Prognostic markers in pediatric dilated cardiomyopathy: Focus on the neutrophil-to-lymphocyte ratio and the systemic inflammatory index

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Abstract. Dilated cardiomyopathy (DCM) is a major cause of heart failure and transplantation in children. Despite advances in care, predicting outcomes remains difficult. Inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic inflammatory index (SII), have demonstrated prognostic value in adults, but their role in pediatric DCM remains unclear. The present study aimed to assess the association of NLR, SII and other clinical, laboratory and echocardiographic parameters with mortality in pediatric DCM. In the present retrospective single-center study, 52 pediatric patients with DCM diagnosed between January 2000 and June 2021 were analyzed. Demographic, clinical, laboratory and echocardiographic data at diagnosis were collected from hospital electronic medical records. NLR and SII were calculated from complete blood counts, whereas mortality was the primary outcome. Statistical methods included receiver operating characteristic (ROC) curve analysis, Kaplan-Meier survival estimates and Cox regression. In the present study, 16 patients (30.8%) succumbed during follow-up, and NLR and SII were found to be significantly higher in deceased patients compared with survivors (P=0.003 and P=0.016, respectively). ROC analysis confirmed the predictive value of NLR (AUC, 0.785) and SII (AUC, 0.728). The optimal cut-off values were >2.75 for NLR and >1,428,898 for SII. Cox regression identified parameters associated with mortality, including low serum sodium and magnesium levels, elevated NLR and SII, reduced mitral E wave velocity and positive family history of DCM. In conclusion, elevated NLR and SII at diagnosis are associated with increased mortality in pediatric patients with DCM. As cost-effective and easily accessible markers of systemic inflammation, these indices may serve as useful adjuncts to conventional risk assessment, particularly in settings with limited access to advanced laboratory testing. However, further prospective multicenter studies are needed to validate their prognostic role.

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Introduction

Dilated cardiomyopathy (DCM) is a primary myocardial disorder characterized by dilation and impaired systolic function of the left or both ventricles. In children, DCM is the most common type of cardiomyopathy and a leading indication for heart transplantation (1,2). Despite advances in diagnostic and therapeutic strategies, DCM is associated with considerable morbidity and mortality in the pediatric population (1).

The incidence of pediatric DCM is relatively low but clinically significant, with reported annual rates ranging from 0.34 to 1.13 cases per 100,000 children, depending on geographic region and study methodology (1,2). Etiological factors are heterogeneous and include post-infectious myocarditis, genetic mutations affecting cytoskeletal or sarcomeric proteins, metabolic disorders, neuromuscular diseases, chemotherapy-related cardiotoxicity and idiopathic forms. Several studies have shown that more than one-third of pediatric cases remain idiopathic, highlighting the diagnostic challenges associated with this condition (2).

Clinical presentation is equally diverse. The majority of children present with signs of congestive heart failure, such as tachypnea, feeding difficulties or reduced exercise tolerance, whereas others may present with arrhythmias, syncope or even sudden cardiac death. The clinical course is highly variable, with certain patients demonstrating partial recovery, while others progress to end-stage heart failure, requiring mechanical support or transplantation. Despite optimal management, transplant-free survival remains limited, with 5-year survival rates reported to be only 50-70% (2). Determining prognosis in pediatric DCM remains a clinical challenge. Although echocardiographic parameters such as left ventricular ejection fraction, fractional shortening and left-ventricular end-diastolic diameter (LVEDD), and clinical parameters such as New York Heart Association or Ross functional class and heart failure-related hospitalization, are commonly used to estimate outcomes, they may not fully reflect the complex pathophysiology of disease progression (1,2). These conventional measures are load-dependent and provide only a snapshot of systolic performance and clinical status at

a single time-point, whereas pediatric DCM is influenced by heterogeneous mechanisms, including genetic predisposition, myocardial inflammation, remodeling and arrhythmic risk, which are not adequately captured by baseline echocardiography or bedside clinical scores (2). Previously published evidence has suggested that inflammation may serve a role in the pathogenesis and progression of DCM, raising interest in the potential prognostic value of inflammatory markers (3-5).

Amongst the inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) and the the systemic inflammatory index (SII), calculated as platelet count x neutrophil count/lymphocyte count, have been garnering attention as accessible indicators of systemic inflammation. Previous studies in pediatric DCM have demonstrated the prognostic utility of elevated NLR, showing its association with poor clinical outcomes (4,5). However, to the best of our knowledge, no study has evaluated the prognostic significance of SII in children with DCM, and the present study is the first to assess both NLR and SII simultaneously in this patient population.

The present study aims to evaluate the prognostic significance of clinical, echocardiographic and laboratory parameters, particularly NLR and SII, in pediatric patients diagnosed with DCM. By analyzing a long-term, single-center cohort, the present study aims to contribute to the current understanding of the prognostic value of systemic inflammatory markers in pediatric DCM.

Patients and methods

Patient cohort. The present study included 52 pediatric patients (age, 0-18 years) diagnosed with DCM who were followed at the Department of Pediatric Cardiology of Marmara University Faculty of Medicine (Istanbul, Turkey) between January 2000 and June 2021. Inclusion criteria were a DCM phenotype defined by LV dilatation with impaired systolic function on echocardiography, including cases with various underlying causes, such as idiopathic, post-myocarditis, anthracycline-related or genetic/metabolic. Exclusion criteria were structural heart disease causing ventricular dilatation/dysfunction (e.g., critical aortic stenosis, aortic coarctation with LV dysfunction, coronary anomalies/ischemic heart disease), and other primary cardiomyopathy phenotypes not consistent with DCM (e.g., hypertrophic, LV noncompaction, restrictive or arrhythmogenic cardiomyopathy).

