Retrospective Study

Very high values of age-adjusted NT-proBNP could help in the early identification and follow-up of children at risk for severe multisystem inflammatory syndrome associated with COVID-19 (MIS-C)

Moises Rodriguez-Gonzalez, Ana Castellano-Martinez

Abstract

BACKGROUND

Multisystem Inflammatory Syndrome in Children (MIS-C) emerged as a new disease associated with COVID-19, that presents in acute critically ill children with acute cardiovascular dysfunction.

AIM

To explore if the age-adjusted N-terminal pro-brain natriuretic peptide (NT-proBNP) value (Z-log-NT-proBNP) is associated with severe MIS-C and myocardial dysfunction.

METHODS

A retrospective study including children with MIS-C managed at our institution between April 1, 2020, and February 28, 2022. We divided the population into groups of severity based on PICU admission. We compared Z-log-NT-proBNP values across these groups and analyzed Z-log-NT-proBNP dynamics throughout a one-month follow-up.

RESULTS
We included 17 participants (median age of 3 (2-9) years) and seven (41%) required PICU admission. All (100%) these cases presented very high (Z-log > 4) levels of NT-proBNP at the time of admission compared to only 5 (50%) patients with non-severe MIS-C ($P = 0.025$). NT-proBNP significantly correlated significantly with high-sensitive Troponin I levels ($P = 0.045$), Ross modified score ($P = 0.003$) and left ventricle ejection fraction ($P = 0.021$).

CONCLUSION
Raised NT-proBNP, specifically very high values ($Z$-log-NT-proBNP > 4) could help in the early identification of MIS-C patients with myocardial dysfunction requiring inotropic support and PICU admission.

INTRODUCTION
The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a stressful and challenging situation globally. Since its onset in early 2020 has led to widespread morbidity and mortality worldwide, and it is noteworthy that a new disease has emerged: the COVID-19-associated multi-systemic inflammatory response syndrome (MIS-C). The reports across the world of cases of children presenting with hyperinflammatory shock, myocardial dysfunction, and multiorgan involvement, sharing clinical characteristics with Kawasaki disease and toxic shock syndrome, led the World Health Organization (WHO) to identify these cases as a novel condition and to define MIS-C criteria for diagnosis.

MIS-C is a relatively rare disease affecting 0.6% of children infected by COVID-19; most were previously healthy children with a mild-symptomatic/asymptomatic COVID-19. Previous to the description of MIS-C, the pediatric population was not considered to be at serious risk for developing severe COVID-19 infection and complications compared with adult patients. Although MIS-C is characterized by multisystem involvement, acute cardiovascular dysfunction is a prominent and critical
manifestation. This significant cardiovascular compromise includes vasoplegic and cardiogenic shock, severe valve regurgitation, ventricular dysfunction, and coronary artery dilatation. Remarkably, a high proportion of children with MIS-C present as acute critically ill children, requiring admission to the PICU in more than half of the cases, most requiring inotropic support and even extracorporeal membrane oxygenation (ECMO) in a few of them. Furthermore, the mortality rate is estimated at around 1%, higher than the 0.1%-0.6% mortality rate for pediatric COVID-19 reported before MIS-C.

Despite this critical presentation, the clinical outcomes of MIS-C are favorable. Fortunately, most children recover rapidly from their acute presentation after initiating immunomodulatory therapy, with complete resolution of cardiac alterations. Cardiac sequelae in mild myocardial dysfunction or coronary artery alterations were present in up to 5-10% of cases at the time of hospital discharge. Studies with long-term follow-up periods of 6-9 mo, assessing cardiac function by speckle tracking echocardiography and myocardial fibrosis by Cardiac MRI, have shown a complete cardiac recovery in most children.

