Outcomes

The optimized cut-off point of SII value for predicting PICU admission was 798 with likelihood ratio 49.6. The AUC for PICU admission was 0.956 (95% CI = 0.919–0.994, $p < 0.001$). The best cut-off point of the SII value to predict the evolution of mechanical ventilator need was 878, with likelihood ratio 19.3. The AUC for developing mechanical ventilator need is 0.879 (95% CI = 0.802–0.955, $p < 0.001$). The best cut-off point of the SII value to predict the evolution of inotrope need was also 1003, with likelihood ratio 51.5. The AUC for developing mechanical ventilator need is 0.953 (95% CI = 0.911–0.995, $p < 0.001$). Finally, the best

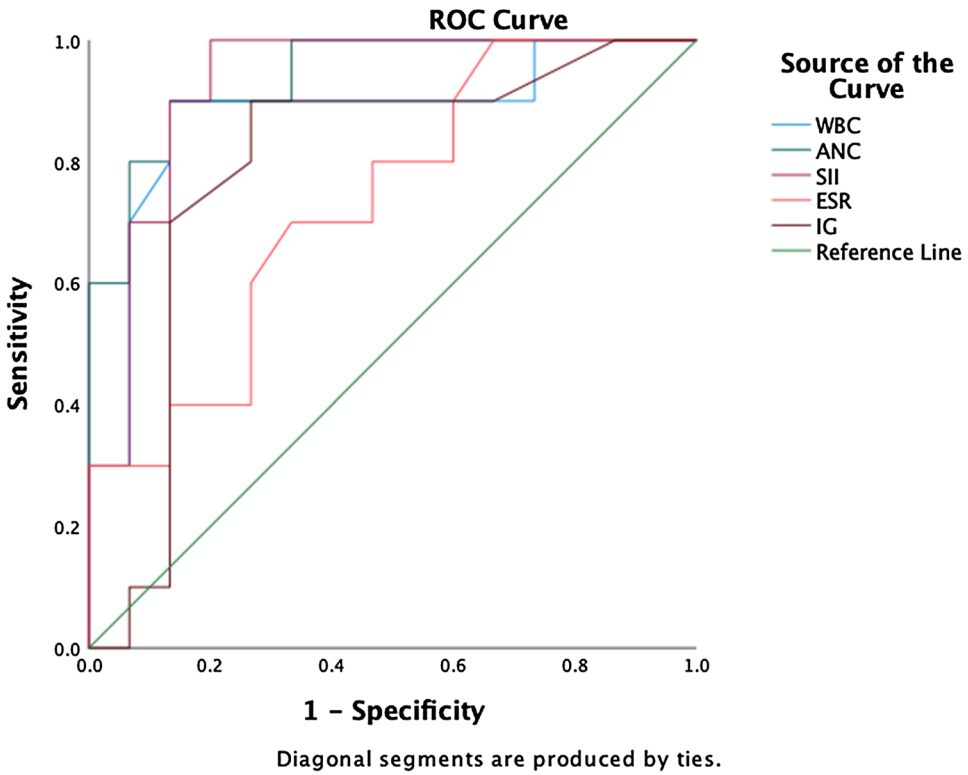

Fig. 2 ROC curves of inflammation markers to predict fulminant myocarditis. *WBC* white blood cell count, *ANC* absolute neutrophil count, *SII* systemic immune-inflammation index, *ESR* erythrocyte sedimentation rate, *IG* immature granulocytes

Table 3 Efficiency of inflammation markers in predicting fulminant myocarditis

	Cut-off	AUC	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
WBC ($\times 10^9$/L)	8.65	0.87	35 (4.4–278.4)	93.8	70	35.7	98.4
ANC ($\times 10^9$/L)	6.55	0.94	45.5 (9.1–225.6)	87.5	86.7	53.8	97.5
SII ($\times 10^9$/L)	1378.0	0.92	37.4 (9.3–150.0)	68.8	94.4	68.8	94.4
ESR (mm/h)	38.5	0.73	4.66 (0.91–23.7)	70	66.7	50	82.4
IG %	0.55	0.79	25.5 (6.1–106.1)	81.3	85.5	56.5	95.2

WBC white blood cell count, *ANC* absolute neutrophil count, *SII* systemic immune-inflammation index, *ESR* erythrocyte sedimentation rate, *IG* immature granulocytes, *AUC* area under the curve, *OR* odds ratio, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value

p value < 0.05 statistically significant

cut-off point for the SII to predict mortality was 1818, with likelihood ratio 9.03. AUC to estimate mortality was 0.909 (95% CI = 0.853–0.964, $p = 0.040$).