Relevant clinical, diagnostic and outcome data were retrospectively reviewed using patient charts and electronic medical records. Data collected included age at diagnosis, sex, presenting symptoms, etiological classification, echocardiographic and rhythm monitoring findings (including Holter rhythm monitoring and ECG), treatment modalities, duration of follow-up and survival status. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The SII was calculated using the following formula: Platelet count x neutrophil count/lymphocyte count. These values were obtained retrospectively from complete blood count results derived from peripheral venous blood samples collected at the time of diagnosis. All analyses were performed using standardized automated hematology analyzers in the Central Laboratory of Marmara University Hospital (Istanbul, Turkey). Echocardiographic measurements were extracted from standardized reports prepared by experienced pediatric cardiologists at the time of diagnosis. Although formal inter-observer variability testing was not performed due to the retrospective nature of the study, all evaluations were conducted using consistent institutional protocols.

The aim of the present study was to evaluate the prognostic impact of various clinical and laboratory parameters, particularly the NLR and the SII, on mortality.

Ethical approval for the present study was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval no. 09.2022.463). The requirement for informed consent was waived due to the retrospective design of the study, in accordance with the approval granted by the ethics committee.

Statistical analysis. Overall survival (OS) was defined as the time from the diagnosis of DCM to either mortality or the last follow-up. Statistical analyses were performed using SPSS 15.0 (SPSS, Inc.) for Windows. Descriptive statistics are presented as numbers and percentages for categorical variables, and as mean ± standard deviation for numerical variables with normal distribution. Group comparisons for categorical variables were made using the χ^2 test, with Fisher's exact test applied when expected cell counts were <5. For continuous variables, the independent-samples t-test was used when the assumption of normality, as assessed by the Shapiro-Wilk test, was met; otherwise, the Mann-Whitney U test was applied. Within-patient comparisons (namely FS and EF from baseline to final follow-up) were analyzed using the Wilcoxon signed-rank test. Survival rates were analyzed using Kaplan-Meier analysis, whereas risk factors were evaluated using Cox regression analysis. Cut-off values were determined using receiver operating characteristic (ROC) curve analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographic characteristics. A total of 52 pediatric patients diagnosed with DCM were included in the present study. The mean age at diagnosis was 58.8±69.8 months (range, 1-216 months). Within the cohort, 48.1% were female (n=25), and no statistically significant difference was observed in the sex distribution between deceased (n=16) and surviving patients. Although the mean age at diagnosis tended to be higher among patients who succumbed (73.2±67.6 months) compared with that in survivors (52.4±70.7 months), this difference did not reach statistical significance (Table I).

Consanguinity was present in 41.2% of +patients overall and was more frequent in the deceased group (60.0%) compared with that in the survivor group (33.3%), though this was not statistically significant. The mean weight and height at diagnosis were 19.5±16.9 kg (range, 4-70 kg) and 116.1±34.1 cm (range, 55-185 cm), respectively. However, there was no significant difference in these anthropometric parameters between the two groups. A total of 37.3% patients had weight in the <3rd percentile and 46.2% had height in the <3rd percentile. No significant difference was observed between the deceased and surviving patient groups for either of the aforementioned parameters. All baseline demographic and clinical characteristics of the patients are summarized in Table I.

Etiological classification and outcome. Among the 52 patients diagnosed with DCM, 15 (28.8%) had a history of suspected

Table I. Demographic and clinical characteristics of patients with DCM according to survival status.

Patient demographic and clinical characteristics	Total (n=52)	Deceased (n=16)	Survived (n=36)	P-value
Sex, n (%)				0.677[a]
Female	25 (48.1)	7 (43.8)	18 (50.0)	
Male	27 (51.9)	9 (56.3)	18 (50.0)	
Age at diagnosis, months (mean ± SD)	58.8±69.8	73.2±67.6	52.4±70.7	0.051[b]
Weight, kg (mean ± SD)	19.5±16.9	23.3±17,1	17.8±16.8	0.111[b]
Height, cm (mean ± SD)	116.1±34.1	97.3±28.9	121.7±34.8	0.271[b]
Weight percentile range, n (%)				0.831[a]
<P3	19 (37.3)	4 (25)	15 (42.9)	
P3-P10	5 (9.8)	2 (12.5)	3 (8.6)	
P10-P25	11 (21.6)	4 (25.0)	7 (20.0)	
P25-P50	9 (17.6)	4 (25.0)	5 (14.3)	
P50-P75	4 (7.8)	1 (6.3)	3 (8.6)	
>P75	3 (5.9)	1 (6.3)	2 (5.7)	
Height percentile range, n (%)				0.770[a]
<P3	6 (46.2)	1 (33.3)	5 (50.0)	
P3-P10	1 (7.7)	0 (0.0)	1 (10.0)	
P10-P25	1 (7.7)	0 (0.0)	1 (10.0)	
P25-P50	3 (23.1)	1 (33.3)	2 (20.0)	
P50-P75	1 (7.7)	0 (0.0)	1 (10.0)	
>P75	1 (7.7)	1 (33.3)	0 (0.0)	
Admission symptoms, n (%)				0.773[a]
Heart failure symptoms	31 (59.6)	10 (62.5)	21 (58.3)	
Heart failure symptoms + GI symptoms	6 (11.5)	3 (18.8)	3 (8.3)	
GI symptoms (isolated)	5 (9.6)	1 (6.3)	4 (11.1)	
Isolated murmur	2 (3.8)	0 (0.0)	2 (5.6)	
Incidentally detected	8 (15.4)	2 (12.5)	6 (16.7)	
Family history of DCM, n (%)				0.116[a]
Negative	42 (80.8)	10 (62.5)	32 (88.9)	
Positive	5 (9.6)	3 (18.8)	2 (5.6)	
Consanguinity, n (%)	21 (41.2)	9 (60.0)	12 (33.3)	0.078[a]
Etiology, n (%)[c]				0.469[a]
Idiopathic	36 (69.2)	11 (30.6)	25 (69.4)	
Post-myocarditis	15 (28.8)	4 (26.7)	11 (73.3)	
Anthracycline-associated	1 (1.9)	1 (100.0)	0 (0.0)	
Hospitalization duration at diagnosis, days (mean ± SD)	8.29±10.5	10.06±13.94	7.50±8.71	0.212[b]
Follow-up duration, months (mean ± SD)	25.3±30.2	17.6±24.1	28.7±32.2	0.264[b]

