ORIGINAL ARTICLE

Factors Associated With PICU Admission In Children With Multisystem Inflammatory Syndrome (MIS-C): An Observational Cohort Study

Facteurs associés à l'admission en USIP des enfants atteints du syndrome inflammatoire multisystémique (MIS-C) : Une étude de cohorte observationnelle

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Abstract

Purpose: To investigate factors associated with Pediatric Intensive Care Unit (PICU) admission in children with severe MIS-C.
Methods: We conducted an observational cohort study between July 1, 2020, and May 31, 2021, in the only pediatric hospital in Tunisia.
Results: A total of 45 children (33 males) with no recent history of COVID-19 infection were included. Mean age was 7±3.2 years. Sixteen patients (35%) required PICU admission. There was no significant difference in mean age of patients with and without PICU admission (7.5±2.7 vs. 6.76±3.46 years; p=0.4). The frequency of respiratory distress (p=0.001), shock (p=0.001), cardiac dysfunction (p=0.003), mean CRP (p=0.001), and median troponin (p=0.003) were significantly higher in patients with PICU admission than in those without. The independent predictive factor for PICU admission was cardiac dysfunction; adjusted Odds Ratio (aOR) = 12.8, 95% CI = (2.1-76.4), p=0.002.
Conclusion: The only independent risk factor for PICU admission in patients with MIS-C was cardiac dysfunction.

Key words: Africa, COVID-19, children, intensive care, multisystem inflammatory disease, northern

Résumé

Objectif: Étudier les facteurs associés à l'admission en unité de soins intensifs pédiatriques (USIP) chez les enfants atteints de MIS-C sévère.
Méthodes: Nous avons mené une étude de cohorte observationnelle entre le 1er juillet 2020 et le 31 mai 2021 dans le seul hôpital pédiatrique de Tunisie.
Résultats: Au total, 45 enfants sans antécédents (33 garçons) ont été inclus. L'âge moyen était de 7±3,2 ans. Seize patients (35 %) ont été transférés en USIP. Il n'y avait pas de différence significative entre l'âge moyen des patients avec et sans admission en USIP (7,5±2,7 vs. 6,76±3,46 ans ; p=0,4). Les fréquences de détresse respiratoire (p=0.001), de choc (p=0.001), de dysfonctionnement cardiaque (p=0.003), de CRP moyenne (p=0.001) et de troponine médiane (p=0.003) étaient significativement plus élevées chez les patients transférés en USIP. Le facteur prédictif indépendant de l'admission en USIP était le dysfonctionnement cardiaque ; Odds Ratio Ajusté (AOR) = 12,8, IC à 95 % = (2,1-76,4), p=0,002.
Conclusion: Le seul facteur de risque indépendant d'admission en USIP chez les patients atteints de MIS-C est le dysfonctionnement cardiaque.

Mots clés: Afrique, COVID-19, enfants, soins intensifs, maladie inflammatoire multisystémique, nord.

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LA TUNISIE MEDICALE-2025; Vol 103 (03): 363-368 DOI: 10.62438/tunismed.v103i3.5381

Introduction

Since April 2020, multisystem inflammatory syndrome in children (MIS-C) has emerged as a rare and serious disease related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the pediatric population[1] and has been reported worldwide[2]. MIS-C is characterized by a sudden onset of rapidly progressing multisystem inflammation that particularly affects the cardiovascular system, resulting in cardiac dysfunction and shock (3–5).
The incidence of pediatric intensive care unit (PICU) admission was reported to be around 70% in both American and Australian cohorts as high-income countries (HICs)[6,7]. There is scarce data regarding the predictors of PICU admission in the literature.
In Africa, there are very few reports about MIS-C [8] and the incidence of PICU admission on the continent is unknown. In Tunisia, the first cluster of patients requiring PICU admission was described in November 2020[9]. The main characteristic in low- and middle-income countries (LMICs) is the lack of PICU beds and fewer resources than in high-income countries (HICs). It is therefore important to identify the factors linked associated with severe forms of MIS-C.
In Tunisia, the population of children aged 0-15 years is approximately 2.6 million, of whom approximately 589,671 live in Tunis (22.1% of the Tunisian pediatric population) [10]. There is no national registry for MIS-C, and the incidence of the disease is unknown. The Bechir Hamza Children's Hospital is the only pediatric hospital in the country, with a bed capacity of 347. The PICU has 14 beds and provides care for severe forms of MIS-C when available.
The aim of our study was to investigate factors associated with PICU admission among patients with MIS-C to increase knowledge of the challenges faced by countries with limited resources as the pandemic continues.