As the long-term prognosis seems excellent, prompt initiation of anti-inflammatory therapy and cardiovascular support in the acute phase is crucial for a successful, rapid, and complete recovery. Therefore, identifying early markers of cardiac dysfunction would be helpful to both directed therapy and identifying MIS-C patients at the highest risk for deterioration. As echocardiography is a non-widely available technique in all emergency departments and requires training and experience for its proper application, it would be interesting to investigate laboratory markers of more widespread use that identify patients with MIS-C in whom there may be echocardiographic alterations. Using cardiac biomarkers such as N-terminal (1-76) pro-brain natriuretic peptide (NT-proBNP) seems to be a promising tool. The NT-proBNP secretion from the ventricular myocardium is up-regulated by myocardial stress in situations of myocardial volume/pressure over-load. Thus, it is an excellent biomarker for heart failure and myocardial dysfunction on echocardiography. Notably, its secretion is also
influenced by the inflammatory response. NT-proBNP is increasingly used as a biomarker in pediatric conditions that combine myocardial stress and inflammatory diseases, such as sepsis or Kawasaki disease. Therefore, it is not surprising that NT-proBNP levels are markedly raised in almost all patients with MIS-C, where the proposed mechanism for the cardiovascular dysfunction is the myocardial inflammation related to the systemic inflammation with a cytokine storm.

An increasing number of studies reported the characteristics of cardiac markers in MIS-C patients. Some investigations suggested that those patients requiring PICU admission present with the highest peak NT-proBNP values at the time of hospitalization. However, all studies exploring the role of NT-proBNP in MIS-C use heterogeneous and fixed or static cut-off points based on adult reference values for diagnosing congestive heart failure in adults (150-300 pg/mL). This is a significant limitation, as pediatric NT-proBNP values are strongly age-dependent, with a continuous decrease from birth to adolescence, with a constant decline from infant to adult, being more marked in the neonatal period and the first year of life. This age dependence makes it impossible to compare absolute NT-proBNP values in age-heterogeneous populations such as MIS-C. Recently, Palm et al. introduced NT-proBNP values adjusted for the age in days, providing continuous reference values across all the pediatric age intervals, which is a more physiological approach. These authors also demonstrated the superiority of the age-adjusted approach compared with the use of absolute values to detect severe myocardial dysfunction in a pediatric population with congenital heart diseases. Therefore, the age-adjusted (Z-log-NT-proBNP) system could provide uniformity to research studies using NT-proBNP.

This study describes the dynamics of NT-proBNP and echocardiographic alterations in our MIS-C case series during the first month of disease. The primary objective is to explore if the Z-log-NT-proBNP values are associated with severity and echocardiographic alterations during the acute phase of the disease.

**MATERIALS AND METHODS**
Design, setting, and participants: This is a retrospective case series study conducted in the Pediatric Division of our institution, a tertiary-level university hospital in Cadiz, Spain. We included children aged less than 16 years old meeting classification criteria for MIS-C according to the World Health Organization definition (Table 1) between April 1, 2020, and February 28, 2022. All patients were managed following current international recommendations at the discretion of the attending pediatrician. We excluded patients with a known underlying or new diagnosis of heart disease during hospitalization and patients lost to follow-up, or those with incomplete data. Because retrospective data were collected from clinical reviews only, consent from patients, parents, or guardians was not obtained. As the data analysis was retrospective and no additional data were collected beyond those required for standard medical care, a full ethics review was not required.

Cardiac management and follow-up: All MIS-C patients admitted to our institution were evaluated by the Pediatric Cardiology Division through a physical exam, ECG, cardiac biomarkers (hs-TnI and NT-proBNP), and 2D-Doppler echocardiography at least at four different time points: 1. First 24 h of admission; 2. 24 h after administering immunomodulatory therapy; 3. Hospital discharge and 4. 1-month post-admission. The start and discontinuation of any cardiac medication were done at the discretion of the attending pediatric cardiologist, following local protocols and international guidelines for cardiogenic shock and heart failure. Further cardiac controls were done for each patient during admission and post-discharge follow-up based on their clinical state and evolution. These data were not collected for the study. Cardiac MRI was not performed on any patient during the acute or subacute phase.

Data collection: Our institution's electronic clinical records were reviewed by one investigator (ACM), who abstracted data for each time point described previously. Information collected included patient demographics and preexisting comorbidities, clinical presentation, laboratory findings, imaging findings, microbiological investigations, treatment, and outcomes.
Main cardiac measurements and definitions

Heart failure: Clinical heart failure status was defined based on the age-based Ross modified score\textsuperscript{31}. In this score, each age range (0–3 mo, 4–12 mo, 1–3 years, 4–8 years, and 9–18 years) has ten variables with scores of 0, 1, or 2 possible for a range of 0 to 20. The scoring system can be used as a continuous data set for comparison with outcomes, or it can be categorized by points assessed as Ross classes I (0–5; no heart failure), II (6–10; mild heart failure), III (11–15; moderate heart failure) and IV (16–20; severe heart failure).

