Cardiology in the Young

cambridge.org/cty

Evaluation of Pentraxin-3 levels in children with multisystem inflammatory syndrome

Dolunay Gürses[1], Münevver Yılmaz[1], Esin Avcı[2], Merve Oğuz[1], Emine Sayın[1] and Selçuk Yüksel[3]

[1]Department of Pediatric Cardiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey; [2]Department of Medical Biochemistry, Faculty of Medicine, Pamukkale University Denizli, Denizli, Turkey and [3]Department of Pediatric Rheumatology, Faculty of Medicine, Onsekiz Mart University Çanakkale, Pamukkale, Turkey

Original Article

Cite this article: Gürses D, Yılmaz M, Avcı E, Oğuz M, Sayın E, and Yüksel S (2025) Evaluation of Pentraxin-3 levels in children with multisystem inflammatory syndrome. *Cardiology in the Young* **35**: 317–323. doi: 10.1017/S1047951124036175

Received: 14 May 2024
Revised: 9 October 2024
Accepted: 26 October 2024
First published online: 2 December 2024

Keywords:
Multisystem inflammatory syndrome in children; Pentraxin-3; Cardiac involvement

Corresponding author:
Münevver Yılmaz;
Email: munevveryl@yahoo.com

Abstract

Background: Early recognition of cardiac involvement and prediction of disease prognosis are essential for the management of inflammatory diseases such as multisystem inflammatory syndrome. This study aimed to investigate the role of Pentraxin-3 levels in identifying cardiac involvement and evaluating disease severity in patients with multisystem inflammatory syndrome. *Methods:* The study included 56 multisystem inflammatory syndrome patients and 26 healthy children as a control group. The multisystem inflammatory syndrome group was divided into those with cardiac involvement ($n = 34$) and those without ($n = 22$), as well as those with clinically mild-moderate ($n = 30$) and severe ($n = 26$) multisystem inflammatory syndrome. Blood samples for measurement of Pentraxin-3 levels were obtained from all patients before treatment and from the healthy controls. *Results:* In the patient group, the mean age was 8.2 ± 4 years (range: 2–17 years), and the male-to-female ratio was 1.8. In the control group, these values were 9.5 ± 3.7 years (range: 2–16 years) and 1.9, respectively ($p > 0.05$). Plasma Pentraxin-3 levels were significantly higher in multisystem inflammatory syndrome patients compared to controls (7.1 ± 5 ng/mL vs. 2.9 ± 2.1 ng/mL, $p = 0.001$). Patients with cardiac involvement had a significantly higher median Pentraxin-3 level than those without (5.8 ng/mL vs. 4.1 ng/mL, $p = 0.004$). Severe disease was also associated with a higher median Pentraxin-3 level compared to mild-moderate disease (6.1 ng/mL vs. 4.4 ng/mL, $p = 0.001$). Pentraxin-3 level was negatively correlated with left ventricular ejection fraction and positively correlated with B-type natriuretic peptide, troponin. *Conclusion:* Elevated Pentraxin-3 levels in multisystem inflammatory syndrome patients may help predict the clinical course of the disease and cardiac involvement. However, larger-scale prospective studies are needed to further elucidate this.

Introduction

Multisystem inflammatory syndrome in children is a newly defined syndrome associated with severe acute respiratory syndrome coronavirus 2.[1] Cardiac involvement has been reported in 67–80% of children with multisystem inflammatory syndrome.[1] Echocardiographic evaluations have demonstrated decreased cardiac function and localised contraction defects in more than a third of these children and mild to moderate valve insufficiencies in approximately 29%.[2] These findings are followed by coronary artery involvement and pericardial involvement at rates of up to 25 and 20%, respectively.[2] Cardiac involvement is the main reason for intensive care unit admissions in multisystem inflammatory syndrome. In case series, a 1–2% mortality rate and cardiovascular sequelae including aneurysms or decreased cardiac function at rates of up to 15% have been described.[2,3]

Pentraxin-3 is an acute phase protein released from vascular endothelial cells in response to inflammatory signals. High plasma Pentraxin-3 concentrations have been associated with disease severity and mortality in conditions such as sepsis and infections.[4,5] Pentraxin-3 plays a role in vascular inflammation and endothelial dysfunction via different mechanisms. It may be indirectly involved in tissue repair and remodelling by regulating inflammation.[4,6] Increased Pentraxin-3 plasma levels have been observed in different cardiovascular diseases.[7–9]

In patients with severe acute respiratory syndrome coronavirus 2 infection, Pentraxin-3 was reported to be reliable in predicting short-term mortality and a better prognostic indicator than other markers such as C-reactive protein and interleukin 6.[10,11] High Pentraxin-3 levels in people with severe acute respiratory syndrome coronavirus 2 infection are believed to indicate uncontrolled inflammation.[12] However, only one small study has investigated Pentraxin-3 levels in multisystem inflammatory syndrome, a hyperinflammatory syndrome associated with severe acute respiratory syndrome coronavirus 2.[13] In this study, Pentraxin-3 levels were found to be

higher in multisystem inflammatory syndrome patients, but no relationship was reported between Pentraxin-3 levels and disease severity.[13]

The clinical and laboratory findings of multisystem inflammatory syndrome overlap with those of other febrile diseases, and the underlying cause of its cardiac involvement is not fully understood. In inflammatory diseases such as multisystem inflammatory syndrome, predicting cardiac involvement and disease severity at the time of diagnosis is important in disease management. In this study, we aimed to investigate the role of Pentraxin-3 in identifying cardiac involvement and evaluating disease severity in patients with multisystem inflammatory syndrome.