Comparison of SII in Virus-Related Inflammatory Reaction and Viral-Induced Inflammatory Response

Comparison of SII in virus-related inflammatory reaction and viral-induced inflammatory response is given in Table 4. The SII median value was 1594.00 (IQR 942.25–2411.75) in multisystem inflammatory syndrome in children, [MIS-C, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced], and significantly higher than the other groups ($p < 0.001$). The median SII values of MIS-C patients in the fulminant and non-fulminant groups were 1051 (701–3629.5) and 2081 (920–2652), respectively ($p = 0.602$).

Treatment and Prognosis

The treatment and prognosis of patients in the total cohort, fulminant and non-fulminant myocarditis groups are shown in Table 1. In the fulminant myocarditis group, all of the patients were followed up in the PICU and 93.7% of them had a stay longer than 48 h. Eight patients (50%) received mechanical ventilator support, and two underwent dialysis treatment. One patient received ECMO support and no patient was performed pericardiocentesis. Pacing was applied to a patient with complete atrioventricular block and a patient who developed bradycardia during ECMO support.

Table 4 Comparison of SII in virus-related inflammatory reaction and viral-induced inflammatory response

	MIS-C	SARS-CoV-2	Others[a]	*p* value
Myocarditis [*n* (%)]	10 (9.4)	3 (2.8)	22 (2.0)	0.001
Fulminant myocarditis	6 (5.6)	0	1 (0.9)	
Non-fulminant myocarditis	4 (3.7)	3 (2.8)	21 (19.8)	
SII × 10^9/L, median (IQR)	1594.00 (942.25–2411.75)	192 (146–)	369 (261–650)	< 0.001

MIS-C multisystemic inflammatory syndrome-child, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SII* systemic immune–inflammatory index

$p < 0.05$ significant

[a]One patient Epstein–Barr virus, one patient mycoplasma, one patient influenza, and others non-specific virus-related inflammatory reaction

Discussion

In our study, we investigated different variables that affect the negative outcomes of patients diagnosed with acute myocarditis. The younger age, female gender, low LVEF%, high percentage of WBC, ANC, SII, ESR, and IG, and low ALC were associated with adverse outcomes in patients diagnosed with myocarditis. We focused on the effect of inflammatory markers for the prediction of fulminant myocarditis. Among these markers, ANC, SII, and WBC had the highest OR.

Inflammation, immune response, and cytokines are important in the pathogenesis of myocarditis [1]. Inflammation and immune response can be evaluated using various hematological and biochemical markers. To date, hemogram parameters such as ANC, ALC, PLT, monocytes, and biomarkers such as CRP have been studied in relation to myocarditis prognosis [10]. In our study, PLT and CRP levels were not associated with fulminant myocarditis. The percentage of WBC, ANC, ESR, and IG was higher in the fulminant myocarditis group. For prediction of fulminant myocarditis, WBC and ANC had the highest AUC, while the percentage of IG had an NPV of 0.95 and AUC of 0.79 (0.59–0.98). These parameters can be used to predict negative outcomes in patients with myocarditis. Neutrophil is the main inflammatory marker and our study shows a stronger association between increased neutrophils and fulminant myocarditis.