[a]χ^2 test (Fisher's exact test applied when expected cell counts <5), [b]Mann-Whitney U-test. [c]Several patients in the idiopathic group had identifiable genetic or metabolic syndromes (Duchenne muscular dystrophy n=1, Pompe disease n=2, Prader-Willi syndrome n=1, propionic acidemia n=2). These were included in the idiopathic group for statistical purposes. Weight percentile data were unavailable for one patient and height percentile data were available for 13 patients; percentages were calculated based on available data. Family history data were missing for five patients; percentages were calculated based on available data. DCM, dilated cardiomyopathy; GI, gastrointestinal; P, percentile.

post-myocarditis and 1 patient (1.9%) had anthracycline-associated cardiomyopathy, whereas 36 patients (69.2%) were classified as idiopathic in the absence of a clearly identifiable secondary cause. Additionally, several patients in the idiopathic group had identifiable genetic or metabolic syndromes, including Duchenne muscular dystrophy (n=1), Pompe disease (n=2), Prader-Willi syndrome (n=1) and propionic acidemia (n=2). However, these syndromic cases were included into the idiopathic group as they could not be considered separate categories due to their small numbers. Etiological subgroup comparisons between deceased and surviving patients showed no statistically significant differences (Table I).

Clinical findings. Patients presented with a variety of symptoms at diagnosis (Table I). The most frequent presentation was typical signs of heart failure, observed in 59.6% patients.

This group included clinical findings, such as reduced exercise tolerance, tachypnea and tachycardia.

A total of 21.1% patients reported gastrointestinal (GI) symptoms, including nausea, vomiting or abdominal pain. Among them, 6 patients (11.5%) had GI symptoms in combination with heart failure signs, whereas 5 patients (9.6%) presented with isolated GI complaints. An isolated murmur was the referral reason in 2 patients (3.8%), whilst 15.4% were referred after incidental findings during routine pediatric evaluations. No statistically significant difference was found in the presenting symptoms between deceased and surviving patients.

Laboratory parameters. All laboratory results were obtained at the time of diagnosis, prior to the initiation of medical treatment (Table II).

The mean white blood cell count was 10,420.9±3,629.7/mm^3 (range, 2,800-19,600/mm^3). Neutrophil and lymphocyte percentages were 59.3±20.8% (range, 14-91%) and 31.6±17.3% (range, 3.5-77%), respectively. Hemoglobin level averaged 11.47±2.10 g/dl (range, 6.3-16.1 g/dl) and hematocrit was 34.81±6.06% (range, 20.2-47.5%). Platelet count was 319,046.5±137,517.3/mm^3 (range, 103,000-742,000/mm^3).

The mean C-reactive protein level was 6.24±9.11 mg/l (range, 0-80 mg/l). Electrolyte analysis revealed a mean sodium level of 136.7±2.6 mmol/l (range, 129-143 mmol/l) and a mean magnesium level of 2.19±0.42 mg/dl (range, 1.2-2.9 mg/dl). Serum sodium levels were significantly lower in the deceased group compared with the survivors (134.3±2.4 vs. 137.6±2.1 mmol/l; P<0.001). Serum magnesium levels were also lower in the deceased group (1.98±0.24 vs. 2.26±0.45 mg/dl), although this difference did not reach statistical significance (P=0.084). Serum potassium and calcium levels showed no significant differences between groups (P=0.913 and P=0.736) and remained within normal limits, with mean values of 4.68±0.78 mmol/l and 9.50±0.89 mg/dl, respectively (Table II).

Cardiac biomarkers included B-type natriuretic peptide (BNP), creatine kinase (CK), CK-MB and troponin I. They were all markedly elevated compared with the reference range. BNP levels were also markedly elevated, with a mean of 15,317.3±13,311.1 pg/ml (range, 100-57,000 pg/ml). The mean CK level was 599.1±1,390.8 U/l (range, 70-5,000 U/l), the CK-MB mean level was 7.37±6.75 U/l (range, 1.2-28 U/l) and the mean troponin I level was 0.06±0.10 ng/ml (range, 0-0.50 ng/ml). No significant differences were observed in cardiac biomarkers between the two groups (Table II).

Renal function markers measured included blood urea nitrogen, urea and creatinine, with mean values of 14.45±8.89 mg/dl (range, 3.0-45.0 mg/dl), 30.9±19.9 mg/dl (range, 10-80 mg/dl) and 0.67±1.50 mg/dl (range, 0.2-6.0 mg/dl), respectively. Liver function tests showed mean aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of 77.3±103.7 and 54.8±75.7 U/l, respectively. Although these means were above the reference ranges, the elevation was driven by a few patients with markedly high transaminase levels, while the majority of the cohort had values within normal limits. These findings are summarized in Table II.