Raised hs-Tnl: hs-Tnl was the biomarker used in our institution to assess myocardial injury or ischemia. hs-cTnl levels were measured in ng/L using the Architect i1000SR platform (Abbott Diagnostics\textsuperscript{®}, Spain) with 1.1–1.9 ng/L of a lower detection limit, 2.5\% intra-run variation, and <4\% inter-run variation). In the absence of clear pediatric reference values for hs-cTnl, we defined myocardial injury as the presence of serum levels plus 50 ng/L, the reported 75th percentile for this assay in infants and children\textsuperscript{22}.

Raised NT-proBNP: NT-proBNP was the biomarker used in our institution to assess myocardial strain. NT-proBNP levels were measured in pg/mL using the Alere NT-proBNP for Alinity I assay (Abbott Diagnostics\textsuperscript{®}, Spain). The intra-assay and inter-assay coefficients of variation were 1.9\% to 2.9\% and 2.6\% to 5.4\%, respectively, with an analytical range of 8.3 to 35 000 pg/mL. As reference values for children are markedly age-dependent, we calculated Z-log-NT-proBNP values adjusted for age as recommended by Palm \textit{et al}\textsuperscript{20}, and Z-log > 1.96 was considered high NT-proBNP. We anticipate that all patients in our case series presented Z-log-NT-proBNP > 1.96. For the statistical analysis, we defined very high NT-proBNP as Z-log-NT-proBNP > 4 (double of average values for age).

Abnormal echocardiographic findings: Standard techniques to obtain M-mode, two-dimensional, and Doppler echocardiograms were performed in all patients by the senior pediatric cardiologist as recommended in the guidelines for pediatric echocardiography\textsuperscript{30}. Images were obtained using IE33 (Phillips\textsuperscript{®}) or Aplio i-series (Canon Medical Systems \textsuperscript{®}) machines with a 5, 8, or 12-MHz sectorial transducer. This
study focused on left and right ventricular function and coronary artery dimensions, as these are the main cardiac alterations previously described in MIS-C patients. Left ventricular (LV) dysfunction was defined as an LV ejection fraction (LVEF) < 55%, and graded as mild (LVEF 45% to 54%), moderate (LVEF 35% to 44%), or severe (LVEF < 35%). Right ventricular (RV) dysfunction was defined as tricuspid annular plane systolic excursion (TAPSE) < 2 Z-score for body surface area. In cases where LVEF or TAPSE were unavailable, ventricular dysfunction definition was based on the qualitative grade of hypokinesis. Coronary artery dilation was defined as diameter > 2 Z-scores for body surface area (BSA) by the published reference standard in the affected segment, and graded as dilation 2.0–2.49, small aneurysm > 2.5 to < 5, medium aneurysm > 5 to < 10, and large aneurysm > 10.

Cardiac sequelae: All children with MIS-C who had any abnormal cardiac measurement of those described above at the time of discharge or after one month were defined as cardiac sequelae.

Research endpoints: The research endpoints in this study were: 1. Development of a severe MIS-C during hospitalization is defined as the need for PICU admission; 2. The presence of abnormal echocardiography at admission; 3. The presence of cardiac sequelae. The study population was divided into two groups based on the predefined research endpoints. The analysis focused on comparing cardiac biomarkers values across these groups and the cardiac dynamics throughout the follow-up.

Statistics: Descriptive statistics were used to summarize our population's baseline key features and outcomes. The hs-TnI values were log-transformed and standardized to account for widely varying ranges, and Z-log-NT-proBNP values were calculated as previously described. These values of cardiac biomarkers were those used in statistical analysis and graphics. Continuous data were expressed as median and interquartile range (IQR) values. Categorical data were expressed as frequencies and proportions (%). Continuous variables were analyzed using the nonparametric U-Mann Whitney test as normality was not assumed with the sample size of our case series. Categorical variables were analyzed using the chi-square and Fisher's exact test. Spearman rank
correlation coefficients were used to identify relationships between continuous variables. Differences in repeat-ed cardiac measurements between the four-time points used in this study were assessed using Wilcoxon signed rank-sum test. Due to the limited sample size of this study, we were unpowered to establish cut-off points to identify outcomes. For all analyses, p values of < 0.05 were considered significant. Because of the potential for type I error due to multiple comparisons, our findings should be interpreted as exploratory. All statistical analyses were performed with Stata v.16 software (StataCorp., College Station, Texas).