Methods

Setting

The study was conducted in the Department of Pediatrics and the Pediatric Intensive Care Unit (PICU) of the Children's Hospital of Tunis.

Study Design

We conducted an observational cohort study between July 1, 2020, and May 31, 2021. We included all patients aged less than 15 years who met the six criteria for MIS-C according to the World Health Organization (WHO) case definition[11]. All patients were tested for SARS-CoV-2 using nasopharyngeal reverse transcription–polymerase chain reaction (QIASTAT-RP-SARS-COV-2) and had serologic tests (electrochemiluminescence immunoassay/Cobas e 411).
Patients with acute forms of SARS-CoV-2 infection were not included. We excluded patients with missing data upon admission. The study was approved by the local ethical committee (Approval number: 05/2021), and written informed consent was obtained from all parents.

Data collection

During the study period, we recorded demographic data, including age, sex, past history of coronavirus infection disease (COVID-19) with a positive SARS-CoV-2 polymerase chain reaction (PCR) test, underlying medical conditions, and body mass index (BMI, kg/m²). Obesity was defined as a BMI above the 95th percentile for age and sex. We also collected clinical data such as symptoms (fever, diarrhea, vomiting, abdominal pain, headache, sore throat, rash, conjunctivitis, cheilitis, lymphadenopathy, respiratory distress, hypotension, shock, acute cardiac dysfunction, altered mental status, and seizures) and vital signs upon admission (respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP)).
We defined respiratory distress as tachypnea with or without intercostal retraction. Hypotension was defined as systolic or diastolic blood pressure values below the 5th percentile of the reference values for height, or less than 90/50 mmHg for children aged 10 years or older[12]. The diagnosis of shock was established in the presence of arterial hypotension, the need for vasoactive therapy to maintain normal blood pressure, or the presence of signs of hypoperfusion despite adequate fluid resuscitation [13]. Acute cardiac dysfunction was defined by a left ventricular ejection fraction (LVEF) of less than 55%[14]. Echocardiography was performed in all patients.
We recorded laboratory test results, including markers of inflammation (C-reactive protein (CRP), fibrinogen, D-dimer, ferritin), cardiac enzymes (troponin, pro-brain natriuretic peptide (pro-BNP)), liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT)), kidney function tests (natremia, creatinine), and creatine kinase (CK).
Cardiac enzymes were measured in patients who developed cardiac dysfunction. Troponin was considered elevated at > 40 ng/l and pro-brain natriuretic peptide (pro-BNP) at > 100 pg/ml. Renal involvement was defined as an increase in serum creatinine levels of double the normal limits for age, according to the Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE) score [15]. Cytolysis was defined as an increase in transaminase levels twice above baseline or normal values for age. The upper limit of alanine aminotransferase (ALT) serum levels varies with age and sex. For boys aged between 18 months and 12 years, the limit is 40 IU/L; for girls in the same age range, it is 35 IU/L. Above 12 years old, the limit is 25.8 IU/L for boys and 22.1 IU/L for girls [16].
Outcomes recorded included PICU admission if needed, mechanical ventilation if required, length of stay, and mortality. Treatment with immunoglobulin and corticosteroids was only recorded for patients admitted to the PICU.
PICU admission indications were determined by PICU intensivists based on criteria such as hemodynamic instability, myocardial dysfunction, severe arrhythmia, acute respiratory failure, encephalopathy, and progressive clinical deterioration despite standard treatment.

Data analysis

Statistical analysis was conducted using SPSS software version 24. Continuous data were expressed as mean±standard deviation or as median and interquartile range [IQR, 25th-75th percentile], and were analyzed using the Student's t-test or non-parametric tests for comparing medians. Categorical data were presented as numbers (n) and were analyzed using the chi-square test or Fisher's exact test. Logistic regression analysis was performed to identify independent predictive variables for PICU admission.
A level of $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of patients

A total of 45 patients, including 33 males, were included in the study. None of the children had a confirmed past COVID-19 infection in the preceding six weeks. The mean age was 7±3.2 years. Most patients were healthy children (84%). Seven patients had underlying medical conditions: obesity (2), asthma (2), epilepsy (1), autism (1), and urinary tract malformation (1). All patients met the diagnostic criteria for MIS-C according to the WHO case definition. Serology for SARS-CoV-2 was positive in most patients (97%), while RT-PCR for SARS-CoV-2 was positive in six patients. The median delay between symptom onset and admission was 5 days [IQR: 4-7]. All patients presented with fever. The frequency of symptoms and mean values of vital signs are detailed in Table 1.

