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From Presentation to Intensive Care: Predictors of PICU Admission in Croatian Children with MIS-C

Od kliničke prezentacije do intenzivnog liječenja: prediktori potrebe za intenzivnim liječenjem bolesnika s MIS-C u Hrvatskoj

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Summary

Aim: Multisystem Inflammatory Syndrome in Children (MIS-C) is a hyperinflammatory condition associated with COVID-19 characterized by immune dysregulation that may lead to organ dysfunction and shock, with cardiac involvement being the most important manifestation. Patients often require PICU admission (43-88%) but usually with favorable outcomes. Elevated inflammatory markers, cardiac involvement and shock have been identified as major predictors of PICU admission.

Methods: This retrospective multicenter study aimed to identify risk factors for PICU admission among MIS-C patients treated from 2020 to 2024 in Croatia. Demographic, clinical, laboratory and echocardiographic data were compared between PICU and non-PICU patients.

Results: We analyzed 136 patient records treated for MIS-C with a 52.2% PICU admission rate. Elevated CRP levels along with myocarditis, congestive heart failure, mitral regurgitation and pleural effusion were significantly more common in the PICU group. Multivariate analysis identified CRP (per 10 mg/L increase, aOR 1.10, 95% CI: 1.03–1.18, p = 0.002), myocarditis (aOR 3.04, 95% CI: 1.10–9.16, p = 0.038) and mitral regurgitation (aOR 2.87, 95% CI: 1.24–6.93, p = 0.016) as factors associated with PICU admission.

Conclusion: Considering the potential severity of the disease, prompt recognition of risk factors and early echocardiographic evaluation are crucial for early assessment of cardiac involvement and the need for intensive care. In this context, our findings indicate that mitral regurgitation, myocarditis, and elevated CRP levels are important indicators of increased risk, as they were associated with a higher likelihood of PICU admission.

Sažetak

Cilj: Multisistemski upalni sindrom u djece (engl. *Multisystem Inflammatory Syndrome in Children,* MIS-C) jest hiperinflamatorno stanje povezano s bolešću COVID-19 obilježeno poremećajem imunološkog odgovora koji može rezultirati akutnom ozljedom organa i šokom, pri čemu je zahvaćenost srca najvažnija manifestacija. Bolesnici često zahtijevaju prijam u jedinicu za intenzivno liječenje djece (JILD) (43–88%), ali uglavnom uz povoljan ishod. Povišene vrijednosti upalnih parametara, zahvaćenost srca i šok identificirani su kao glavni prediktori prijma u JILD.

Metode: Cilj ove retrospektivne multicentrične studije bio je utvrditi čimbenike rizika za prijam u JILD među bolesnicima s MIS-C liječenima u Hrvatskoj u razdoblju od 2020. do 2024. godine. Učinjena je analiza demografskih, kliničkih, laboratorijskih i ultrazvučnih parametara pacijenata liječenih u JILD-u u usporedbi s onima koji nisu zahtijevali prijem u JILD.

Rezultati: Analizirana je medicinska dokumentacija 136 bolesnika liječenih zbog MIS-C-a, od kojih je 52,2% bilo primljeno u JILD. Povišene vrijednosti CRP-a te miokarditis, kongestivno zatajenje srca, mitralna regurgitacija i pleuralni izljev bili su znatno češći u skupini bolesnika liječenih u JILD-u. Multivarijatna analiza pokazala je da su CRP (za povećanje od 10 mg/L, aOR 1,10, 95% CI: 1,03–1,18, p = 0,002), miokarditis (aOR 3,04, 95% CI:

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1,10–9,16, p = 0,038) i mitralna regurgitacija (aOR 2,87, 95% CI: 1,24–6,93, p = 0,016) čimbenici povezani s prijmom u JILD.

Zaključak: Uzimajući u obzir potencijalnu težinu bolesti, pravodobno prepoznavanje čimbenika rizika i rana ultrazvučna evaluacija od ključne su važnosti za ranu procjenu zahvaćenosti srca i potrebe za intenzivnim liječenjem. U tom kontekstu, naši rezultati pokazuju da su mitralna regurgitacija, miokarditis i povišene vrijednosti CRP-a važni pokazatelji povećanog rizika, budući da su bili povezani s većom vjerojatnošću prijma u JILD.

Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity that typically develops several weeks after COVID-19 disease[1]. It was first observed by pediatricians in Europe and North America in 2020 described as a hyperinflammatory syndrome in children resembling Kawasaki disease characterized by abnormal activation of both the innate and adaptive immune systems[2]. Patients present with persistent fever, gastrointestinal symptoms, mucocutaneous lesions and cardiovascular involvement with significant elevation in inflammatory markers.

Despite being a relatively rare complication of SARS-CoV-2 infection with an estimated incidence of 1-5 per 100 000 infected children, MIS-C represents a significant burden for Pediatric Intensive Care Units (PICUs) due to multiorgan involvement resulting in hemodynamic instability, organ dysfunction and shock. Previous studies report PICU admission rates of 43–88%, with elevated inflammatory markers, cardiac involvement, and shock identified as key predictors for PICU admission[3,4,5]. This study aimed to identify risk factors for PICU admission among MIS-C patients treated in Croatia from January 2020 to December 2024.

Patients and methods

We conducted a retrospective analysis of 136 pediatric patient records who were treated for MIS-C from January 1st 2020 to December 31st 2024. Most patients were treated at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević" while the rest were treated at other Croatian University Hospitals in Osijek, Rijeka, and Split[6]. We analyzed demographic, laboratory and clinical characteristics of all patients who fulfilled the World Health Organization (WHO) diagnostic criteria for MIS-C (WHO, 2020), including fever lasting for at least 3 days and at least two of the following: mucocutaneous manifestations, signs of myocardial dysfunction, coagulopathy and gastrointestinal symptoms, elevated inflammatory markers, evidence of a previous COVID-19 infection and the absence of alternative microbiological diagnosis. Categorical variables are presented as absolute numbers and percentages, whereas continuous variables are reported using means and medians.

Chi-square test was used to compare categorical variables, while medians were compared using Wilcoxon test. Factors associated with PICU admission were assessed using univariate and multivariable logistic regression. Collinearity was evaluated using the variance inflation factor, and the linearity assumption for continuous predictors was assessed using the Box–Tidwell test.

Variables for the model were selected based on internal data analysis and based on previous research. We selected demographic variables (age, sex), along with laboratory and ultrasound findings. C-reactive protein (CRP) values were expressed per 10 mg/L increase. Variables with p value ($p<0.05$) in univariate analysis were included in multivariate analysis. Despite showing unsignificant relation with PICU admission in univariate analysis, we included myocarditis in multivariate analysis due to a possible confounding effect, as it might be underlying cause of CHF. A total of 122 patient records were included, as those with missing values were omitted from the analysis. Analyses were performed in R (v 4.1.1).

Results

This study included 136 patients, of whom 87 were male (63.9%). A total of 71 patients (52.2%) required PICU admission. Patients admitted to the PICU were slightly older than those not requiring intensive care; however, this difference was not statistically significant (110.8 vs. 107.3 months, p = 0.466). The two groups were otherwise comparable, with similar lengths of hospital stay and duration of fever prior to admission (10.2 vs. 8.5 days; 5.1 vs. 4.8 days respectively). (Table 1)

Inflammatory markers differed notably between groups, with PICU patients having significantly higher mean CRP values than non-PICU group (197.6 vs. 148.5 mg/L, p < 0.001). Other laboratory abnormalities, including anemia, thrombocytopenia, hepatic involvement, hyponatremia, hypoalbuminemia, and coagulopathy, were also more common in the PICU group but with no significant difference. As expected, cardiac manifestations were commonly observed in this cohort. Although myocarditis (29.6% vs. 20.0%, p = 0.276) and pericarditis (18.3% vs. 10.8%, p = 0.236) were more common among PICU patients, these dif-

ferences were not statistically significant. In contrast, signs of congestive heart failure were significantly more prevalent in the PICU group (36.6% vs. 13.8%, p = 0.005), along with mitral regurgitation (54.9% vs. 29.0%, p = 0.004) and pleural effusion (30.9% vs. 12.3%, p = 0.016). Using multivariate analysis we identified mitral regurgitation (aOR 2.87, 95% CI: 1.24–6.93, p = 0.016), myocarditis (aOR 3.04, 95% CI: 1.10–9.16, p = 0.038), and elevated CRP value (per 10 mg/L increase; aOR 1.10, 95% CI: 1.03–1.18, p = 0.002) as factors associated with PICU admission. All patients recovered completely. (Table 2 and Table 3)