RESULTS

Baseline characteristics: This case series included 17 MIS-C participants (9 (53%) male sex; 14 (82%) white race) with a median age of 3 (2-9) years. Tables 2 and 3 summarize baseline clinical, laboratory, and echocardiographic data at admission. Sixteen (94%) cases were previously healthy children. Four cases (24%) were diagnosed with COVID in the previous 4-8 wk, and in 15 (88%), we documented IgG antibodies to SARS-CoV-2, with 7 (41%) RT-PCR positive tests. No other microbial cause of the illness was identified in any patient.

All patients presented with fever with a median duration of 4 (3-4) days before hospitalization, with mucocutaneous inflammatory (41%) and gastrointestinal symptoms (58%) as the common non-cardiac manifestations. Eleven (65%) cases were diagnosed with heart failure by the age-based Ross modified score. Of them, 5 (29%) had severe heart failure, and 3 (17%) were in a cardiogenic shock at presentation.

At the time of hospitalization, 8 (47%) patients presented anemia, 5 (29%) thrombocytopenia, and 9 (53%) lymphopenia, and all laboratory markers of an inflammatory response (C-reactive protein (CRP), procalcitonin, ferritin, and Dimer-D) were markedly elevated (Table 2). Regarding cardiac biomarkers, both NT-proBNP (median values of 5221 (2638-10020) pg/mL) and hs-Tnl (35 (10-116) ng/L) were markedly raised. All patients presented with high (Z-log > 2) NT-proBNP, most of them
(71%) with very-high (Z-log >4) plasmatic levels, whereas 5 (29%) participants showed hs-TnI concentrations indicative of myocardial injury. Abnormal echocardiographic findings were found in 10 (58%) cases; 9 (53%) patients had LV dysfunction, 2 (11%) of them with concomitant RV dysfunction. On admission, the medial LVEF was 58 (48-65) %; in 2 (11%) patients, the myocardial dysfunction was graded as severe and in the other 2 (11%) as moderate. There was mild coronary artery dilation (Zscore 2-2.5) in 3 (17%). ECG was performed in all patients with sinus tachycardia in 14 (82%) and T-wave inversion at left precordial leads in 2 (11%) cases. Chest X-ray was performed in 12 (70%) children and considered abnormal in 3 (17%), 2 cases with cardiomegaly, and 1 (6%) case with lung edema. Abdominal ultrasound was carried out on 8 (47%) participants with unspecific lymphadenopathy and ileocolitis as the main findings.

**Treatment and outcomes:** Treatment was provided as recommended per the standard treatment guidelines for MIS-C. All our patients showed an excellent short-term clinical course in this study and were discharged after 7 (5-10) days of hospitalization. Table 4 summarizes the treatment and outcomes of the study population. Immunomodulatory therapy was administered to all patients. Steroids plus IVIG were used in 14 (82%), and only steroids were used in 2 (11 %) cases. In 4 (23%) children, the inflammatory response was not controlled with fist line therapy and required a biological medication; anakinra in 3 (17%) cases and tocilizumab in 1 (6%) case leading to rapid control of the hyperinflammatory state. All patients continued steroids until fever disappeared and all inflammatory markers were in normal ranges. Aspirin was used in most (88%) cases, whereas anticoagulation with low weight heparin was administered only in 3 (17%) critically ill patients presenting with shock and myocardial dysfunction. Empirical broad-spectrum antibiotics were started for many patients (88%) at the time of hospitalization and were discontinued after the blood and urine cultures were noted to be sterile. Ten (53%) children required diuretics to relieve congestive heart failure, and in 6 (35%), therapy against myocardial remodeling (enalapril + carvedilol) was started. Of these patients, 8 (59%) continued on cardiac medications at discharge, and all were
tapered off after one month of hospitalization in the outpatient clinic. There were no arrhythmic events, and no anti-arrhythmic medication was needed.