Materials and methods

This prospective study included children with multisystem inflammatory syndrome who were hospitalised and treated in the paediatric cardiology ward of Pamukkale University Faculty of Medicine Hospital. Multisystem inflammatory syndrome was diagnosed according to the criteria defined by the United States Centers for Disease Control and Prevention and the World Health Organization in 2020[14,15]. The control group consisted of children of similar age and sex distribution who presented to the paediatric cardiology outpatient clinic due to chest pain, palpitations, or murmur and had normal echocardiography results. Patients who were referred to our hospital after diagnosis and initiation of treatment in other centres were excluded from the study. In the control group, subjects with a history of infectious disease or drug use in the last 15 days or with chronic systemic disease were excluded. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Pamukkale University (02.22.2022/04).

Blood samples for measurement of Pentraxin-3 levels were obtained from the multisystem inflammatory syndrome patients before treatment and from the healthy controls. A 10-cc sample of venous blood was collected in a biochemistry tube and left at room temperature for approximately 15 minutes, then centrifuged at 3500 r.p.m. for 10 minutes. The resulting serum was stored at −80°C until analysis. Pentraxin-3 was quantified using commercial human Pentraxin-3 kits from BioAssay Technology Laboratory (Shanghai, China). The absorbance values of the wells were read at 450 nm using a BioTek Elx800 Microplate reader (BioTek Instruments Inc., USA). The kit is based on the sandwich immunoassay method and has a sensitivity of 0.05 ng/mL and range of 0.1–30 ng/mL.

The patients' demographic characteristics, physical examination and laboratory findings, treatment received, and length of hospital stay were recorded. All patients underwent electrocardiography and echocardiographic evaluation using 2.5–3.5 MHz and 2.7–8 MHz probes with a GE Vivid S5 echocardiography device. Left ventricular systolic dysfunction was defined as an ejection fraction being below 55%[1–3]. On echocardiographic evaluation, the presence of left ventricular dysfunction, valve insufficiency, coronary artery lesion, or pericardial effusion was accepted as cardiac involvement. The patients were divided into those with and without cardiac involvement and the two groups were compared.

Multisystem inflammatory syndrome severity was classified depending on the extent of respiratory or hemodynamic support and organ damage. Patients with no or very little respiratory or cardiovascular support and minimal organ damage [Pediatric Logistic Organ Dysfunction-2 score ≤ 2] were classified as having mild multisystem inflammatory syndrome. Those with no or very little respiratory or cardiovascular support and mild organ damage (Pediatric Logistic Organ Dysfunction-2 score $3 \leq$) were classified as having moderate multisystem inflammatory syndrome.[16] Patients who needed any respiratory, vasoactive, or inotropic support and those who had severe organ damage and required intensive care were classified as having severe multisystem inflammatory syndrome.[17] For comparison according to disease severity, the patients were grouped as mild-moderate multisystem inflammatory syndrome and severe multisystem inflammatory syndrome.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (version 18 for Windows, SPSS Inc., Chicago, IL, USA). Continuous data were tested for normal distribution using the Kolmogorov–Smirnov test. Student's *t*-test was used for comparisons of normally distributed data and the Mann–Whitney *U*-test for nonnormally distributed data. Categorical data were compared using chi-square and Fisher's exact test. Receiver operating characteristic curve analysis was used to determine the threshold value for Pentraxin-3. The results were presented as number and percentage for categorical variables; mean, standard deviation, minimum, and maximum for continuous variables showing a normal distribution; and median and interquartile range for continuous variables showing a non-normal distribution. Logistic regression model was used to compare the effect of disease severity and cardiac involvement on Pentraxin-3 level. Statistical significance was accepted at $p < 0.05$.

Results

The study included 56 multisystem inflammatory syndrome patients (68%) and 26 healthy children (32%). There was no difference between the study and control groups in terms of age, sex, weight, or height ($p > 0.05$) (Table 1). The multisystem inflammatory syndrome patients had significantly lower mean haemoglobin level and platelet count ($p = 0.001$) and higher mean leukocyte count ($p = 0.02$). Mean C-reactive protein, erythrocyte sedimentation rate, and troponin levels were also significantly higher in the multisystem inflammatory syndrome group than the control group ($p = 0.0001$). The mean Pentraxin-3 level was 7.1 ± 5 (2.8–24.9) ng/mL in the multisystem inflammatory syndrome group, compared to 2.9 ± 2.1 (0.1–6.6) ng/mL in the control group ($p = 0.001$) (Table 1).