Echocardiographic findings. Echocardiographic evaluation at the time of diagnosis demonstrated varying degrees of left ventricular dilatation and systolic dysfunction, consistent with the clinical profile of DCM. The mean LVEDD was 4.38±1.10 cm. Although LVEDD values were higher in the deceased group of patients compared with those in the survivors, the difference did not reach statistical significance (Table III).

Left ventricular systolic function, as measured by FS and EF, was reduced in both groups compared with the expected normal pediatric ranges (FS <28% and EF <55% indicating systolic dysfunction). The mean FS was 19.1±7.97% and the mean EF was 39.3±13.8%. Although deceased patients had lower values for both FS and EF compared with those in the survivor group (FS: 16.6±5.6 vs. 20.3±8.7%; EF: 34.8±10.1 vs. 41.3±14.9%), the differences were not statistically significant. Mitral E wave velocity was, however, found to be significantly lower in the deceased group (0.78±0.18 vs. 0.94±0.22 m/sec; P=0.031).

Although the mean aortic root diameter was statistically larger in deceased patients (1.98±0.76 cm) compared with that in the survivor group (1.50±0.49 cm; P=0.017), all measurements fell within the normal Z-score range for age (-2 to +2). This difference was likely attributable to the older mean age of patients in the deceased group and was not considered clinically significant.

Other parameters, including left atrial diameter, mitral A wave velocity, deceleration time, isovolumic relaxation time and flow velocities across the aortic valve, pulmonary valve and descending aorta, showed no statistically significant differences between groups (Table III).

Rhythm monitoring findings. Electrocardiograph and Holter rhythm monitoring data were available for all patients. Ventricular ectopic activity (VEA) was detected in 7 patients (13.5%) and supraventricular VEA in 1 patient (1.9%). In these cases, the ectopic beat burden was <1% on 24-h Holter rhythm recordings. Therefore, these arrhythmias were considered rare and clinically insignificant. Supraventricular tachycardia was observed in 5 patients (9.6%) and no episodes of ventricular tachycardia were recorded.

Additional electrocardiographic findings included left axis deviation, low-voltage QRS complexes, ST-T wave abnormalities and biventricular or left ventricular hypertrophy. No statistically significant association was found between any electrocardiographic or Holter rhythm abnormality and mortality. All Holter rhythm and electrocardiographic findings are summarized in Table III.

Heart failure management and follow-up echocardiography. All patients received standard heart failure therapy. The most commonly prescribed medications were diuretics (82.7%), angiotensin-converting enzyme inhibitors (80.8%) and digoxin (69.2%), followed by beta-blockers (19.2%). In addition, supportive treatments, such as carnitine (50%) and coenzyme Q10 (48.1%), were frequently utilized. Follow-up echocardiographic evaluations, performed after a mean follow-up duration of 25.3±30.2 months (range, 1-108 months), demonstrated significant improvements in both EF and FS (Table IV). The mean EF increased from 39.3% at diagnosis to 49.8% at the final follow-up (P<0.001), whilst FS improved from 19.1 to 25.6% (P<0.001). Final echocardiographic measurements revealed that deceased patients had significantly lower EF and FS values compared with the survivors group (both P=0.002).

Table II. Laboratory parameters and prognostic comparison.

Parameter (reference range)	Total (n=52)	Deceased (n=16)	Survived (n=36)	P-value
White blood cell, x10³/μl (4.5-13.5)	10.4±3.6	10.6±4.1	10.3±3.4	0.809[a]
Neutrophil, % (40.0-75.0)	59.3±20.8	71.7±14.7	52.1±20.7	0.003[a]
Lymphocyte, % (20.0-45.0)	31.6±17.3	22.0±13.2	37.2±17.1	0.005[a]
Hemoglobin, g/dl (11.0-16.0)	11.47±2.10	10.95±1.45	11.74±2.35	0.239[a]
Hematocrit, % (33.0-45.0)	34.81±6.06	33.7±4.12	35.38±6.82	0.391[a]
Platelet, x10³/μl (150.0-450.0)	319.0±137.5	310.5±155.1	323.6±129.9	0.980[b]
Neutrophil-to-lymphocyte ratio	2.96±2.49	4.53±2.72	2.06±1.85	0.003[b]
Systemic inflammatory index	929,393.6±972,589.4	1,532,880.4±1,312,699.9	581,228.2±451,576.3	0.016[b]
C-reactive protein, mg/l (<5.0)	6.24±9.11	10.66±16.21	4.72±4.39	0.176[b]
B-type natriuretic peptide, pg/ml (<100.0)	15,317.3±13,311.1	11,777.0±12,360.1	17,399.9±13,767.8	0.290[b]
Na, mmol/l (135.0-145.0)	136.7±2.6	134.3±2.4	137.6±2.1	<0.001[b]
Mg, mg/dl (1.7-2.3)	2.19±0.42	1.98±0.24	2.26±0.45	0.084[a]
K, mmol/l (3.5-5.0)	4.68±0.78	4.71±0.77	4.67±0.80	0.913[b]
Ca, mg/dl (8.5-10.5)	9.50±0.89	9.42±0.68	9.53±0.97	0.736[a]
Blood urea nitrogen, mg/dl (7.0-20.0)	14.45±8.89	16.77±7.22	13.46±9.47	0.069[b]
Urea, mg/dl (10.0-50.0)	30.9±19.9	37.7±16.4	28.61±20.71	0.050[b]
Creatinine, mg/dl (0.3-1.0)	0.67±1.50	0.39±0.16	0.78±1.76	0.174[b]
Aspartate aminotransferase, U/l (5.0-40.0)	77.3±103.7	100.9±163.4	67.4±66.8	0.842[b]
Alanine aminotransferase, U/l (7.0-56.0)	54.8±75.7	78.9±111.7	44.9±54.9	0.430[b]
Albumin, g/dl(3.5-5.5)	4.02±0.61	3.92±0.60	4.05±0.62	0.351[b]
CK, U/l(20.0-200.0)	599.1±1,390.8	249.3±341.8	721.6±1,596.6	0.472[b]
CK-MB, U/l (0.0-24.0)	7.37±6.75	10.94±9.80	5.81±4.45	0.216[b]
Troponin I, ng/ml(<0.04)	0.06±0.10	0.06±0.04	0.06±0.12	0.155[b]
Troponin T, ng/l (<14.0)	82.3±97.3	75.2±65.3	85.8±113.1	0.391[b]

