ORIGINAL ARTICLE

# Multisystem Inflammatory Syndrome in Children: The Importance of Early Evaluation of Laboratory Parameters

## *Síndrome inflamatorio multisistémico en pediatría: importancia de la evaluación inicial de los parámetros de laboratorio*

JULIÁN RODRÍGUEZ KIBRIK[1], MARIANA E. CAZALAS[1], MARÍA LUCILA PETRILLO[1], GONZALO G. GUIÑAZÚ[1], CLAUDIO MOROS[1], HYON J. CHOE[1], ALEJANDRO GOLDSMAN[1], MARÍA GRIPPO[MTSAC,1], ÁNGELA SARDELLA[MTSAC,1], SILVIA BALEANI[1]


## ABSTRACT

**Background:** Multisystem inflammatory syndrome in children (MIS-C) is an uncommon condition associated with COVID-19 with a wide spectrum of presentations, ranging from Kawasaki-like disease to multisystem involvement with shock. The association between the laboratory characteristics and unfavorable outcome has been described, but the cut-off points associated with higher risk have not yet been defined.
**Objective:** The aim of this study was to describe and analyze the characteristics of patients with MIS-C and their associations with the laboratory findings.
**Methods:** We conducted an analytical and retrospective study of pediatric patients hospitalized between May 2020 and June 2021 with diagnosis of MIS-C in Hospital General de Niños Dr. Ricardo Gutiérrez (HNRG). The cohort was made up of 23 patients, 17 female (53.13%) and 15 male (46.87%); mean age was 7.67 years (range 0.5-14.91). Ten patients (31.25%) presented shock.
Clinical and echocardiographic data and values of high-sensitive troponin I, N-terminal pro–B-type natriuretic peptide (NT-proBNP), platelets and lymphocytes at the time of diagnosis were obtained and compared between those with shock during evolution (group 1) and those without shock (group 2).
**Results:** There was a significant difference in baseline elevated NT-proBNP values between both groups (p = 0.008), but not in troponin levels and lymphocyte and platelet counts. Of the 13 patients who required inotropic agents, 58% had baseline lymphopenia (p = 0.006 vs those who did not require inotropic drugs).
**Conclusions:** Although mortality due to MIS-C is low, cardiac involvement and hemodynamic impairment may be common. The availability of a commonly used laboratory tool for patient categorization could help to mitigate risks and obtain early referral to specialized centers.


**Key words:** Systemic Inflammatory Response Syndrome - COVID-19/Complications - Natriuretic Peptide, Brain - Lymphopenia - Thrombocytopenia - Child- Child, Preschool


## RESUMEN

**Introducción:** El síndrome inflamatorio multisistémico en pediatría (SIM-C) es una infrecuente entidad asociada a COVID-19 con un amplio espectro de presentación: desde un cuadro similar a la enfermedad de Kawasaki a una afectación multisistémica con shock. Se han descripto asociaciones entre valores de laboratorio y mala evolución, pero no existen puntos de corte que predigan la misma.
**Objetivo:** El objetivo de este estudio fue describir y analizar las características de los pacientes con SIM-C y las relaciones de estas con los hallazgos de laboratorio.
**Material y métodos:** Se realizó un estudio analítico y retrospectivo de niños internados con diagnóstico de SIM-C entre mayo 2020 y junio 2021 en el HNRG. Se estudiaron 32 pacientes, 17 femeninas (53,13%) y 15 masculinos (46,87%), edad promedio de 7,67 años (rango 0,5-14,91). Diez de los pacientes (31,25%) presentaron shock. Se obtuvieron datos clínicos, ecocardiográficos y valores de troponina I ultrasensible, NT-proBNP, plaquetas y linfocitos al momento del diagnóstico; y se analizaron comparativamente entre quienes presentaron shock durante la evolución (Grupo 1) y quienes no (Grupo 2).
**Resultados:** La diferencia en un valor inicial de NT-proBNP elevado fue estadísticamente significativa entre ambos grupos (p=0,008), en tanto que la troponina y el recuento de linfocitos y plaquetas, no. De los 13 pacientes que requirieron inotrópicos, el 58% presentó linfopenia inicialmente (p=0,006 vs aquellos que no los necesitaron)
**Conclusiones:** Si bien la mortalidad debido al SIM-C es baja, la afectación cardiovascular y el compromiso hemodinámico en los pacientes que presentaron este síndrome puede ser frecuente. Poder contar con una herramienta de laboratorio amplia¬mente difundida para la categorización de pacientes podría ayudar a mitigar riesgos y obtener una derivación temprana a centros especializados.