Of the 45 patients studied, sixteen (35%) required PICU admission during the study period. There was no significant difference between the mean age of patients with and without PICU admission (7.5±2.7 vs. 6.76±3.46 years; p=0.4). Among patients admitted to the PICU, the frequencies of diarrhea (p=0.01), respiratory distress (p=0.001), hypotension (p=0.001), shock (p=0.001), cardiac dysfunction (p=0.003), renal involvement (p=0.001), mean respiratory rate (p=0.001), and heart rate (p=0.007) were significantly higher, whereas systolic blood pressure was significantly lower (p=0.036).

Laboratory test results

The values of laboratory test results for patients with and without PICU admission, are detailed in Table 2.
Among patients requiring PICU admission, significant differences were found in several laboratory markers compared to those not admitted: mean C-reactive protein (CRP) (p=0.001), mean creatinine (p=0.001), median troponin (p=0.003), median aspartate aminotransferase (AST) (p=0.026), median creatine kinase (CK) (p=0.002) were significantly higher, while mean natremia (p=0.01) and mean platelet count (p=0.017) were significantly lower.

Table 1. Demographic data and clinical characteristics of patients admitted with MIS-C: Results of univariate analysis

	Total cohort (N=45)	PICU admissions (n=16)	Non PICU admissions (n=29)	P value
Male sex, n (%)	33 (73.3)	11 (68.8)	22 (75.9)	1[1]
Age, mean (SD)	7 (3.2)	7.5 (2.7)	6.76 (3.46)	0.4[2]
BMI, median [IQR]	18 (15-22.5)	18 (15-22.5)	19 (15.75-25.25)	1[3]
Fever, n (%)	44 (100)	16 (36.4)	28 (63.6)	-
Median delay between onset and admission, median [IQR]	5 (4-7)	6 (4.25-7)	5 (4-7)	0.57[3]
Diarrhea, n (%)	19 (43.2)	11 (68.8)	8 (28.6)	**0.01**[4]
Abdominal pain, n (%)	30 (68.2)	13 (81.3)	17 (60.7)	0.15[4]
Vomiting, n (%)	26 (59.1)	10 (62.5)	16 (57.1)	0.72[4]
Headaches, n (%)	12 (27.3)	6 (37.5)	6 (21.4)	0.3[1]
Odynophagia, n (%)	18 (41.0)	8 (50)	10 (35.7)	0.35[4]
Skin rash, n (%)	35 (79.5)	13 (81.3)	22 (78.6)	1[1]
Conjunctivitis, n (%)	35 (79.5)	14 (87.5)	21 (75)	0.45[1]
Cheilitis, n (%)	33 (75)	13 (81.3)	20 (71.4)	0.7[1]
Adenopathy, n (%)	11 (25)	2 (12.5)	9 (32.1)	0.27[1]
Respiratory distress, n (%)	11 (25)	11 (68.8)	0 (0)	**0.001**[1]
Seizure, n (%)	1 (2.3)	1 (6.3)	0 (0)	0.36 [1]
Impaired consciousness, n (%)	5 (11.4)	3 (18.8)	2 (7.1)	0.33[1]
Shock, n (%)	9 (21.0)	8 (50)	1 (3.7)	**0.001**[1]
Cardiac dysfunction, n (%)	25 (58.1)	14 (87.5)	11 (40.7)	**0.003**[4]
Hypotension, n (%)	15 (34.9)	12 (75)	3 (11.1)	**0.001**[4]
Arrythmias and conduction disorders, n (%)	3 (7)	0 (0)	3 (11.1)	0.28[1]
Cytolysis, n (%)	8 (18.6)	4 (25)	4 (14.8)	0.44[1]
Renal involvement, n (%)	6 (14.0)	6 (37.5)	0 (0)	**0.001**[1]
Respiratory rate, mean (SD)	30 (12.1)	40,75 (13,5)	25,29 (6,5)	**0,001**[2]
Heart rate, mean (SD)	126.2 (21.5)	137,38 (22,8)	119,79 (18,1)	**0,007**[2]
Systolic blood pressure, mean (SD)	91.9 (15.6)	84 (20,6)	96,36 (9,6)	**0,036**[2]