[a]Independent-samples t-test, [b]Mann-Whitney U-test. CK, creatine kinase.

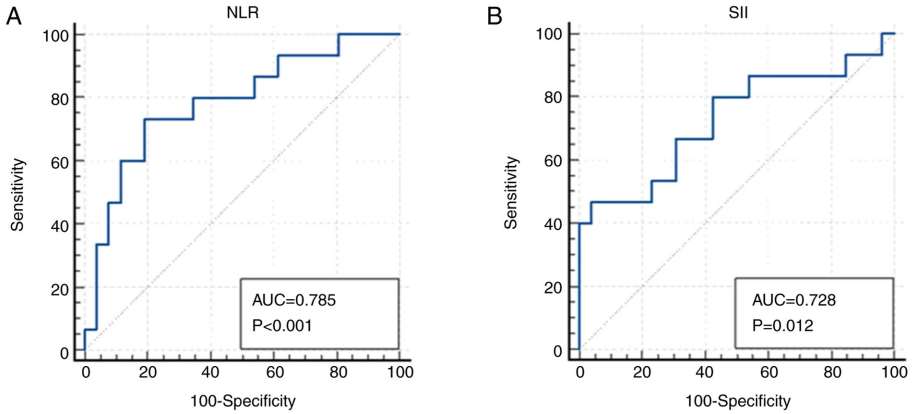

Figure 1. ROC curve analysis of inflammatory markers. (A) ROC curve of NLR for predicting mortality. (B) ROC curve of SII for predicting mortality. ROC, receiver operating characteristic; AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; SII, systemic inflammatory index.

These final post-treatment follow-up measurements according to survival status are summarized in Table IV.

Inflammatory markers and prognostic indices. At the time of diagnosis, inflammatory indices, including the NLR and SII, were calculated from complete blood count parameters (Table II). Both NLR and SII values were found to be significantly higher in deceased patients compared with those in the survivors group.

Specifically, the mean NLR value for the entire cohort was 2.96±2.49. NLR was significantly elevated in the deceased group (4.53±2.72) compared with that in the survivors group (2.06±1.85; P=0.003). Similarly, the mean SII was 929,393.6±972,589.4 in the overall cohort, with patients in the deceased group having a significantly higher SII (1,532,880.4±1,312,699.9) compared with that in the survivors group (581,228.2±451,576.3; P=0.016).

Table III. Echocardiographic findings at diagnosis, Holter rhythm monitoring and electrocardiographic abnormalities according to survival status.

Parameter	Total (n=52)	Deceased (n=16)	Survived (n=36)	P-value
Interventricular septal thickness in diastole, cm	0.63±0.17	0.69±0.19	0.60±0.15	0.076[a]
Left ventricular end-diastolic diameter, cm	4.38±1.10	4.74±1.01	4.23±1.11	0.121[a]
Left ventricular end-systolic diameter, cm	3.37±1.30	3.64±1.33	3.26±1.29	0.393[a]
Left ventricular posterior wall thickness in diastole, cm	0.68±0.48	0.69±0.18	0.68±0.56	0.054[b]
Fractional shortening, %	19.1±7.97	16.6±5.6	20.3±8.7	0.132[a]
Ejection fraction, %	39.3±13.8	34.8±10.1	41.3±14.9	0.187[b]
Left atrial diameter, cm	2.44±0.87	2.63±0.91	2.37±0.85	0.362[a]
Aortic root diameter, cm	1.63±0.60	1.98±0.76	1.50±0.49	0.017[a]
Mitral E, m/sec	0.89±0.22	0.78±0.18	0.94±0.22	0.031[a]
Mitral A, m/sec	0.64±0.19	0.59±0.18	0.66±0.19	0.240[a]
Deceleration time, msec	96.6±39.9	92.9±34.4	98.2±42.5	0.695[a]
Isovolumic relaxation time, msec	64.8±18.5	66.9±23.7	63.9±16.3	0.639[b]
Aortic root velocity, m/sec	1.14±0.32	1.05±0.22	1.17±0.35	0.219[b]
Pulmonary artery velocity, m/sec	1.09±0.29	0.98±0.24	1.13±0.30	0.105[a]
Descending Aortic root velocity, m/sec	1.17±0.33	1.08±0.28	1.20±0.35	0.219[b]
Holter rhythm monitoring findings, n (%)				>0.999[c]
Supraventricular ectopic activity	1 (1.9)	0(0)	1 (2.8)	
Ventricular ectopic activity	7 (13.7)	2 (13.3)	5 (13.9)	
Supraventricular tachycardia	5 (9.8)	1 (6.7)	4 (11.1)	
Ventricular tachycardia	0 (0)	0 (0)	0 (0)	
Electrocardiographic findings, n (%)				
No additional ECG finding	16 (31.4)	6 (40.0)	10 (27.8)	0.967[c]
Left ventricular hypertrophy	9 (17.6)	3 (20.0)	6 (16.7)	
Left ventricular hypertrophy + inverted T in V5-V6	5 (9.8)	1 (6.7)	4 (11.1)	
Left ventricular hypertrophy + left axis deviation	5 (9.8)	1 (6.7)	4 (11.1)	
Left ventricular hypertrophy + RBBB	1 (2)	1 (6.7)	0 (0)	
Frequent ventricular ectopic activity	3 (5.9)	1 (6.7)	2 (5.6)	
Left axis deviation	1 (2)	0 (0)	1 (2.8)	
Left axis deviation + left atrial enlargement	1 (2)	0 (0)	1 (2.8)	
Right axis deviation + ST depression	2 (3.9)	0 (0)	2 (5.6)	
Right axis deviation + biventricular hypertrophy	1 (2.0)	0 (0)	1 (2.8)	
Low QRS voltage	3 (5.9)	1 (6.7)	2 (5.6)	
Low QRS voltage + ST elevation	1 (2.0)	0 (0)	1 (2.8)	
Peaked T wave	1 (2.0)	1 (6.7)	0 (0)	
Supraventricular tachycardia episode	1 (2.0)	0 (0)	1 (2.8)	