**Palabras claves:** Síndrome de Respuesta Inflamatoria Sistémica - COVID-19/Complicaciones - Péptido Natriurético Encefálico - Linfopenia - Trombocitopenia - Niño - Preescolar

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*Address for reprints:* Julián Rodríguez Kibrik. División Cardiología del Hospital General de Niños Dr. Ricardo Gutiérrez. Sánchez de Bustamante 1451, PB (CP 1425). C.A.B.A. E-mail: jota.rodriguez1@gmail.com



[1] Department of Pediatric Cardiology, Hospital de Niños Dr. Ricardo Gutiérrez (HNRG).
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## INTRODUCTION

Since the SARS-CoV-2 infection emerged in December 2019, multiple presentations and associated syndromes have been described. Multisystem inflammatory syndrome in children (MIS-C or PIMS) is one of the most aggressive presentations. This rare complication usually occurs between 2 to 6 weeks after the onset of SARS-CoV-2 infection.

Initially, severe pediatric cases were rare, and SARS-CoV-2 did not severely affect the pediatric population. Then, isolated cases of incomplete or atypical Kawasaki-like disease and toxic shock syndrome temporally associated with SARS-CoV-2 infection began to be reported. (1,2)

Nowadays, MIS-C has a wide spectrum of presentations, ranging from a Kawasaki-like syndrome to multisystem involvement with shock. The incidence of Kawasaki-like disease is 3.7 to 30 times higher than the usual incidence of typical cases. (2,3) Cardiac involvement in MIS-C is greater than that of typical Kawasaki's disease, (4) ranging from 30% to 80%, (2,5-7) and accounts for the highest morbidity and mortality rates.

The association between the laboratory characteristics and unfavorable outcome (8,9) has been described, but the cut-off points associated with higher risk have not yet been defined.

The primary objective of the study was to describe the clinical presentation and compare baseline laboratory parameters between patients with diagnosis of MIS-C with shock and without shock in a pediatric referral center in the Autonomous City of Buenos Aires. The secondary objective was to analyze the difference in positive troponin and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, and to establish cut-off points for these parameters.

## METHODS

We conducted an analytical and retrospective study of patients hospitalized between May 2020 and June 2021 with diagnosis of MIS-C in Hospital General de Niños Dr. Ricardo Gutiérrez (HNRG). A total of 32 patients were admitted during that period.

Multisystem inflammatory syndrome in children was considered following the definition of the National Ministry of Health (https://www.argentina.gob.ar/salud/coronavirus-COVID-19/casos-pediatria):

- Patients between 0–19 years of age with fever ≥ 3 days and documented SARS-CoV-2 infection; with ≥2 of the following:

1. Cutaneous rash or non-purulent conjunctivitis or signs of mucocutaneous involvement (mouth, hands or feet).
2. Hypotension or shock.
3. Signs of myocardial dysfunction, pericarditis, valvulitis or coronary artery anomalies (including echocardiographic findings or elevated troponins and NT-proBNP).
4. Evidence of coagulopathy: elevated prothrombin time (PT), elevated partial thromboplastin time (PTT), elevated d-dimer.
5. Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

- AND elevated markers of inflammation: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or procalcitonin and no other obvious cause of inflammation.

The clinical, cardiological and laboratory data of each patient were retrieved from the medical records (MR). The patients were classified in two groups: group 1 (with shock) and group 2 (without shock). Shock was defined as hypotension (blood pressure < 2 SD below the 50th percentile for sex, height and age, Argentine Society of Pediatrics) refractory to fluid resuscitation, and requirement of pressor drugs documented in the MR.