Seven (41%) participants required PICU admission (median PICU stay of 3.5 (3-4.5 days) and administration of inotropic support and constitute the severe MIS-C group. Milrinone was used alone in 3 (17%) cases, milrinone in combination with norepinephrine in 3 (17%) cases, and levosimendan combined with norepinephrine in 1 (6%) case. No patients required ECMO support for the management of cardiogenic shock. Respiratory therapy included invasive ventilation in 1 patient (6%), continuous positive airway pressure in 1 patient (6%), and conventional oxygen therapy in 2 patients (11%). Two (11%) patients presented acute kidney injury without requiring renal replacement therapy. There were no deaths.

**Dynamics of cardiac abnormalities:** Regarding the dynamic changes of cardiac abnormalities, we observed a significant rapid, gradual, and continuous clinical, laboratory, and echocardiographic improvement in our patients following immunomodulatory therapy administration. This improvement was coupled with the disappearance of fever and a marked decrease of the rest of the laboratory inflammatory markers (data not shown). Cardiac abnormalities observed on the four-time points assessed in this study are detailed in Table 5 and Figure 1.

After 24 h of treatment, heart failure persisted in 7 (63%) children, but with no severe cases and a significant decrease in the age-based Ross modified score from 8 (4-12) points to 3 (2-7) points (p<0.001) in parallel to the LVEF significant enhancement from 58 (48-65)% to 68 (65-70)% (p<0.001), with 6 (35%) cases of mild and 1 (6%) case of moderate LV dysfunction, and complete resolution of the RV dysfunction. There was also a significant decrease in the plasmatic levels of both cardiac biomarkers. At this time point, NT-proBNP decreased from Z-log of 4.62 (4.46-5.23) to Z-log of 3.78 (3.26-4.87) (P = 0.001), with still 5 (29%) cases with very high levels; and hs-TnI decreased from 35 (10-116) ng/L to 13 (5-35) ng/L (P = 0.008), with 4 (23%) cases with raised levels.
At discharge, we documented a continuous significant (p<0.001) improvement of all these cardiac measurements and coronary artery dimensions concerning the previous time points assessed. However, some cardiac abnormalities remained: 1 (6%) case of mild heart failure with mild LV dysfunction, the patient presenting with the most severe disease and decreased LVEF; 2 (11%) cases of mild coronary artery dilation; 3 (17%) cases of raised hs-TnI in 3 (17%) levels and 9 (53%) cases of high (Z-log>2) NT-proBNP levels.

In the follow-up visit at the pediatric cardiologist outpatient clinic after one month of the hospitalization, we documented a complete normalization of the cardiac state, without any cardiac sequelae in any patients.

**Cardiac biomarkers to assess severe MIS-C and echocardiographic abnormalities:** The group of severe MIS-C was composed of the 7 (41%) patients that required PICU admission and inotropic support. Compared with those cases of non-severe MIS-C, that patients presented with higher Ross modified score ($P = 0.003$), lower LVEF ($P = 0.034$), and higher Z-log-NT-proBNP ($P = 0.016$) (Table 6 & Figure 2). There were no differences regarding hs-TnI levels, coronary dimensions, demographics, days of fever, and any laboratory marker of inflammation (all $p>0.05$). Focusing on NT-proBNP, we were not powered to assess sensitive laboratory cutoffs of NT-proBNP predictive of severe MIS-C. Therefore we assessed the association of high NT-proBNP with severe MIS-C as a dichotomous variable. We observed that 7/7 (100%) patients with severe MIS-C presented very high (Z-log > 4) levels of NT-proBNP at the time of admission compared to only 5 (50%) patients with non-severe MIS-C ($P = 0.025$). We also found that our patients' NT-proBNP levels were associated with other cardiac abnormalities. Specifically, NT-proBNP was significantly correlated with hs-TnI levels ($P = 0.045$), Ross modified score ($P = 0.003$), and LVEF ($P = 0.021$), but not with the maximal coronary artery diameter (Table 7 & Figure 3).