Multisystem inflammatory syndrome patients most commonly had gastrointestinal involvement ($n = 51$, 91.1%), followed by haematological ($n = 47$, 83.9%) and dermatological involvement ($n = 42$, 75%). Cardiac involvement was detected in 34 patients (60.7%), neurological involvement in 20 patients (35.7%), pulmonary involvement in 10 patients (17.9%), and renal involvement in 6 patients (10.7%).

When the multisystem inflammatory syndrome patients were grouped into those with and without cardiac involvement, no differences in age, sex, weight, or height were observed ($p > 0.05$). Of the hemogram parameters, leukocyte count, and haemoglobin levels were similar in both groups ($p > 0.05$), while patients with cardiac involvement had significant higher neutrophil-to-lymphocyte ratio ($p = 0.032$) and lower lymphocyte and platelet counts ($p = 0.003$ and $p = 0.042$, respectively). In terms of acute phase reactants, there was no significant difference between the groups in terms of C-reactive protein, erythrocyte sedimentation rate, IL-6, and ferritin levels ($p > 0.05$), whereas procalcitonin levels were significantly higher in the group with cardiac involvement ($p = 0.006$). Troponin and B-type natriuretic peptide (BNP) levels were also significantly higher in patients with cardiac

https://doi.org/10.1017/S1047951124036175 Published online by Cambridge University Press

Table 1. Demographic and laboratory findings of the patient and control groups

	MISC ($n = 56$)	Control ($n = 26$)	p
Sex (M/F)	36/20	17/9	0.927
Age (years)	8.2 ± 4 (2–17)	9.5 ± 3.7 (2–16)	0.164
Height (cm)	132 ± 24.7 (78–186)	139 ± 20 (96–180)	0.173
Weight (kg)	34 ± 19.8 (12–97)	37.2 ± 16.4 (16–90)	0.448
Haemoglobin (g/dL)	12 ± 1.5 (8.7–16.2)	13 ± 0.7 (12.6–13.7)	0.001
Leukocytes (10^3/μL)	12 ± 5.9 (2.5–28.8)	8.1 ± 1.8 (5.3–11.5)	0.02
Platelets (10^3/μL)	218 (139–254)	289 (248–343)	0.001
ESR (mm/h)	38.5 ± 18.1 (19–88)	11.3 ± 3.4 (5–18)	0.0001
CRP (mg/dL)	150 (89.9–219.7)	0.88 (0.3–2.2)	0.0001
Troponin (ng/L)	7.7 (3.9–21.4)	3 (3–3.3)	0.0001
Pentraxin-3 (ng/ml)	5.1 (4.1–7.1) 7.1 ± 5 (2.8–24.9)	3.1 (0.7–4.7) 2.9 ± 2.1 (0.1–6.6)	0.001
Lymphocytes (10^3/μL)	1.4 ± 0.9 (0.2–5.1)		
NLR	9.2 ± 6.3 (1.2–30.7)		
Sodium (mmol/L)	134.2 ± 5 (121–146)		
AST (IU/L)	24 (17–35)		
ALT (IU/L)	15.5 (11.2–42.2)		
Creatinine (mg/dL)	0.5 ± 0.2 (0.2–1)		
Albumin (mg/dL)	3.6 ± 6.8 (2.1–46.9)		
Amylase (U/L)	42 (30–55)		
LDH (IU/L)	279.5 (235.5–303.5)		
D-Dimer (ng/mL)	897 (574–1609)		
Fibrinogen (mg/dL)	579.5 ± 176 (226–1095)		
Ferritin (μg/L)	278 (167.2–580.5)		
IL-6 (pg/mL)	116 (11.2–271)		
Procalcitonin (ng/mL)	1.6 (0.6–8.7)		
BNP (pg/mL)	717 (193.8–3508.5)		

Data presented as *n*, mean ± standard deviation (minimum-maximum), or median (interquartile range). M = Male, F = female, ESR = erythrocyte sedimentation rate, NLR = neutrophil-to-lymphocyte ratio, AST = aspartame transaminase, ALT = alanine transaminase, LDH = lactate dehydrogenase, IL-6 = interleukin 6, BNP = B-type natriuretic peptide.

involvement ($p = 0.0001$ and $p = 0.003$, respectively) (Table 2). The median Pentraxin-3 level was 5.8 (4.5–11.3) ng/mL in multisystem inflammatory syndrome patients with cardiac involvement and 4.1 (3.6–5.6) ng/mL in those without ($p = 0.004$). The area under the receiver operating characteristic curve for Pentraxin-3 level in the prediction of cardiac involvement was calculated as 0.668 ($p = 0.039$; 95% CI: 0.516–0.820). At a cut-off of 4.9 ng/mL, Pentraxin-3 had 63.6% sensitivity and 61.9% specificity for cardiac involvement in multisystem inflammatory syndrome. The demographic and laboratory findings of multisystem inflammatory syndrome patients with and without cardiac involvement are presented in Table 2.