The laboratory parameters analyzed were high-sensitive troponin I (VIDAS® High-sensitive troponin I assay- BioMerieux), NT-proBNP (VIDAS® NT-proBNP2- BioMerieux), platelets and lymphocytes at the time of diagnosis. The cut-off points reported by the reference laboratory were used to determine whether these values were abnormal: troponin I >19 ng/L; lymphopenia: < 1000 lymphocytes/mm3; thrombocytopenia: platelet count < 150 000/mm3 and NT proBNP > 300 pg/mL.

These parameters were considered because, according to the literature, troponin is a marker of cardiac injury, thrombocytopenia has a high positive predictive value for cardiac involvement, NT proBNP showed correlation with cardiac dysfunction and severe lymphopenia has a high association with shock. (8-10)

At the same time, complementary cardiological tests, as electrocardiogram (ECG) and echocardiography, were performed to evaluate parameters of cardiac involvement during the disease. To define cardiac involvement, we used a synthesis of the definitions provided by Pignatelli (5) and Valverde (7): *presence of any arrhythmia, premature atrial or ventricular contractions, sustained or nonsustained atrial or ventricular tachycardias, atrioventricular (AV) block of any degree, ventricular repolarization changes; reduced left ventricular systolic function (measured by any method); left ventricular (LV) dilation > +2 z score values; valvular regurgitation; any type of pericardial effusion; dilation of coronary arteries; or elevated cardiac enzymes (CK-MB, troponin)*. Sinus tachycardia was not included as sign of organ injury because this symptom is nonspecific in patients with fever.

Fractional shortening (FS) was used to determine left ventricular systolic function and measured in M-mode echocardiography in a circumferential section of the left ventricle at the level of the papillary muscles using left ventricular diastolic dimension (LVDD) and left ventricular systolic dimension (LVSD) as reference: (LVDD-LVSD)/LVDD x 100. A reduction in FS below 30% was considered systolic dysfunction.

### Statistical analysis

Firstly, we made a descriptive analysis of the population included and studied the differences between group 1 and group 2. Qualitative variables are presented as absolute value and percentage and were compared with the chi-square test or Fisher's exact test. Quantitative variables are presented as mean and standard deviation and are compared with the t-test. Then, we compared the clinical and mean laboratory parameters between both groups and reported the differences. Finally, ROC curves were constructed to analyze the discrimination ability of troponin and NT-proBNP between both groups, and cut-off values were established. All the statistical calculations were performed using SPSS Statistic 25.0 software package (IBM, Chicago, IL).

### Ethical considerations

As this was an observational and retrospective study, we did not perform any intervention on the patients that did not comply with clinical practice standards and consensus statements corresponding to the disease. The study was conducted following the Law 3301 of the city of Buenos Aires, the recommendations of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The data are encrypted to protect patients' confidentiality (Law 25 326).

## RESULTS

A total of 32 patients with diagnosis of MIS-C were analyzed; 15 were male (46.9%) and 17 were female (53.1%). Mean age on presentation was 7.67 years (range 0.5-14.91 years). Cardiac diseases and anomalies of the kidney and urinary tract were the most common comorbidities (Table 1). Most patients had positive serological test for SARS-CoV-2 (28 patients of 32); of the remaining 4, 2 had a previously documented infection and the other 2 had positive epidemiological linkage for COVID-19.

Group 1 was made up of 10 patients (31.2%) and group 2 of 22 (68.8%) Baseline NT proBNP value was not obtained in 3 patients (all in group 2) and baseline lymphocyte and platelet counts were not recorded in 1 patient in group 1. Mean age in group 1 was 6.2 years, ranging from 2.41 to 10.16 years, and 8.33 years in group 2, with a wider range of 0.5 to 14.91 years. Almost 70% of patients in both groups came from the Province of Buenos Aires. There were no significant differences in the baseline characteristics of each group in terms of age, sex, place of residence and comorbidities. (Table 1)

Congenital heart defects were the most common comorbidities (levo transposition of the great arteries, atrial septal defect, repaired ventricular septal defect without residual shunt, and mitral valve dysplasia without dysfunction), and history of anomalies of the kidney and urinary tract (rapidly progressive glomerulonephritis, grade 3 vesicoureteral reflux, chronic kidney disease and a patient with one kidney and myelomeningocele).