**DISCUSSION**
In this article, we described the evolution of cardiac biomarker elevation and echocardiographic findings in 17 MIS-C cases focusing on NT-proBNP dynamics during both the acute phase and recovery. Our cohort's spectrum of cardiac involvement is similar to the larger MIS-C case series. We observed a high rate of echocardiographic abnormalities in the acute phase in our patients, with 53% of cases presenting with myocardial dysfunction. These alterations improved rapidly after immunomodulatory treatment, with 94% of cases asymptomatic and normal LV function at hospital discharge and recovered completely after one month of follow-up. In one of the first multicenter studies focusing on cardiovascular manifestations in MIS-C, Valverde et al. analyzed 286 children and found that LV dysfunction was present in 34% on admission but recovered to normal in 80% during hospitalization. The more extensive case series of MIS-C published \(n = 539\) also found a reduced left ventricular systolic function in 34.2%, with a complete normalization in 91% within 30 days and 99.4% by 90 days. A recent single-center study \(n = 46\) by Penner et al. showed normalization of LVEF in all patients by six months. Matsubara et al. recently showed by speckle tracking echocardiography in 60 children with MIS-C that there is no persistent subclinical dysfunction after three months. Capone et al. reported that 62% and 52% of MIS-C cases required PICU admission and inotropic support for myocardial dysfunction, respectively.

In addition to being very frequent, myocardial dysfunction was associated with severe MIS-C disease in our patients and had prognostic implications. All patients who required PICU had myocardial dysfunction on admission echocardiography. Valverde et al. described those children requiring intensive care unit admission were those with significantly reduced LV systolic ventricular function. Sanil et al., in a longitudinal observational study of 54 patients with MIS-C, reported that impaired LV function at initial presentation indicates a higher risk for adverse acute clinical course and persistent subclinical left ventricular dysfunction at 10-week follow-up they could be applied to identify higher-risk children with MIS-C.
The previously mentioned observations highlight the relevance of identifying myocardial dysfunction in MIS-C patients, and based on our findings, NT-proBNP could be an adequate tool for this purpose. The association of higher levels of NT-proBNP with myocardial dysfunction and severe MIS-C requiring PICU and inotropic support has been previously described in larger studies. Abrams et al analyzed 1080 cases of MIS-C. They determined that PICU admission, LV dysfunction, and the need for inotropic support were associated with increased concentrations of C-reactive protein, troponin, ferritin, D-dimer, NT-proBNP, or interleukin-6, or reduced platelet or lymphocyte counts. A recent meta-analysis about the role of cardiac biomarkers in MIS-C that included 1613 patients from 24 studies determined that NT-proBNP was the only cardiac biomarker able to differentiate between patients with severe non-severe MIS-C. However, there is no evidence about the best cut-off point to use in this context.

Our study is novel in using for the first time Z-log-NT-proBNP to assess the severity and echocardiographic abnormalities in MIS-C, overcoming the main limitation of using this biomarker in children, its strong age dependence. With this approach, we observed that all our patients presented with raised levels of NT-proBNP (Z-log-NT-proBNP > 2) and that 71% were twice the average for their age (Z-log-NT-proBNP > 4). These data point to the importance of NT-proBNP as a biomarker in the differential diagnosis of MIS-C with other conditions with lesser potential severity with which it shares clinical and laboratory findings (acute appendicitis, Kawasaki disease, exanthematous fevers...). Notably, Z-log-NT-proBNP showed a moderate to strong correlation with all the cardiac alterations measured in this study (except for coronary artery dilation): LVEF, the Ross modified score and hs-TnI levels. Furthermore, it is also noteworthy that all patients admitted to the ICU and required inotropic support had Z-log-NT-proBNP > 4 on admission. Z-log-NT-proBNP is increasingly used in congenital heart disease, where it is a suitable marker of severity. Specifically, Palm et al, in a recent study that included 138 children with a wide age range (1 day-7.5 years), concluded that patients with very high NT-proBNP values (Z-log-NT-proBNP > 3) were
at higher risk of developing major adverse events during follow-up, highlighting a negative predictive value of 96% for a cut-off point Z-log-NT-proBNP < 1.96 (average for the age)\textsuperscript{29}. The small sample size limits our ability to calculate the diagnostic accuracy of the NT-proBNP for these outcomes. However, based on our observation, Z-log-NT-proBNP > 4 may be more indicative of concerning echocardiographic findings associated with illness severity, including reduced LVEF and the need for PICU admission for inotropic support. Therefore, it could be an appropriate starting point to explore in future prospective studies with larger sample sizes.