The mean left ventricular ejection fraction of the 34 patients with cardiac involvement was 57.8 ± 6.6% (40–69%). Eighteen patients (53%) had left ventricular systolic dysfunction, 15 (44%) had mitral valve regurgitation, 15 (44%) had pericardial effusion, and 3 patients (8.8%) had coronary artery aneurysm (*Z*-score: 2.7–4.3). Median Pentraxin-3 levels were 6.1 (4.9–17) ng/mL among patients with left ventricular systolic dysfunction and 4.6 (3.8–6.2) ng/mL in those without ($p = 0.003$). Patients with mitral valve insufficiency also had a significantly higher median Pentraxin-3 level than those without (6.2 [4.8–17.5] ng/ml vs. 4.6 [3.9–6.2] ng/mL, $p = 0.011$). Median Pentraxin-3 levels in patients with and without pericardial effusion were 4.8 (4.3–17.5) ng/mL and 5 (4.1–7) ng/mL, respectively, while those in patients with and without coronary artery aneurysm were 5.4 (4.3–7.3) ng/mL and 4.9 (4.0–7) ng/mL, respectively. There was no significant difference in Pentraxin-3 level between these groups ($p = 0.643$ and $p = 0.748$, respectively).

The multisystem inflammatory syndrome patients' mean length of hospital stay was 10.8 days (range: 5–30 days). The 26 patients (46.4%) who had severe clinical findings and required inotropic support were followed up in the intensive care unit for an average of 4.1 days (range, 2–10 days). None of the patients needed extracorporeal membrane oxygenation and there was no mortality.

When patients with severe multisystem inflammatory syndrome were compared according to disease severity, there were 26 patients (46.4%) in the severe group and 30 patients (53.4%) in

https://doi.org/10.1017/S1047951124036175 Published online by Cambridge University Press

Table 2. Demographic and laboratory findings of MISC patients with and without cardiac involvement and severe and mild-moderate

	Cardiac involvement ($n = 34$)	No cardiac involvement ($n = 22$)	p	Severe ($n = 26$)	Mild-moderate ($n = 30$)	p
Sex (M/F)	21/13	15/7	0.625	14/12	22/8	0.085
Age (years)	9.3 ± 3.7 (3–17)	7.6 ± 4.3 (2–17)	0.391	8.5 ± 3.8 (2–17)	7.3 ± 4.1 (2–17)	0.164
Height (cm)	137.5 ± 22 (104–183)	128.4 ± 26 (78–178)	0.396	134.2 ± 23.6 (83–186)	127.1 ± 25.7 (78–186)	0.173
Weight (kg)	37.7 ± 20.7 (15–97)	34 ± 20.1 (12–86)	0.938	34 ± 19.5 (13–97)	30.1 ± 18.7 (12–86)	0.448
Haemoglobin (g/dL)	11.9 ± 1.7 (8.7–13.2)	12.2 ± 1.4 (9–16.2)	0.451	11.8 ± 1.7 (8.7–13.2)	12 ± 1.4 (9–156.2)	0.413
Leukocytes (10^3/μL)	11.7 ± 5.4 (3.8–25.5)	12.4 ± 6.8 (2.5–28.9)	0.673	11.7 ± 5.7 (2. 6–25.5)	12.4 ± 6.2 (9–15.2)	0.551
Lymphocytes (10^3/μL)	1.1 ± 0.52 (0.2–2.8)	1.8 ± 1.2 (0.5–5.2)	0.003	0.99 ± 0.52 (0.2–2.2)	1.7 ± 1.1 (0.5–5.2)	0.01
NLR	10.7 ± 5.2 (1.2–26.5)	7 ± 7.2 (1.3–30.7)	0.032	11.5 ± 6 (1.4–30.7)	7.3 ± 6 (1.2–26.5)	0.016
Platelets (10^3/μL)	185 (123–240)	237 (180.3–360.8)	0.042	169 (100.5–233.5)	238.5 (186.5–308.3)	0.001
Sodium (mmol/L)	133.6 ± 5.6 (121–146)	135 ± 3.8 (128–143)	0.285	133 ± 5.8 (121–146)	135.3 ± 4 (128–143)	0.120
AST (IU/L)	24 (17–35)	24.5 (15.5–40)	0.795	23.5 (15.8–33.5)	24 (18–38.5)	0.656
ALT (IU/L)	15.5 (11–25.3)	15.5 (13.3–41)	0.475	14.5 (11–22)	16 (13.3–39.5)	0.882
Creatinine (mg/dL)	0.6 ± 0.22 (0.4–0.7)	0.5 ± 0.2 (0.3–1.05)	0.840	0.6 ± 0.2 (0.4–0.7)	0.5 ± 0.2 (0.4–0.6)	235
Albumin (mg/dL)	3.5 ± 0.7 (2.3–4.7)	3.8 ± 0.6 (2.2–4.5)	0.113	3.4 ± 0.7 (2.8–4.3)	3.8 ± 0.6 (2.2–4.7)	0.047
Amylase (U/L)	42 (29–60)	37.5 (31–53.3)	0.556	49 (29–62)	37 (30.3–50.3)	0.331
LDH (IU/L)	280 (237–303)	279 (255.5–298.5)	0.882	280 (243–303)	279 (240–298)	0.612
D-Dimer (ng/mL)	924 (615.3–1887.3)	698 (372–1438.3)	0.127	900 (588.5–2181.3)	890.5 (509–1428.5)	0.443
Fibrinogen (mg/dL)	611 ± 181 (226–1095)	530 ± 160 (264–941)	0.095	602 ± 207 (226–1095)	559 ± 146 (306–941)	368
CRP (mg/dL)	165 (103–255)	117 (73–170.5)	0.115	154.5 (115.3–240.2)	128.9 (83.6–159.3)	0.161
ESR (mm/h)	39.7 ± 15.8 (19–78)	36.7 ± 17.7 (23–88)	0.525	38.7 ± 16.7 (20–78)	38.3 ± 16.6 (19–88)	0.935
Ferritin (μg/L)	336 (232.8–612)	191 (103.3–396.5)	0.047	336 (226.8–612)	206.5 (141–482)	0.226
IL-6 (pg/mL)	126 (10.8–252.3)	44.6 (13.7–484.5)	0.938	116 (10.4–202)	119.5 (16–284)	0.66
Procalcitonin (ng/mL)	4.1 (1–17.2)	0.84 (0.4–2.8)	0.006	2.6 (1–17.2)	0.9 (0.4–2.6)	0.011
Troponin (ng/L)	15.2 (4.7–55.3)	4.2 (3–10)	0.001	15.2 (4.3–102.3)	5.1 (3–18.6)	0.006
BNP (pg/mL)	2170 (312–10649)	253 (91–755)	0.003	2640 (468–1273)	270(91.3–1201.5)	0.0001
Pentraxin-3 (ng/mL)	5.8 (4.5–11.3) 8.3 ± 5.9 (2.8–24.9)	4.1 (3.6–5.6) 5.4 ± 2.4 (3.1–11.2)	0.004	6.1 (4.9–15.7) 9.3 ± 6.2 (3.9–24.9)	4.4 (3.6–5.7) 5.1 ± 2.3 (3.6–5.7)	0.001