Table 1. Demographic characteristics of patients (N=136)
Tablica 1. Demografska obilježja bolesnika (N=136)

	Total (N=136)	Admitted to PICU (N=71)	Not admitted to PICU (N=65)
Mean length of hospital stay Median (IQR)	9.4 9 (7, 11)	10.2 10 (7, 12)	8.5 8 (6, 10.25)
Male (%)	87 (65.9%)	44 (61.9%)	43 (66.2%)
Mean age (months) Median (IQR)	109.1 111 (70, 144)	110.8 116 (73, 145)	107.34 109 (64.8, 141)
Mean duration of fever before admission Median (IQR)	5 5 (4, 6)	5.1 5 (4, 6)	4.8 5 (4, 6)

Table 2. Clinical, laboratory and ultrasound characteristics of patients (N=136)
Tablica 2. Klinička, laboratorijska i ultrazvučna obilježja bolesnika (N=136)

	Total (N=136)	Admitted to PICU n (%)	Not admitted to PICU n (%)	p*
Avg. days of fever before admission	5	5.1	4.8	0.242
Myocarditis	34 (25.0)	21 (29.6)	13 (20.0)	0.276
Pericarditis	20 (14.7)	13 (18.3)	7 (10.8)	0.236
Signs of congestive heart failure	35 (25.7)	26 (36.6)	9 (13.8)	**0.005**
Mitral regurgitation	58 (42.6)	39 (54.9)	19 (29.0)	**0.004**
Mean CRP value (10mg/L)**	1741	1976	1485	**<0.001**
Mean leukocyte count (x 10^9/L)**	10.7	10.9	10.6	0.073
Anemia	67 (49.3)	40 (56.3)	27 (41.5)	0.121
Thrombocytopenia	65 (47.8)	36 (50.7)	29 (44.6)	0.590
Hepatic lesion	58 (42.6)	34 (47.8)	24 (36.9)	0.234
Hyponatremia	63 (46.7)	37 (52.1)	26 (40.6)	0.245
Hypoalbuminemia	47 (35.3)	28 (40.6)	19 (29.7)	0.258
Coagulopathy	35 (27.3)	24 (33.8)	11 (19.3)	0.103
Ascites	59 (43.4)	36 (50.7)	23 (35.4)	0.104
Pleural effusion	30 (22.1)	22 (30.9)	8 (12.3)	**0.016**

* p<0.05, Chi-square test, ** Wilcoxon test; CRP – C-reactive protein

Table 3. Risk factors for PICU admission (N=122)
Tablica 3. Rizični čimbenici za prijam u JILD (N=122)

Parameter	OR (CI 95%)	p	aOR (CI 95%)	p
Gender (female)	0.93 (0.44 – 1.96)	0.857	1.04 (0.43 – 2.47)	0.930
Age in months	1.01 (0.93-1.11)	0.681	1.00 (0.98 – 1.00)	0.559
Myocarditis	2.3 (0.98 – 6.28)	0.061	**3.04 (1.10 – 9.16)**	**0.038**
Signs of congestive heart failure	**3.34 (1.41 – 8.66)**	**0.008**	2.11 (0.72-6.49)	0.176
Mitral regurgitation	**2.69 (1.29 – 5.74)**	**0.008**	**2.87 (1.24 – 6.93)**	**0.016**
Pleural effusions	**2.57 (1.07 – 6.71)**	**0.042**	0.96 (0.29-3.16)	0.945
CRP value (mg/L)*	**1.10 (1.04-1.17)**	**0.001**	**1.10 (1.03– 1.18)**	**0.002**
Coagulopathy	2.1 (0.91 – 5.11)	0.088	-	-

* per 10mg/L

Discussion

In this study we compared demographic, laboratory and clinical findings of children diagnosed with MIS-C based on the need for PICU admission.

The incidence rate of PICU admission varies greatly globally, probably due to different admission criteria, different PICU capacities between hospitals and depending on the time period in which the research was conducted, considering different strains of SARS-COV-2 circulating[7]. Out of our 136 patients, 52.2% required PICU admission which is comparable with rates reported by other studies and within the range of 43-88% reported in a systematic review[3,4,5].