After obtaining the clinical, echocardiographic and laboratory data, the mean results in each group were compared (Table 2, Figure 1). Mean length of hospital stay was 11.6 days, significantly longer in patients with shock requiring admission to the pediatric intensive care unit (PICU): 17 days vs. 9.2 days ($p < 0.001$). Twp patients in group 2 had prolonged hospitalization due to social issues. A total of 13 children required inotropic agents (due to shock or myocardial dysfunction without shock).

The incidence of cardiac involvement was 84.4% (27 patients), all with at least one abnormal parameter. The most common abnormalities were elevation of high-sensitive troponin I above the laboratory reference values (21 patients, 77%), mitral or aortic valvular regurgitation of any kind in 19 patients (70%), repolarization abnormalities in the electrocardiogram (13 patients, 48%) and systolic dysfunction (8 patients, 29.6%). Coronary artery dilations occurred in 4 patients (12.5%), 3 in group 1 and 1 in group 2 ($p=0.009$). Other disorders included first- or second-degree AV block and incomplete right bundle branch block; all these findings recovered after appropriate treatment was initiated. Ventricular function measured by FS was reduced in group 1: 31.7 ± 1.97 vs. 39.2 ± 2.15% ($p = 0.027$). Pericardial effusion documented by echocardiography was significantly more common in patients with shock (80% vs. 22.7%; $p = 0.001$)

Thrombocytopenia (platelet count < 150 000/mm3) on admission was present in 30% (3/10) of patients with shock, while in group 2 the incidence was 13% (3/22), $p = 0.138$. Lymphopenia (lymphocyte count < 1000/mm3) was present in 4 patients in group 1 (40%) and in 4 in the control group (18%), with no statistically significant differences ($p = 0.14$). Among those requiring any inotropic agent, lymphopenia was present in 7 (58.3%) of the 12 patients with baseline lymphocyte count available, while among the 19 patients who did not require inotropic drugs, only 1 (5.2%) had lymphopenia upon diagnosis (p =

**Table 1.** Demographic characteristics and comorbidities

| Baseline characteristics | Group 1 (patients with shock) | Group 2 (patients without shock) | p value |
|---|---|---|---|
| Age | 6.2 ± 0.77 years | 8.33 ± 0.99 years | 0.20 |
| Female sex | 50% | 54% | 0.80 |
| Place of residence (PBA) | 70% | 68% | 0.92 |
| Comorbidities | 2/10 patients: 1 with one kidney. myelomeningocele with ventriculoperitoneal shunt and 1 levo transposition of great arteries | 6/22 patients: 1 VSD repaired; 1 malnourished with ASD; 1 chronic kidney disease; 1 rapidly progressive glomerulonephritis; 1 mitral valve dysplasia; 1 grade 4 vesicoureteral reflux. | 0.66 |

ASD: atrial septal defect. PBA: Province of Buenos Aires. VSD: ventricular septal defect.

**Table 2**. Clinical, echocardiographic, and laboratory data in patients with and without shock

| | Group 1 (patients with shock) | Group 2 (patients without shock) | p value |
|---|---|---|---|
| Number of patients | 10 | 22 | – |
| Length of hospital stay | 17 ± 2.2 days | 9.2 ± 1.5 days | < 0.001 |
| Cardiac involvement | 9 (90%) | 18 (81%) | 0.551 |
| Left-sided valve regurgitation | 8 (80%) | 11 (50%) | 0.108 |
| 2.<t0/>First or second-degree AV block. | 1 (10%) | 3 (13.6%) | 0.772 |
| Repolarization abnormalities †. | 4 (40%) | 9 (40%) | 0.964 |
| Pericardial effusion | 8 (80%) | 5 (22.7%) | 0.001 |
| Coronary artery dilation | 3 (30%) | 1 (4.5%) | 0.009 |
| FS (%) | 31.7 ± 1.97 | 39.2 ± 2.15 | 0.027 |
| Troponin I (ng/L) | 643.7 ± 478.7 | 171.3 ± 70.8 | 0.188 |
| NT-proBNP (pg/mL) | 19 770 ± 9024 | 7332. ± 5109.3 | 0.008 |
| Platelets (n/mm$^3$) | 166 333 ± 27 079 | 219 590 ± 19 129 | 0.154 |
| Lymphocytes (n/mm$^3$) | 2853 ± 1220 | 1893 ± 259 | 0.766 |

† repolarization abnormalities: T wave flattening, T wave inversion, ST-segment elevation. FS: fractional shortening.