Data presented as *n*, mean ± standard deviation (minimum-maximum), or median (interquartile range). M = Male, F = female, ESR = erythrocyte sedimentation rate, NLR = neutrophil-to-lymphocyte ratio, AST = aspartame transaminase, ALT = alanine transaminase, LDH = lactate dehydrogenase, IL-6 = interleukin 6, BNP = B-type natriuretic peptide.

the mild-moderate group. There was no difference between these groups in terms of age, sex, weight, or height ($p > 0.05$) (Table 2). Patients in the severe multisystem inflammatory syndrome group had a significantly higher NLR and significantly lower lymphocyte and platelet counts ($p = 0.01$, $p = 0.016$, and $p = 0.001$, respectively). There was no significant difference between the groups in terms of leukocyte or haemoglobin levels ($p > 0.05$). Procalcitonin levels were significantly higher in the severe multisystem inflammatory syndrome group ($p = 0.011$) but there were no differences in C-reactive protein, erythrocyte sedimentation rate, interleukin-6, or ferritin levels between the groups ($p > 0.05$). Both troponin and BNP levels were significantly higher in the severe multisystem inflammatory syndrome group compared to the mild-moderate group ($p = 0.006$ and $p = 0.0001$, respectively). The median Pentraxin-3 level was 6.1 (4.9–15.7) ng/mL in the severe group and 4.4 (3.6–5.7) ng/mL in the mild-moderate group ($p = 0.001$). The receiver operating characteristic area under the curve for Pentraxin-3 level in the prediction of multisystem inflammatory syndrome severity was calculated as 0.786 ($p < 0.001$; 95% CI: 0.666–0.907). At a cutoff value of 5.1 ng/mL, Pentraxin-3 had 73.1% sensitivity and 71.4% specificity for clinically severe multisystem inflammatory syndrome. The demographic and laboratory findings of the groups according to multisystem inflammatory syndrome severity are given in Table 2.

Logistic regression model was used to compare the effect of disease severity and cardiac involvement on Pentraxin-3 level. The Pentraxin-3 value above 4.95 had a 12.0-fold effect on patients in the severe group (OR:12.033) ($p < 0.001$) and a 7.6-fold effect on patients with cardiac involvement (OR:7.600) ($p < 0.001$).

Pentraxin-3 was negatively correlated with left ventricular ejection fraction ($r = -0.430$, $p = 0.0001$), platelet count ($r = -0.331$, $p = 0.003$), and lymphocyte count ($r = -0.271$, $p = 0.048$) and positively correlated with BNP ($r = 0.515$,

https://doi.org/10.1017/S1047951124036175 Published online by Cambridge University Press