Finally, another interesting finding of our case series is the delayed improvement of NT-proBNP levels regarding myocardial function normalization. We observed that 94% of our patients were free of symptoms of congestive heart failure and with normal LVEF at discharge, whereas 53% still presented biochemical signs of myocardial stress with a Z-log-NT-proBNP > 1.96. NT-proBNP secretion would be stimulated by myocardial stress and the systemic inflammatory response in MIS-C\textsuperscript{20,25,26}. Several reasons could explain the persistence of elevated NT-proBNP levels in patients with normal myocardial function. Subtle systemic inflammatory responses may persist, although this is unlikely since all patients had normal inflammatory marker levels at discharge. More likely, this is due to the persistence of subclinical myocardial dysfunction. Although myocardial function recovered when measured by standard methods such as LVEF, recent studies using speckle tracking imaging demonstrated that subclinical LV dysfunction persists in these patients for at least 1-3 mo after hospitalization\textsuperscript{13,15,36}. Therefore, NT-proBNP could be used as a laboratory marker of this subclinical dysfunction, aiding in the appropriate monitoring of cardiovascular complications in these patients during their post-hospitalization follow-up, especially in centers where speckle tracking echocardiography is not available.

The main limitations of this study include the single-center nature, retrospective design, and small sample size. In addition, laboratory values of NT-proBNP are assay-dependent and cannot be compared between centers using different laboratory methods for its determination. Finally, the follow-up period was limited to 1 mo, and
we did not perform advanced imaging techniques (STE or Cardiac MRI) to determine subclinical myocardial impairment. This approach prevents us from establishing a long-term prognosis and ensuring that there are no mid-term myocardial alterations in MIS-C patients.

CONCLUSION
Our experience supports previous findings that MIS-C presents a high rate of myocardial involvement, impacting the severity of the disease. This myocardial involvement appears to recover quickly and with near-complete normalization of cardiac function in a few days after immunomodulatory therapy and cardiovascular support administration. Therefore, the early identification of cardiac dysfunction is crucial to start prompt treatment modalities and prevent cardiovascular complications. Based on our observations, NT-proBNP seems to be a promising biomarker for the initial screening and monitoring of the myocardial dysfunction during the acute phase, where Z-log-NT-proBNP > 4 may be more indicative of concerning echocardiographic findings associated with illness severity; also, it would have a role in the posthospitalization follow-up in these patients. Using Z-log-NT-proBNP values would provide constant reference values of NT-proBNP in children with MIS-C and would lead to consistency in data analysis across centers worldwide.

ARTICLE HIGHLIGHTS

Research background
Multisystem Inflammatory Syndrome in Children (MIS-C) emerged as a severe new disease associated with COVID-19. One of the most critical issues is the high prevalence of cardiovascular involvement in these children, leading to a high percentage of cardiogenic shock, myocardial dysfunction secondary to the inflammatory response, and the need for inotropic support and extracorporeal circulation support (ECMO).

Research motivation
MIS-C is a severe new entity, and we still know very little about it. Therefore, it is necessary to communicate the experience in the management of these patients as well as to generate scientific evidence on all aspects of MIS-C that allow the best management of these patients.

**Research objectives**

This study was designed to identify clinical and laboratory markers of severity in this new disease. MIS-C is a condition with cardiac involvement in almost all cases. Therefore, we decided to analyze whether NT-proBNP, one of the most widely used cardiac biomarkers in routine clinical practice, was capable of identifying the most severe cases that required admission to the intensive care unit (PICU) and inotropic support administration. We also aimed to explore if NT-proBNP was an adequate follow-up parameter in this setting.

**Research methods**

A retrospective study including children with MIS-C managed at our institution between April 1, 2020, and February 28, 2022. We divided the population into groups of severity based on PICU admission. We compared Z-log-NT-proBNP adjusted for age in days values across these groups and analyzed Z-log-NT-proBNP dynamics throughout a one-month follow-up.