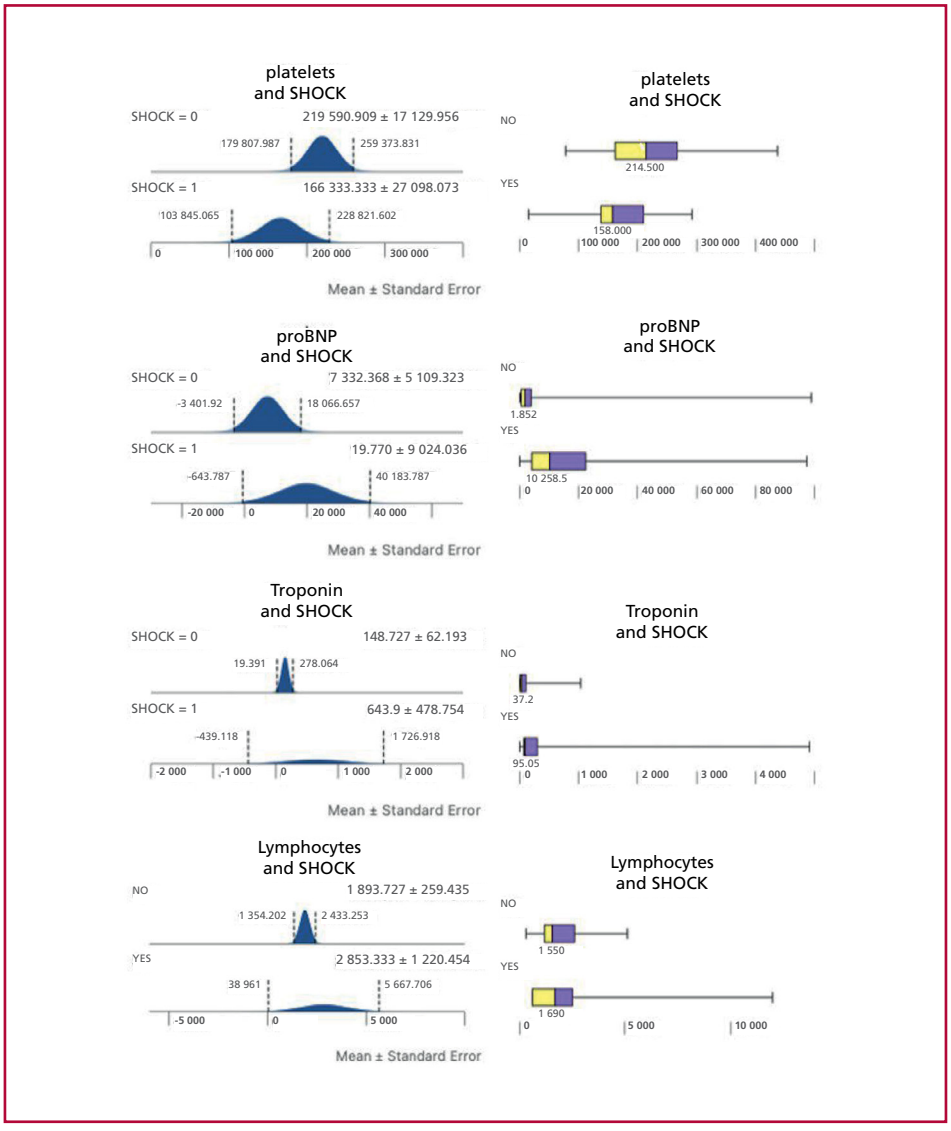


**Fig. 1.** The left of each row shows the distribution of a determined value (platelets, proBNP, high-sensitive troponin I and lymphocytes) expressed as mean and standard error according to the presence (1 or YES) or absence (0 or NO) of shock. The right side shows the distribution chart for each value expressed as median and the dispersion of values also according to the presence (1 or YES) or absence (0 or NO) of shock.

0.006). The specificity of lymphopenia for the use of inotropic drugs was 95%, with a positive predictive value of 88%. There were no differences in the absolute value of platelets and lymphocytes between both groups.