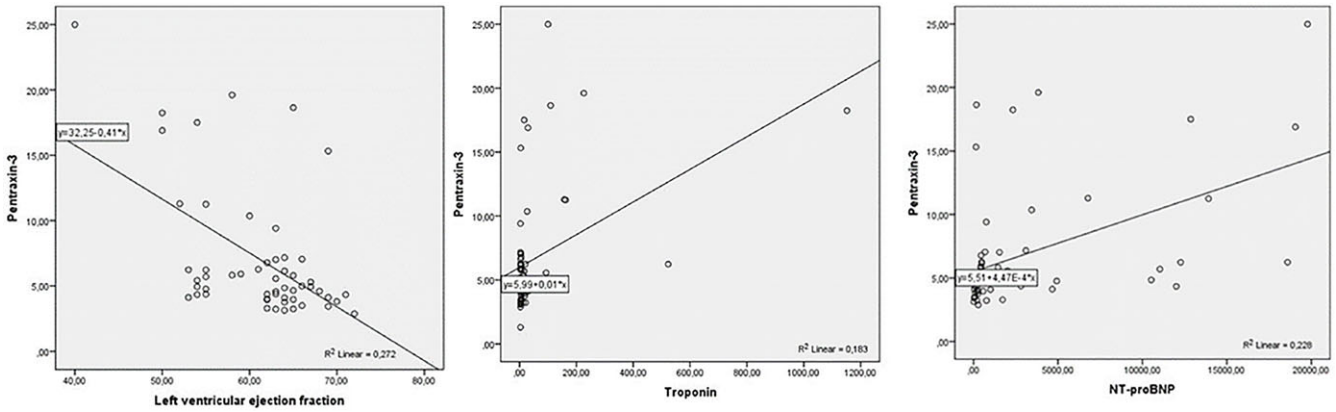

Figure 1. Negative correlation between serum PTX-3 level and left ventricular ejection and positive correlation between serum PTX-3 level and BNP and troponin.

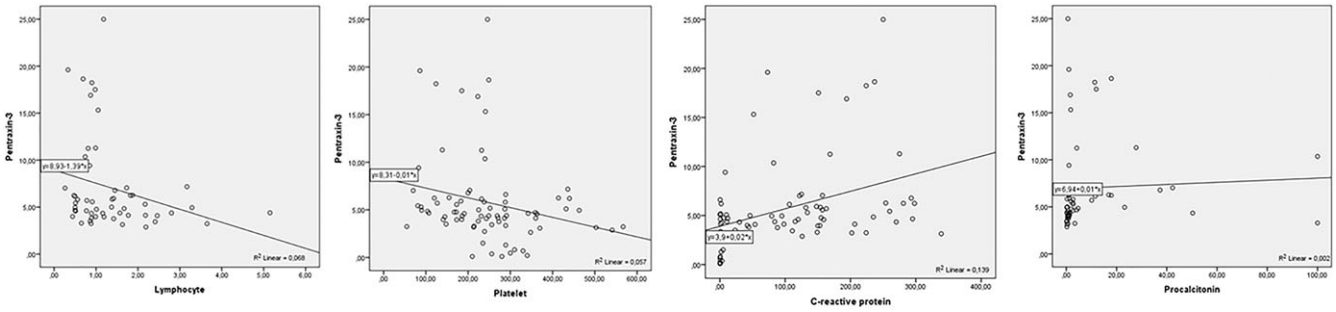

Figure 2. Negative correlation between serum PTX-3 level and platelet count and lymphocyte count and positive correlation between serum PTX-3 level and CRP and procalcitonin.

$p = 0.0001$), troponin ($r = 0.274$, $p = 0.027$), C-reactive protein ($r = 0.491$, $p = 0.0001$), and procalcitonin ($r = 0.477$, $p = 0.0001$) (Figures 1–2).

Discussion

Multisystem inflammatory syndrome is a relatively new but serious clinical entity, and cardiac involvement is a major cause of intensive care admissions in these patients.[1–3] However, there is still no specific biomarker that can predict cardiac involvement or prognosis in multisystem inflammatory syndrome.

Pentraxin-3 is a new acute phase reactant that is still being investigated in terms of its role in the inflammatory process.[4] It has been reported to be a strong prognostic indicator of mortality in adult COVID-19 patients. Previously found to be a prognostic marker in intensive care patients with sepsis, Pentraxin-3 was also reported to be positively associated with adult COVID-19 mortality.[11,18] The strong prognostic significance of Pentraxin-3 in COVID-19 may reflect its position at the intersection between macrophage-induced inflammation and vascular involvement.[10,11,18] A significant correlation has been demonstrated between Pentraxin-3 and troponin, a marker of myocardial disease, in COVID-19 patients.[11] The literature includes only one small study evaluating Pentraxin-3 levels in multisystem inflammatory syndrome patients.[13] Syrimi et al. compared eight multisystem inflammatory syndrome patients and seven healthy controls and found that Pentraxin-3 levels were higher in the multisystem inflammatory syndrome patients, but no relationship was reported between Pentraxin-3 and disease severity.[13] In our study, we found that serum Pentraxin-3 levels were significantly higher in patients who had cardiac involvement and those who had severe multisystem inflammatory syndrome requiring intensive care. We found that, Pentraxin-3 had a sensitivity of 63.6% and specificity of 61.9% at a cut-off of 4.95 ng/mL for cardiac involvement, Pentraxin-3 for severe multisystem inflammatory syndrome had sensitivity 73.1% and specificity 71.4% at a cut-off of 5.15 ng/mL. In addition, we determined that Pentraxin-3 was positively correlated with troponin and proBNP levels. Pentraxin-3 has a regulatory role in inflammation by altering selectin-dependent neutrophil uptake and regulating the complement cascade.[11,12,19,20] The high Pentraxin-3 levels found in our study may reflect uncontrolled inflammation.