SII index, based on platelet counts and neutrophil–lymphocyte ratio, is a novel inflammation biomarker and can comprehensively reflect the body's inflammatory and immune status [11]. Recently, studies evaluating this index in the field of cardiology have attracted attention. Agus et al. [12] demonstrated that SII was an independent predictor of in-hospital mortality in adult patients diagnosed with infective endocarditis. Peng et al. [13] emphasized that high SII level was associated with short- and long-term mortality in adult patients with cardiogenic shock. Gok and Kurtul [14] found that SII was an independent predictor of severe disease in acute pulmonary embolism and a stronger predictor than traditional inflammatory markers. Based on these findings, we investigated SII, a marker that has not yet been studied in patients with myocarditis. The cut-off value of SII for fulminant myocarditis was 1378 and it was the highest predictor factor together with ANC. There was a significant moderately strong negative correlation between SII and LVEF. In addition, high SII was effective in predicting PICU admission, need for mechanical ventilation, need for inotropes, and mortality in children with myocarditis. SII is a parameter that is easy to calculate, it can help to identify the high-risk patient quickly and make better medical decisions in clinical practice.

The percentage of IG, that is another marker examined in our study and can be automatically measured in new generation hemogram devices, has started to take place among the infection markers and has been associated with negative outcomes, especially in diseases such as sepsis and serious bacterial infection [15]. The percentage of IG has not been studied as a prognostic marker in pediatric patients with myocarditis. In our study, the IG% was significantly higher in patients with fulminant myocarditis, but the AUC value was 0.79 (cut-off value 0.55, NPV 95%) and was lower than the ANC and SII values. It can be used to exclude severe myocarditis, and can be evaluated together with other markers.

We found no difference between troponin and pro-BNP levels in both groups. Although troponin I and T levels reflect myocardial damage, it has been reported that they are not associated with disease severity [16]. Pro-BNP levels may be elevated in myocarditis, but its utility as a prognostic indicator is also unclear in this disease group [17]. Pro-BNP has high values in the presence of acute and chronic heart failure, and the association of high values with mortality and hospitalization has been shown in previous studies [17, 18]. In conclusion, we concluded that troponin or pro-BNP levels alone are not significant for the prediction of fulminant myocarditis. It can be evaluated together with other biomarkers to predict the severity and prognosis of the disease.

As with other viral agents, SARS-CoV-2 has the potential to cause myocarditis, and cases of acute fulminant myocarditis due to SARS-CoV-2 infection are rarely seen

in children [19]. There are several studies have described the changes of hematological parameters in patients with SARS-CoV-2 [20, 21]. Previous studies have reported that laboratory markers of inflammation correlate with disease severity, particularly higher neutrophil counts and lower lymphocyte counts. In addition, elevated inflammatory markers and lymphocytopenia may indicate MIS-C and it was reported that neutrophilia was a predictive factor with poor outcomes in patients with SARS-CoV-2. In our study, we found that the SII value of MIS-C with myocarditis cases was significantly higher than the other groups. There was a different SII in those patients with inflammatory reactions associated with the virus versus those viral-induced inflammatory response (i.e., SARS-CoV-2–MIS-C). Further multicenter studies are needed to confirm our data.

Limitations

Our study has some limitations. Firstly, our study is a retrospective study, and therefore there is a bias in the nature of the study. Secondly, it covers single-center data and has a limited number of cases of fulminant myocarditis. Therefore, evaluation of inflammatory markers for mortality and the need for ECMO or pericardiocentesis could not be performed.

Conclusion

In conclusion, the highest AUC values were associated with ANC, SII, and WBC levels to predict fulminant myocarditis. The high SII was a novel prognostic indicator in predicting PICU admission, mechanic ventilatory need, inotrope need, and mortality. SII, a readily available biomarker from routine blood parameters, allows early recognition of negative outcomes and can independently predict the prognosis of myocarditis in children. This is the first study to evaluate the performance of SII in children with acute myocarditis. Prospective studies with larger sample sizes are needed to further validate our results.

Author Contributions RMY, MMG, NT, and CDK conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. BÖ, AG, AG, and Kaya designed the data collection instruments, collected data, reviewed, and revised the manuscript. RMY, IB, OA, and UAÖ carried out the initial analyses, reviewed and revised the manuscript. All authors approve the final version of manuscript and accept all the responsibilities.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.Consent for Publication N/A.

Declarations

Conflict of interest The authors have no conflicts of interest to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Ethical Approval The protocol for this study was approved by the Local Ethics Committee (Date E-21/11-242).

Informed Consent N/A.

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