High-sensitive troponin I was elevated (> 19 ng/L) in 21/32 patients (65.6%), 80% (8/10) in group 1 and 59% (13/22) in group 2. Mean troponin value was higher in group 1, but this difference was not statistically significant (p = 0.188). The best cut-off value of troponin I defined by the ROC curve was 50 ng/L, and when we used this value as a dichotomous variable (positive-negative), the positivity rate was 80% in group 1 vs. 31.8% in group 2 (p = 0.01).

With the cut-off point of NT-proBNP established by the reference laboratory (high if > 300 pg/mL), a baseline positivity rate of 90% (9/10) was observed in patients with shock, and of 89% (17/19 tested) in the control group. Mean NT-proBNP levels were significantly higher in patients with shock (19 770 vs. 7332 pg/mL, p = 0.008).

The analysis of the ROC curve demonstrated that the best cut-off value of NT-proBNP to predict shock was 3900 pg./mL. This cut-off value and the adjusted cut-off value of high-sensitive troponin I (50 ng/L) were used in combination. These variables were dichotomized (both values positive vs. any other combination) and analyzed. The combination had a negative predictive value (NPV) of 86% for shock.

## DISCUSSION

We described 32 patients meeting criteria for MIS-C. The characteristics of the population in terms of age on presentation and distribution by sex are similar to those described in other series, (6-8,11-13) with a slight predominance of female patients. Patients in group 1 were younger. While 31% presented shock during disease progression, 40% required use of any inotropic agent.

Cardiac involvement did not differ from other publications and was about 84%. While the incidence of coronary artery dilation reported by international publications was 8-24%, the incidence in our series was 12.5%. (4,5,8,11,14,15) Pericardial effusion was present in 40% of patients, with significant differences between group 1 and group 2.

The main difference between the studies by Valverde and Pignatelli in the definition of cardiac involvement lies in the classification of valvular regurgitation; Pignatelli's criteria are more restrictive, as they only include moderate or severe regurgitation. We believe that trivial, mild or moderate left-sided valve regurgitations should be considered as markers of organ injury despite having healed after treatment, even though this criterion increases the total number of patients with cardiac involvement.

Although mortality associated with this disease has been reported, there were no deaths in our series. (5)

Pignatelli found that elevated troponin values and thrombocytopenia had high sensitivity and negative predictive value for requirement of PICU stay. In our series, patients with the highest mean troponin and NT-proBNP values and the lowest platelet count had an unfavorable course with shock, although the only statistically significant value was that of NT-proBNP. After adjusting for ROC curves, elevated troponin levels were also associated with shock.

When analyzing laboratory data in relation with the use of inotropic agents, the results are similar to those of the international literature (described in patients requiring PICU): high-sensitive troponin I (p = 0.029), NT-proBNP (p = 0.002), and lymphopenia (p < 0.001), showed a statistically significant difference between patients who required inotropic agents and those who did not.

According to our experience, we consider that the role of pediatric cardiologists is still essential when considering the best therapy for each patient. The possible cardiac involvement implies routine collection of samples for laboratory tests and performing an ECG and echocardiogram on hospital admission.

The strength of this study lies in the collection of most of the data searched, since there were few missing values in the context of the health emergency due to the pandemic. The general characteristics of the population were not significantly different from those of the populations reported in other studies. The statistically significant data obtained can be associated with an adverse clinical course in patients with MIS-C.

The number of patients and the retrospective design constitute the main weakness of this study. While not all centers have availability of measuring troponin or NT-proBNP, blood differential and platelet count are widely available.

## CONCLUSION

Multisystem inflammatory syndrome in children may affect any organ. In our study we observed a high incidence of cardiac involvement and significant differences in coronary artery dilation and pericardial effusion between those with and without shock; therefore, we consider that the initial evaluation by pediatric cardiologists is essential for the management of patients. The presence of lymphopenia or elevated NT-proBNP and troponin values should be considered for the initial therapeutic approach in both peripheral centers and referral hospitals.

### Conflict of Interests

No conflicts of Interest or financing concerning the study have been declared.

(See authors' conflict of interests forms on the web/Additional material.)

### Sources of funding

None

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