Previous studies have shown the correlation between male sex, older age and African-American race with higher PICU admission rates[5]. Although no significant association with age or sex was observed, PICU admission was more frequently seen among older children and males, consistent with previously reported data[7]. We couldn't assess potential racial differences because Croatian population is almost entirely Caucasian.

We analyzed the presence of anemia, thrombocytopenia, hyponatremia, hypoalbuminemia, hepatic lesions, and coagulopathy which were all more prevalent in the PICU group along with higher levels of leukocyte count and C-reactive protein (CRP); however, only the difference in mean CRP values was statistically significant.

These findings support the underlying pathophysiological processes in MIS-C, driven by cytokine storm–mediated inflammation which also results in endothelial injury and therefore increased vascular permeability[8]. These fluid shifts can lead to dilutional hyponatremia as well as hypoalbuminemia which have both been recognized as key predictors of MIS-C, with hypoalbuminemia considered an independent predictor of shock and PICU admission in a multivariate model by *Tran et al.* and a predictor for PICU admission by *Torres et al.* and *Abrams et al.*[3,5,9].

Myocardial injury and elevated CRP have previously been identified as predictors, which aligns with our findings[4]. The observed myocardial injury, together with other cardiovascular complications, likely reflects a combination of direct cytopathic effects on cardiomyocytes and concomitant endothelial dysfunction, along with hyperinflammatory state[5]. Experimental evidence shows that SARS-CoV-2 can directly infect cardiomyocytes through ACE2 receptors, leading to cytopathic effects such as impaired contractility, apoptosis, and disruption of sarcomere structure. However, in clinical conditions like MIS-C, myocardial injury is predominantly related to immune-mediated processes rather than direct viral damage[10]. These pathophysiological processes further contribute to a hypercoagulable state in MIS-C, as evidenced by elevated D-dimer level[5].

In clinical assessment, we focused on objective parameters rather than patient symptoms eliminating the possible subjectivity bias. Numerous studies have consistently documented a broad spectrum of cardiovascular dysfunction[4]. Building on these findings, we defined cardiovascular involvement as presence of at least one of the cardiac manifestations listed in Table 2 with congestive heart failure defined as elevation of troponin and NT-proBNP levels with US evidence of decreased ejection fraction. While prior studies have also demonstrated variable incidence and differing patterns of cardiovascular involvement, in our cohort,

however, mitral regurgitation and myocarditis were uniquely identified as independent factors associated with PICU admission highlighting the potential value of early echocardiographic assessment.

Mitral regurgitation observed in MIS-C is most often functional in nature, arising as a consequence of acute left ventricular dysfunction and annular dilatation in the context of myocardial involvement and systemic inflammation[11].

Although the development of mitral regurgitation is closely linked to ventricular dysfunction, the higher prevalence of mitral regurgitation compared to clinically evident congestive heart failure in our cohort suggests that additional mechanisms may be involved. Mitral regurgitation remained independently associated with PICU admission after adjustment for congestive heart failure, despite earlier differences between non-PICU and PICU groups. One possible explanation is that myocardial dysfunction in this setting appears to be largely transient, likely driven by acute inflammation characterized by a cytokine storm leading to reversible myocardial injury, which may not persist long enough for patients to develop the structural and hemodynamic changes required for clinically manifest congestive heart failure[12]. Second, early recognition and timely management may further limit progression to overt heart failure despite the presence of valvular insufficiency. Systemic inflammation in MIS-C promotes myocardial edema, interstitial inflammatory infiltration, vasodilatation, and increased vascular permeability, leading to capillary leak and fluid extravasation[11,13]. Consequently, pleural effusion and ascites may result from both cardiac dysfunction and inflammation-related vascular leakage. These processes, together with hypoalbuminemia and hyponatremia, further contribute to fluid redistribution into the interstitial and third spaces. In this setting, systemic vasodilatation may modify the hemodynamic expression of mitral regurgitation, although this remains speculative. Consequently, despite the presence of mitral regurgitation and volume overload, patients may not develop clinically overt heart failure, further supporting the notion that mitral regurgitation in this context represents a distinct and independent marker of disease severity. All of our patients had favorable outcomes, which is consistent with findings from a systematic review reporting a low mortality rate of 0.9% although higher mortality rates of approximately 2% have also been reported in US cohorts[4,5].