[a]Independent-samples t-test, [b]Mann-Whitney U-test and [c]χ^2 test (Fisher's exact test applied when expected cell counts <5). All echocardiographic, Holter and electrocardiographic data were obtained at the time of diagnosis. Percentages were calculated according to the number of patients with available Holter rhythm data.

ROC curve analyses were performed separately for NLR and SII to predict mortality (deceased vs. surviving). The AUC for NLR was 0.785 (P<0.001) and for SII, it was 0.728 (P=0.012) (Fig. 1). Based on ROC-derived thresholds, a cut-off value of >2.75 for NLR and >1,428,898 for SII was associated with increased mortality risk. The AUC values and corresponding P-values were calculated using the DeLong test, 95% confidence intervals were computed with the binomial exact method and optimal cut-off values were determined according to the Youden index. These findings are summarized in Table V and illustrated in Fig. 1.

Survival and regression analysis. During the follow-up period, 16 of the 52 patients (30.8%) succumbed. Survival rates were therefore analyzed using Kaplan-Meier analysis. The OS rates at 1, 2, 3, 5 and 7 years were 77.3, 66.2, 61.8, 56.2 and 42.2%, respectively (Fig. 2). At the end of the follow-up period, 36 of the 52 patients (69.2%) were alive. This crude observed survival reflects the survival status at a median follow-up time of 25 months (mean, 25.3±30.2 months), whereas the Kaplan-Meier estimate at 7 years (42.2%) was based on a much smaller number of patients remaining under

Table IV. Baseline and final echocardiographic measurements according to survival status.

Parameter	All patients			Current status		
	Baseline (mean ± SD)	Final (mean ± SD)	P-value[a]	Deceased group (mean ± SD)	Surviving group (mean ± SD)	P-value[b]
Fractional shortening, %	19.1±7.97	25.6±8.9	<0.001	19.4±8.1	28.4±7.9	0.002
Ejection fraction, %	39.3±13.8	49.8±15.3	<0.001	38.5±14.5	54.7±13.1	0.002

[a]Wilcoxon signed-rank Test, [b]Mann-Whitney-U test.

Table V. ROC curve analysis parameters for NLR and SII.

Parameter	NLR	SII
Area under the ROC curve, area under the curve	0.785	0.728
Standard error[a]	0.0777	0.0904
95% Confidence interval[b]	0.628-0.897	0.567-0.855
z statistic	3.661	2.524
Significance level P-value (area=0.5)	0.0003	0.0116
Youden index J	0.5410	0.4282
Associated criterion	>2.75	>1,428,898
Sensitivity	73.33	46.67
Specificity	80.77	96.15

[a]DeLong test; [b]Binomial exact test. NLR, neutrophil-to-lymphocyte ratio; SII, systemic inflammation index; ROC, receiver operating characteristic.

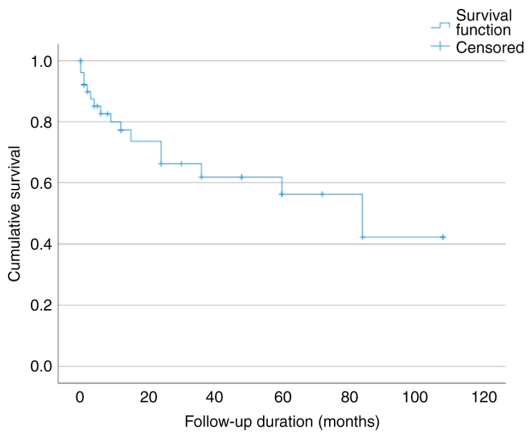

Figure 2. Kaplan-Meier survival curve of the study cohort. Overall survival probability was calculated using the Kaplan-Meier method. Censored patients are marked with a plus symbol (+).

observation. Although the median follow-up duration was shorter in deceased patients (17.6 months) compared with that in the survivors group (28.7 months), this difference was not statistically significant.