Elevated Pentraxin-3 levels have been reported in cardiovascular diseases.[7–9,21–23] Pentraxin-3 is produced by phagocytes, neutrophils, fibroblasts, and endothelial cells in the first stage of the inflammatory process. It coordinates the functions of macrophages and dendritic cells and promotes apoptosis/necrosis. It also plays a role in vascular repair and remodelling. In addition to the regulation of inflammation, Pentraxin-3 contributes to the formation of extracellular matrix, which promotes fibrocyte differentiation. It is through these effects that Pentraxin-3 is believed to participate in the regulation of cardiovascular damage and the inflammatory response.[7,9,22,23] Pentraxin-3 expression by both macrophages and endothelial cells was shown to increase in acute myocardial infarction and myocarditis.[24] Gürses et al. showed that serum Pentraxin-3 levels increased significantly in patients with acute rheumatic fever and carditis compared to the control group.[8] In our study, Pentraxin-3 levels were significantly

https://doi.org/10.1017/S1047951124036175 Published online by Cambridge University Press

increased in patients with cardiac involvement compared to those without cardiac involvement. This supports the association between Pentraxin-3 and cardiovascular disease.

Left ventricular dysfunction and mitral valve involvement are frequently echocardiographic findings in multisystem inflammatory syndrome patients.[2,3] Similarly, our patients most commonly had left ventricular systolic dysfunction, followed by mitral valve regurgitation. In our study, we found that Pentraxin-3 levels were higher both in patients with left ventricular dysfunction and those with any degree of mitral valve insufficiency compared to those without. There are no studies in the literature evaluating echocardiographic data together with serum Pentraxin-3 level in multisystem inflammatory syndrome patients. In an animal study, Pentraxin-3 overexpression was shown to increase left ventricular dysfunction and myocardial fibrosis.[25] Studies in adults have indicated that Pentraxin-3 is independently and significantly associated with the severity of heart failure. In addition, Pentraxin-3 levels were found to be higher in individuals with ventricular dysfunction.[26,27]

Multisystem inflammatory syndrome and Kawasaki disease have overlapping clinical and laboratory findings. In both diseases, immune system activation plays a role in the pathogenesis and anti-inflammatory drugs are used in treatment.[1,3,28,29] Pentraxin-3 has been associated with vascular dysfunction in Kawasaki disease . In two different studies evaluating Pentraxin-3 levels in Kawasaki disease patients, Pentraxin-3 was found to be significantly elevated in Kawasaki disease patients with coronary artery lesions compared to those with normal coronary arteries. In addition, Pentraxin-3 levels were found to be significantly higher in patients with resistant to intravenous immunoglobulin therapy.[28,29] In the present study, we observed no relationship between coronary involvement and Pentraxin-3. This may be due to the small number of patients with coronary aneurysms and differences in the pathogenesis of Kawasaki disease and multisystem inflammatory syndrome. While the immune response in Kawasaki disease mostly causes mild or moderate vascular damage, the immune response in multisystem inflammatory syndrome more often causes multisystem organ damage to the heart, lungs, gastrointestinal tract, and other critical tissues. Endothelial dysfunction has been reported to occur in multisystem inflammatory syndrome patients, but the extent of this dysfunction is limited.[30] To gain a better understanding of this situation, there is a need for further studies that include larger patient series and evaluate echocardiographic data together with serum Pentraxin-3 levels.

This study has limitations that should be acknowledged. Firstl, our study included a small sample size. Secondly, other ventricular function measurements have not examined in the absence of global systolic dysfunction in multisystem inflammatory syndrome patients.

In conclusion, elevated Pentraxin-3 levels in multisystem inflammatory syndrome patients may help predict multisystem inflammatory syndrome in children disease severity and cardiac involvement.

Financial support. This work was supported by Pamukkale University Research Fund (Grant number: 2022HZDP015)

The authors have no relevant financial or non-financial interests to disclose.

Declaration. This study was performed in line with the principles of the Declaration of Helsinki.

Ethical standard. Approval was granted by the Ethics Committee of Pamukkale University (02.22.2022/04).