This study is limited by the mostly single-center design which may introduce a sampling bias. We were unable to assess racial differences, which limits the representativeness of the sample, as Croatian population is almost exclusively Caucasian. Considering that cardiac follow up was performed in another institution, we were not able to derive definite conclusions regarding long term cardiovascular involvement and recovery; however, in the subset of patients with available follow-up data, majority have completely recovered. Our sample size was relatively small raising the possibility that a larger cohort might reveal a relationship between higher levels of inflammation and greater severity of mitral regurgitation.

Conclusion

MIS-C is a transient hyperinflammation state characterized by immune dysregulation and myocardial injury which leads to severe disease and patients often require PICU admission. Using multivariate analysis we identified mitral regurgitation (aOR 2.87, p=0.016), myocarditis (aOR 3.04, p=0.038), and elevated CRP (aOR 1.1 per 10mg/L, p=0.002) as independent risk factors. All patients recovered completely.

Despite high admission rates, MIS-C generally has a favorable outcome. Considering the high rates of cardiac involvement, early identification of risk factors is crucial for timely intensive care, underscoring the importance of early echocardiographic assessment. Further research should explore other biomarkers such as cytokines and genetic predisposition as possible risk factors. Prospective/longitudinal studies including greater number of patients are needed to properly address different types of cardiac involvement, including valvular damage and dysfunction and their impact on overall disease morbidity and long-term outcomes.

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REFERENCES

[1] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P et al.; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2. JAMA. 2020;324(3):259-269.

[2] Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): Report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. Int J Infect Dis. 2020;100:75-81.

[3] Matsubara D, Matsubara Y, Ayusawa M, Hamada H, Seki M, Yamagishi H et al. Nationwide Survey of Multisystem Inflammatory Syndrome in Children Associated with Coronavirus Disease 2019 in Japan. J Clin Immunol. 2024;45(1):51.

[4] Abu Hammour K, Abu Farha R, Manaseer Q, Dawoud T, Abu Hammour W. Is COVID-19 multisystem inflammatory syndrome a new variant of Kawasaki Disease? Arch Rheumatol. 2021;37(2):230-244.

[5] Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5(5):323-331.

[6] Stemberger Marić L, Trkulja V, Petrović D, Lah Tomulić K, Bartulović I, Tešović G; CroMIS-C Study Group. Incidence and Clinical Phenotype of Multisystem Inflammatory Syndrome in Children After Two SARS-CoV-2 Pandemic Waves: A Croatian Prospective Nationwide Study. Pediatr Infect Dis J. 2023;42(7):e229-e231.

[7] Dourdouna MM, Mpourazani E, Tatsi EB, Tsirogianni C, Barbaressou C, Dessypris N et al. Clinical and Laboratory Parameters Associated with PICU Admission in Children with Multisystem Inflammatory Syndrome Associated with COVID-19 (MIS-C). J Pers Med. 2024;14(9):1011.

[8] Bukulmez H. Current Understanding of Multisystem Inflammatory Syndrome (MIS-C) Following COVID-19 and Its Distinction from Kawasaki Disease. Curr Rheumatol Rep. 2021;23(8):58.

[9] Tran DM, Pham DV, Cao TV, Hoang CN, Nguyen HTT, Nguyen GD, et al. Severity predictors for multisystemic inflammatory syndrome in children after SARS-CoV-2 infection in Vietnam. Sci Rep. 2024; 14(1):15810.

[10] Dmytrenko O, Lavine KJ. Cardiovascular Tropism and Sequelae of SARS-CoV-2 Infection. Viruses. 2022;14(6):1137.

[11] Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation. 2020;142(5):429-436.

[12] Viadero MT, Caldeiro MJ, Fernández-Suarez N, Garde J, Cabero MJ, González-Lamuño D. Molecular Mechanisms and Pathophysiology of Myocardial Disease: Insights from Pediatric Inflammatory Multisystem Syndrome (PIMS) Associated with SARS-CoV-2. Int J Mol Sci. 2025;26(8):3580.

[13] McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017;135(17):e927-e999. Erratum in: Circulation. 2019;140(5):e181-e184.