Univariate Cox regression analysis (Table VI) identified several variables that were significantly associated with mortality, including low serum sodium levels, elevated NLR, higher SII values, increased aortic root diameter, decreased mitral E wave velocity, low magnesium levels (within the normal reference range), elevated neutrophil percentage, decreased lymphocyte percentage and a positive family history of DCM (the per-unit HR for SII approximated 1.0 due to its large numeric scale, which limits interpretability per single-unit increase; however, both group comparisons and ROC analysis confirmed a significant association with mortality). Serum sodium levels emerged as one of the most consistently associated parameters with mortality among all variables analyzed (P<0.001 for group comparison; HR=0.669, 95% CI 0.527-0.850; P=0.001 in Cox regression).

Discussion

DCM in childhood is a rare condition characterized by impaired ventricular function and progressive heart failure. The annual incidence of pediatric DCM ranges between 0.57 and 1.13 cases per 100,000 children, with an estimated prevalence of ~1 per 250,000 (2). DCM remains one of the leading indications for cardiac transplantation in the pediatric population. Despite advances in medical therapy and heart failure management, predicting outcomes in pediatric DCM continues to be a major clinical challenge (6). This is largely due to the disease's heterogeneous etiology, variable clinical course and the limited data regarding prognostic indicators in children (2,6).

In previous years, systemic inflammation has been increasingly recognized to be a contributing factor in various cardiovascular conditions (7). Inflammatory responses may

Table VI. Univariate Cox regression analysis of risk factors for mortality.

Patient characteristics	P-value	Hazard ratio	95% CI	
			Min	Max
Sex (ref: Female)	0.953	1.031	0.380	2.793
Age at diagnosis, months	0.134	1.005	0.998	1.011
Medical history present (ref: Absent)	0.287	1.800	0.609	5.317
Family history positive (ref: Negative)	0.049	2.808	1.006	7.838
Consanguinity present (ref: Absent)	0.120	2.274	0.806	6.411
Left ventricular end-diastolic diameter, cm	0.164	1.404	0.871	2.265
Left ventricular end-systolic diameter, cm	0.335	1.258	0.789	2.006
Fractional shortening, %	0.618	0.980	0.905	1.061
Ejection fraction, %	0.510	0.985	0.942	1.030
Left atrial diameter, cm	0.182	1.467	0.836	2.574
Ao diameter, cm	0.006	2.746	1.344	5.612
Mitral E, m/sec	0.034	0.018	0.000	0.741
Mitral A, m/sec	0.210	0.126	0.005	3.221
Ao velocity, m/sec	0.511	0.471	0.050	4.441
Pulmonary artery velocity, m/sec	0.176	0.266	0.039	1.815
Descending Ao velocity, m/sec	0.476	0.529	0.092	3.045
CK, U/l	0.432	0.999	0.998	1.001
CK-MB, U/l	0.229	1.048	0.971	1.132
Troponin I, ng/ml	0.811	0.299	0.000	5.942
Troponin T, ng/l	0.579	1.003	0.992	1.015
B-type natriuretic peptide, pg/ml	0.215	1.000	1.000	1,000
White blood cells, $x10^3/\mu l$	0.645	1.000	1.000	1.000
Neutrophil, %	0.017	1.047	1.008	1.088
Lymphocyte, %	0.025	0.953	0.913	0.994
Hemoglobin, g/dl	0.268	0.828	0.593	1.156
Hematocrit, %	0.446	0.957	0.854	1.072
Platelet, $x10^3/\mu l$	0.801	1.000	1.000	1.000
Neutrophil-to-lymphocyte ratio	0.006	1.303	1.077	1.575
Systemic inflammation index	0.001	1.000	1.000	1.000
C-reactive protein, mg/l	0.905	1.003	0.959	1.048
Blood urea nitrogen, mg/dl	0.100	1.045	0.992	1.102
Urea, mg/dl	0.182	1.021	0.990	1.053
Creatinine, mg/dl	0.679	0.801	0.280	2.293
Albumin, g/dl	0.359	0.549	0.152	1.979
Aspartate aminotransferase, U/l	0.199	1.003	0.999	1.007
Alanine aminotransferase, U/l	0.285	1.003	0.997	1.010
Na, mmol/l	0.001	0.669	0.527	0.850
K, mmol/l	0.631	0.773	0.270	2.211
Ca, mg/dl	0.463	0.768	0.381	1.552
Mg, mg/dl	0.019	0.026	0.001	0.547

Ao, aortic root; CK, creatine kinase.

influence myocardial function through cytokine-mediated pathways, microvascular dysfunction and myocardial remodeling (7,8). Among the accessible inflammatory markers, NLR and SII have gained attention as simple cost-effective indicators reflecting the balance between proinflammatory and regulatory immune responses (9,10).

In pediatric DCM, data on the prognostic role of inflammatory markers remain limited. The majority of studies to date have focused solely on the NLR. Ahmed *et al* (5) demonstrated that elevated NLR levels were significantly associated with disease severity and adverse outcomes in children with DCM-related acute heart failure. Similarly,

da Rocha Araújo *et al* (4) reported that elevated NLR was associated with poor clinical progression, increased mortality and the necessity for cardiac transplantation. To the best of our knowledge, no study to date has evaluated the prognostic role of the SII or investigated both NLR and SII in the same pediatric DCM population. By introducing SII into the pediatric cardiology literature, the present study provides a contribution to the understanding of inflammation-based risk assessment in this population.