BMI: body mass index; **IQR**: interquartile range; **PICU**: pediatric intensive care unit; **SD** : standard deviation [1]Fisher test [2] t test [3] test for comparison of medians [4] chi square test

Independent risk factors

The independent predictive factor for PICU admission was cardiac dysfunction, with an Adjusted Odds Ratio (AOR) of 12.8 (95% CI: 2.1-76.4, p=0.002) (Table 3)

Treatment and outcomes

All patients received intravenous immunoglobulin (IVIG), methylprednisolone, and a low dose of aspirin. The median length of stay was 7 days [IQR: 5-8 days].
Of the 16 patients admitted to the PICU, all required vasoactive drugs, and five required mechanical ventilation. In our cohort, there was one death (2%). The deceased was a 3-year-old male with a severe, misdiagnosed form of MIS-C complicated by septic shock. He died shortly after admission and before receiving IVIG or corticosteroids.

Table 2. Laboratory tests' results in patients admitted with MIS-C: Results of univariate analysis

	Total cohort (N=45)	PICU admissions (n=16)	Non PICU admissions (n=29)	P value
CRP, mean (SD)	204.3 (106)	274,18 (90,6)	162,89 (92)	**0,001***
Lymphocyts count, median [IQR]	895 [665-1705]	960 [680-2820]	880 [557.5-1322.5]	0,75*
Platelets count, mean (SD)	224230.9 (129257)	172000 (79919)	256373 (144040)	**0,017***
D-dimers levels, median [IQR]	2815 [1374.75-4650.5]	4502 [1640-8200]	1770 [1076-3820]	0,05**
Fibrinogene levels, mean (SD)	5 (1.4)	4,68 (1,3)	5,2 (1,3)	0,257*
Ferritin levels, mean (SD)	727.9 (621)	937,1 (645)	257 (68,6)	0,065*
Troponin levels, median [IQR]	98 [6.5-725.5]	455,5 [115-952,5]	7 [6-64,5]	**0,003****
ProBNP levels, median [IQR]	3000 [784-7643.5]	5216 [1403-10112]	784 [443,25-2877]	0,131**
Natremia, mean (SD)	129.7 (4.42)	127,5 (5)	131 (3,4)	**0,01***
AST levels, median [IQR]	34.5 [31.75-61.5]	51,8 [34-109]	27 [19,25-47,25]	**0,026****
ALT levels, median [IQR]	29 [16.75-50.25]	44 [22,2-59,5]	19,5 [13,75-39]	0,112**
Creatinin levels, mean (SD)	46.8 (30.9)	70,9 (37,4)	31,2 (8,6)	**0,001***
CPK, median [IQR]	55 [29.25-279.5]	253,5 [64,5-392,25]	33,5 [25-54]	**0,002****

AST: aspartate aminotransferase; **ALT** : alanine aminotransferase; **CPK** : creatin phosphokinase; **CRP** : C-Reactive Protein; **IQR** : interquartile range; **ProBNP** : pro-Brain Natriueritic Peptide; **SD** : standard deviation
* T test
** comparison of medians by non-parametric test

Table 3. Results of multivariable analysis: binary logistic regression

Factor	AOR	CI 95% of AOR	p
Cardiac dysfunction	**12.8**	**2.1-76.4**	**0.002**
CPK	0.99	0.991-1.001	0.125

Discussion

A total of 45 patients (33 males) were included in the study, with none having a confirmed COVID-19 infection in the preceding six weeks. The mean age was 7±3.2 years, and most patients were previously healthy children (84%). All patients met the diagnostic criteria for MIS-C according to the WHO case definition. Sixteen patients (35%) required PICU admission.

Among those admitted to the PICU, the incidences of diarrhea (p=0.01), respiratory distress (p=0.001), hypotension (p=0.001), shock (p=0.001), cardiac dysfunction (p=0.003), renal involvement (p=0.001), mean respiratory rate (p=0.001), were significantly higher, while systolic blood pressure was significantly lower (p=0.036). Additionally, mean C-reactive protein (p=0.001), mean creatinine (p=0.001), median troponin (p=0.003), median aspartate aminotransferase (p=0.026), and median creatine kinase (p=0.002) levels were significantly higher, while mean sodium (p=0.01) and mean platelet count (p=0.017) were significantly lower.