**Research results**

We included 17 participants (median age of 3 (2-9) years) and seven (41%) required PICU admission. All (100%) of these cases presented very high (Z-log > 4) levels of NT-proBNP at the time of admission compared to only 5 (50%) patients with non-severe MIS-C ($P = 0.025$). NT-proBNP significantly correlated significantly with high-sensitive Troponin I levels ($P = 0.045$), Ross modified score ($P = 0.003$) and left ventricle ejection fraction ($P = 0.021$). NT-proBNP was raised in all of our patients at admission, and we observed a significant rapid, gradual, and continuous decrease in our patients following
immunomodulatory therapy administration. In the follow-up visit at the pediatric cardiologist outpatient clinic after one month of the hospitalization, we documented a complete normalization of the cardiac state, without any cardiac sequelae in any patients.

**Research conclusions**

Raised NT-proBNP, specifically very high values (Z-log-NT-proBNP > 4), could help identify MIS-C patients with myocardial dysfunction requiring inotropic support and PICU admission. NT-proBNP also would have a role in the post-hospitalization follow-up in these patients to monitor their cardiovascular recovery.

**Research perspectives**

NT-proBNP is a promising biomarker for the initial screening and monitoring of myocardial dysfunction during the acute phase of MIS-C. Still, its use in pediatrics is limited by its strong age dependency. Using Z-log-NT-proBNP values would provide constant reference values of NT-proBNP in children with MIS-C and would lead to consistency in data analysis across centers worldwide. NT-proBNP could also be used as a laboratory marker of this subclinical dysfunction, aiding in the appropriate monitoring of cardiovascular complications in these patients during their post-hospitalization follow-up, especially in centers where speckle tracking echocardiography is not available. Therefore, this study could be an appropriate starting point to explore in future prospective studies with larger sample sizes confirming our results.
<table>
<thead>
<tr>
<th>1</th>
<th><a href="http://www.ncbi.nlm.nih.gov">www.ncbi.nlm.nih.gov</a></th>
<th>121 words — 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>link.springer.com</td>
<td>55 words — 1%</td>
</tr>
<tr>
<td>3</td>
<td>Moisés Rodríguez-González, Ana Castellano-Martínez. &quot;Towards Reference Values for NT-proBNP Applicable in Pediatric Clinical Practice&quot;, Pediatric Cardiology, 2022</td>
<td>37 words — 1%</td>
</tr>
<tr>
<td>4</td>
<td><a href="http://www.pubfacts.com">www.pubfacts.com</a></td>
<td>33 words — 1%</td>
</tr>
<tr>
<td>5</td>
<td>pediatrics.aappublications.org</td>
<td>32 words — 1%</td>
</tr>
</tbody>
</table>
Natriuretic Peptide Excretion in Patients With Chronic Heart Failure", Circulation, 2009

Sonali Basu, Esther J. Kim, Matthew P. Sharron, Ashley Austin, Murray M. Pollack, Ashraf S. Harahsheh, Niti Dham. "Strain Echocardiography and Myocardial Dysfunction in Critically Ill Children With Multisystem Inflammatory Syndrome Unrecognized by Conventional Echocardiography", Pediatric Critical Care Medicine, 2021


Elizabeth C. Mitchell, Angela Romano, Christine A. Capone, Rubin Cooper et al. "Multisystem inflammatory syndrome in children: Salient echocardiogram findings in the acute phase and longitudinal follow-up", Progress in Pediatric Cardiology, 2022

Moisés Rodríguez-González, Lorena Estepa-Pedregosa, Ana Estalella-Mendoza, Ana Castellano-Martínez et al. "Early elevated NT-proBNP but not troponin I is associated with severe bronchiolitis in infants", Clinica Chimica Acta, 2021

Caselli, Chiara, Rosetta Ragusa, Concetta Prontera, Manuela Cabiati, Massimiliano Cantinotti, Giovanni Federico, Silvia Del Ry, Maria Giovanna Trivella, and Aldo Clerico. "Distribution of circulating cardiac biomarkers in healthy children: from birth through adulthood", Biomarkers in Medicine, 2016.

Daisuke Matsubara, Joyce Chang, Hunter L. Kauffman, Yan Wang et al. "Longitudinal Assessment of Cardiac Outcomes of Multisystem Inflammatory
Syndrome in Children Associated With COVID-19 Infections,
Journal of the American Heart Association, 2022
Crossref

he02.tci-thaijo.org
Internet

12 words — < 1%