NLR and SII have both been studied as prognostic markers in adult patients with heart failure and cardiomyopathies, where it has been determined that these markers are associated with poor outcomes and increased mortality (11-14). By evaluating the prognostic value of NLR and SII simultaneously in a pediatric DCM cohort, the present study offers data and contributes to addressing the current knowledge gap in this field.

In present study, both the NLR and the SII were significantly higher in patients who succumbed compared with those in the survivors group. ROC curve analysis confirmed that both markers had prognostic value for mortality, with NLR showing an AUC of 0.785 and SII exhibiting an AUC of 0.728. The identified cut-off values (>2.75 for NLR and >1,428,898 for SII), as determined by ROC analysis, were statistically significant predictors of mortality. Specifically, the NLR cut-off demonstrated a sensitivity of 73.3% and a specificity of 80.8%, indicating balanced diagnostic accuracy. By contrast, the SII cut-off yielded a lower sensitivity (46.7%) but a notably high specificity (96.2%), suggesting that patients exceeding this threshold could be identified as truly high-risk with greater confidence. These findings were further supported by univariate Cox regression analysis, in which both markers showed significant associations with mortality. Notably, low serum sodium levels also demonstrated the strongest statistical association with mortality among all variables included in the analysis. This observation aligns with previous reports from both adult and pediatric populations, where hyponatremia has been independently associated with adverse outcomes in heart failure (15,16).

In addition to systemic inflammatory markers and serum sodium, several other parameters were also found to be significantly associated with mortality in the present study. These included low serum magnesium levels, reduced mitral E wave velocity and a positive family history of DCM. These findings are consistent with previous studies demonstrating that hypomagnesemia may increase cardiovascular mortality risk, whereas reduced mitral E velocity may indicate diastolic dysfunction and worse outcomes, and that a positive family history is associated with disease progression and poorer prognosis in pediatric DCM (17-19).

Notably, although mitral E wave velocity has been previously studied as a diastolic function parameter, its prognostic role in pediatric DCM remains underexplored. Bressieux-Degueldre *et al* (20) did not observe a significant association between mitral E velocity and mortality in their pediatric cohort. By contrast, the present study identified a statistically significant difference in mitral E velocity, with patients in the deceased group showing lower E wave velocities compared with survivors (0.78±0.18 vs. 0.94±0.22 m/sec; P=0.031). This reduction reflects impaired left ventricular relaxation and diastolic filling in patients with more advanced myocardial dysfunction, suggesting that this parameter may warrant further evaluation as a potential prognostic marker in this population.

It is also worth noting that although aortic root diameter was found to be statistically larger in patients who succumbed, all measurements were within the normal Z-score range for age. This difference likely reflects the older mean age of deceased patients, instead of an independent prognostic relationship. Since absolute diameters were used in the analysis without adjustment for age or body surface area, this finding most likely reflects age-related anatomical variation rather than clinically significant aortic dilatation. Therefore, this finding was not interpreted as clinically meaningful.

To the best of our knowledge, the present study was the first to evaluate both NLR and SII as prognostic indicators in pediatric DCM. By integrating two distinct inflammatory markers derived from complete blood count parameters, the present findings highlight the potential value of systemic inflammation-based indices in early risk stratification. Given that NLR and SII are inexpensive, readily accessible and routinely obtained in clinical practice, their incorporation into the initial assessment of children with DCM may enhance prognostic evaluation and inform closer monitoring strategies. These markers may serve as useful adjuncts to echocardiographic and clinical data, particularly in resource-limited settings where advanced biomarkers are not readily available.

Whilst the present study provides important preliminary insights, several limitations should be acknowledged. The present study was a retrospective, single-center analysis with a relatively small cohort, which may limit the generalizability of the findings. Systemic inflammatory markers were evaluated only at the time of diagnosis. Therefore, longitudinal trends and the potential impact of concurrent infections or other inflammatory conditions could not be assessed. Additionally, due to the limited number of events, multivariate analysis could not be performed, restricting the evaluation of independent associations. The etiological heterogeneity of the cohort, encompassing idiopathic, post-infectious, genetic and chemotherapy-related cases, may also have influenced inflammatory responses and outcomes. Despite these limitations, the present study introduces novel findings and highlights the need for prospective multicenter research to further clarify the prognostic role of inflammatory markers in pediatric DCM. The findings of the present study may also help inform clinical decision-making by supporting early risk stratification and identifying children who may benefit from closer monitoring, timely intensification of therapy or earlier referral to transplant centers.

In conclusion, the present study demonstrates that elevated NLR and SII at the time of diagnosis are significantly associated with increased mortality in pediatric patients with DCM. These easily accessible and inexpensive inflammatory markers may serve as complementary tools to traditional clinical assessments, particularly in settings where advanced laboratory testing is not readily available. Although further prospective and multicenter studies are

warranted to validate these findings, the present results highlight the prognostic relevance of systemic inflammation in pediatric DCM and suggest a potential role for NLR and SII in early risk stratification. However, since multivariate analysis could not be performed due to the limited number of events, these findings should be interpreted as associations rather than evidence of independent prognostic value. Further prospective multicenter studies are needed to confirm their utility before they can be incorporated into routine clinical decision-making.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SA contributed to study conception, data collection, statistical analysis, interpretation of results and manuscript drafting. FA contributed to study design, interpretation of data and critical manuscript revision. Both authors read and approved the final manuscript. SA and FA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of Marmara University Faculty of Medicine (Istanbul, Turkey; approval no. 09.2022.463). The requirement for informed consent was waived due to the retrospective design of the study, in accordance with the approval granted by the ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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