We identified cardiac dysfunction as the independent predictive factor for PICU admission, with an Adjusted Odds Ratio (AOR) of 12.8 (95% CI: 2.1-76.4, p=0.002). Of the patients admitted to the PICU, all required vasoactive drugs, and five required mechanical ventilation. In our cohort, there was one death, occurring in a 3-year-old male with a severe, misdiagnosed form of MIS-C complicated by septic shock.

The rate of PICU admission among patients with MIS-C in our cohort was 35%, which is lower than rates reported in some studies (around 70-80%) [17] but similar to findings reported by Batters et al. in South Africa [8]. A comparison between low- and high-income countries suggests a lower percentage of ICU admissions and a higher risk of mortality in low-income settings [18] , possibly due to limited PICU beds availability.

Children requiring intensive care often face challenges accessing PICU beds, highlighting the importance of identifying factors associated with PICU admission for early recognition and management. The median delay from symptom onset to hospital admission was 5 days, similar to other reports [19]. The mean age of our patients (7±3.2 years) and male predominance align with previous findings [18] , where older age was associated with more severe forms of MIS-C. In our study, there was no significant difference in mean age between patients with and without PICU admission (7.5±2.7 vs. 6.76±3.46 years; p=0.04).

Factors significantly associated with PICU admission included higher frequencies of diarrhea, respiratory distress, hypotension, shock, cardiac dysfunction, renal involvement, elevated mean respiratory rate, heart rate, CRP, creatinine, troponin, AST, CK levels, and lower systolic blood pressure, mean platelet count, and mean sodium. These findings are consistent with literature reports, although older age, comorbidities, elevated pro-BNP, D-dimers, ferritin concentrations, and decreased lymphocyte counts have also been reported in other studies (18,20,21). Pro-BNP has been identified as a valuable cardiac marker for diagnosing and stratifying heart failure risk in MIS-C. Zhao et al. [22] reported significantly higher BNP levels in severe MIS-C cases compared to non-severe cases, whereas troponin and AST levels did not show significant differences. In our cohort, median troponin levels were significantly elevated in patients admitted with severe MIS-C in the PICU.

No significant difference was observed in the mean pro-BNP levels, likely due to its limited testing in our cohort (performed in only 21 patients, 46%) because of cost constraints in our country. Non-parametric tests were used for comparisons involving D-dimer, troponin, pro-BNP, natremia, AST, creatinine, and CK levels.

The only independent risk factor identified for PICU admission was acute myocardial dysfunction (Adjusted Odds Ratio = 12.8, 95% CI: 2.1-76.4, p=0.002). This finding highlights the importance of conducting echocardiography for all patients with MIS-C and the need for increased vigilance in pediatric departments for patients presenting with decreased left ventricular ejection fraction (LVEF).

Our observed mortality rate (2%) is consistent with other reports, but we suspect that this incidence may be underestimated. Deaths occurring during the study period with presentations mimicking MIS-C were not included, as these cases didn't meet the WHO's six criteria for MIS-C diagnosis.

Our study's strengths include its prospective design, which allowed for a comprehensive survey of patients, and the detailed investigation of factors associated with PICU admission in patients with MIS-C in a low- and middle-income country (LMIC). We highlighted critical issues such as the scarcity of ICU beds and the challenges involved in conducting essential investigations like cardiac enzyme testing.

However, there are several limitations to consider. The cohort size was small, reflecting the rarity of MIS-C, which resulted in wide confidence intervals for the Adjusted Odds Ratio (AOR) and limited the precision of our estimates. In addition, data on patients admitted to paediatric units nationwide were lacking, which may affect the generalisability of our findings. These limitations highlight the need for larger, multicentric studies to validate our findings in larger populations.

Conclusion

This study has identified several factors were significantly associated with PICU admission in children with MIS-C including diarrhea, respiratory distress, hypotension, shock, renal involvement, elevated mean respiratory rate, heart rate, CRP, creatinine, troponin, AST, CK levels, and lower systolic blood pressure, mean platelet count, and mean sodium. Whereas the only independent risk factor identified for PICU admission was acute myocardial dysfunction.

The incidence of severe MIS-C in low- and middle-income countries (LMICs) is lower compared to high-income countries (HICs), primarily due to the scarcity of published data and limited availability of PICU beds.

As the pandemic continues, children with severe MIS-C encounter difficulties in accessing PICU care, which emphasizes the persistent disparities in healthcare resources. Enhancing efforts for early recognition and management is essential to alleviate the impact on these vulnerable patients.

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