References

1. Santos MO, Gonçalves LC, Silva PAN, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J) 2022; 98: 338–349.
2. Karimi A, Ghafouri P, Alilou S, Rezaei N, Ashraf Talesh S, Ashraf H. Echocardiographic findings in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19: a systematic review. Iran J Pediatr 2022; 32: e119001.
3. Yasuhara J, Masuda K, Watanabe K, et al. Longitudinal cardiac outcomes of multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Cardiol 2023; 44: 892–907.
4. Mantovani A, Garlanda C, Doni A, Bottazzi B. Pentraxins in innate immunity: from C-reactive protein to the long pentraxin PTX3. J Clin Immunol 2008; 28: 1–13.
5. Lee YT, Gong M, Chau A, et al. International heath informatics study (IHIS) network. Pentraxin-3 as a marker of sepsis severity and predictor of mortality outcomes: a systematic review and meta-analysis. J Infect 2018; 76: 1–10.
6. Zlibut A, Bocsan IC, Agoston-Coldea L. Pentraxin-3 and endothelial dysfunction. Adv Clin Chem 2019; 91: 163–179.
7. Fornai F, Carrizzo A, Forte M, et al. The inflammatory protein Pentraxin 3 in cardiovascular disease. Immun Ageing 2016; 13: 25.
8. Gürses D, Oğuz M, Yilmaz M, Aybek H, Akpinar F. Pentraxin 3 levels and correlation with disease severity in patients with acute rheumatic fever. Arch Rheumatol 2021; 36: 233–243.
9. Ristagno G, Fumagalli F, Bottazzi B, et al. Pentraxin 3 in cardiovascular disease. Front Immunol 2019; 10: 823.
10. Laing AG, Lorenc A, Del Molino Del Barrio I, et al. A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med 2020; 26: 1623–1635.
11. Brunetta E, Folci M, Bottazzi B, et al. Macrophage expression and prognostic significance of the long pentraxin PTX3 in COVID-19. Nat Immunol 2021; 22: 19–24.
12. Risitano AM, Mastellos DC, Huber-Lang M, et al. Complement as a target in COVID-19? Nat Rev Immunol 2020; 20: 343–344.
13. Syrimi E, Fennell E, Richter A, et al. The immune landscape of SARS-CoV-2-associated multisystem inflammatory syndrome in children (MIS-C) from acute disease to recovery. iScience 2021; 24: 103215.
14. Multisystem infammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19) 2020. Accessed 1 March 2022. *Available at:* https://emergency.cdc.gov/han/2020/han00432.asp.
15. Multisystem infammatory syndrome in children and adolescents temporally related to COVID-19 2020. Accessed 1 March 2022. *Available at:* https://www.who.int/news-room/commentaries/detail/multisystem-inflammatorysyndrome-in-children-and-adolescents-with-covid-19.
16. Leteurtre S, Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F. Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). PELOD-2: an update of the PEdiatric logistic organ dysfunction score. Crit Care Med 2013; 41: 1761–1773.
17. Akkoyun EB, Most Z, Katragadda H, et al. Impact of anakinra use on clinical outcomes in children with moderate or severe multisystem inflammatory syndrome in children: a propensity score matched retrospective cohort study. Pediatr Rheumatol Online 2023; 21: 141.
18. Gutmann C, Takov K, Burnap SA, et al. SARS-CoV-2 RNAemia and proteomic trajectories inform prognostication in COVID-19 patients admitted to intensive care. Nat Commun 2021; 12: 3406.
19. Deban L, Russo RC, Sironi M, et al. Regulation of leukocyte recruitment by the long pentraxin PTX3. Nat Immunol 2010; 11: 328–334.
20. Deban L, Jarva H, Lehtinen MJ, et al. Binding of the long pentraxin PTX3 to factor H: interacting domains and function in the regulation of complement activation. J Immunol 2008; 181: 8433–8440.
21. Latini R, Maggioni AP, Peri G, et al. Lipid assessment trial Italian network (LATIN) investigators. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. Circulation 2004; 110: 2349–2354.

https://doi.org/10.1017/S1047951124036175 Published online by Cambridge University Press

22. Polat N, Yildiz A, Alan S, Toprak N. Association of pentraxin-3 with the severity of rheumatic mitral valve stenosis. Acta Cardiol 2015; 70: 409–4013.
23. Naito Y, Tsujino T, Akahori H, et al. Increase in tissue and circulating pentraxin3 levels in patients with aortic valve stenosis. Am Heart J 2010; 160: 685–689.
24. Nebuloni M, Pasqualini F, Zerbi P, et al. PTX3 expression in the heart tissues of patients with myocardial infarction and infectious myocarditis. Cardiovasc Pathol 2011; 20: e27–35.
25. Suzuki S, Shishido T, Funayama A, et al. Long pentraxin PTX3 exacerbates pressure overload-induced left ventricular dysfunction. PLoS One 2013; 8: e53133.
26. Matsubara J, Sugiyama S, Nozaki T, et al. Pentraxin 3 is a new inflammatory marker correlated with left ventricular diastolic dysfunction and heart failure with normal ejection fraction. J Am Coll Cardiol 2011:, 57:861–869
27. Latini R, Gullestad L, Masson S, et al. Investigators of the controlled rosuvastatin multinational trial in heart failure (CORONA) and GISSI-heart failure (GISSI-HF) trials. () pentraxin-3 in chronic heart failure: the CORONA and GISSI-HF trials. Eur J Heart Fail 2012; 14: 992–999.
28. Ching LL, Nerurkar VR, Lim E, Shohet RV, Melish ME, Bratincsak A. Elevated levels of pentraxin 3 correlate with Neutrophilia and coronary artery dilation during acute kawasaki disease. Front Pediatr 2020; 8: 295.
29. Kitoh T, Ohara T, Muto T, et al. Increased pentraxin 3 levels correlate with IVIG responsiveness and coronary artery aneurysm formation in kawasaki disease. Front Immunol 2021; 12: 624802.
30. Wang Y, Li T. Advances in understanding kawasaki disease-related immuno-inflammatory response and vascular endothelial dysfunction. Pediatr Investig 2022; 6: 271–279.

https://doi.org/10.1017/S1047951124036175 Published online by Cambridge University Press