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Posted Date: 30 August 2024

doi: 10.20944/preprints202408.2182.v1

Keywords: Critical Care; MIS-C; PICU; SARS-CoV-2; D-dimer; LVEF

 doi:10.20944/preprints202408.2182.v1

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Clinical and Laboratory Parameters Associated with PICU Admission in Children with Multisystem Inflammatory Syndrome Associated with COVID-19 (MIS-C)

Maria-Myrto Dourdouna [1†], Evdoxia Mpourazani [2†], Elizabeth-Barbara Tatsi [1], Chrysanthi Tsirogianni [2], Charikleia Barbaressou [2], Nick Dessypris [3] and Athanasios Michos [1*]

[1] First Department of Pediatrics, Infectious Diseases and Chemotherapy Research Laboratory, Medical School, National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, Athens, Greece; (M.-M.D.) myrtodour@med.uoa.gr; (E.-B.T.) etatsi@med.uoa.gr; (A.M.), amichos@med.uoa.gr
[2] Pediatric Intensive Care Unit, "Aghia Sophia" Children's Hospital, Athens, Greece; (E.M.) mpourazani.e@hotmail.com; (C.T.) chrysanthi.tsirogianni@gmail.com; (C.B.) ch.barbar@gmail.com
[3] Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Athens, Greece; (N.D.) ndessyp@med.uoa.gr
† These authors contributed equally to this work.
* Correspondence: amichos@med.uoa.gr; Tel.: +30-2107467478

Abstract: Background/Objectives: Multisystem Inflammatory Syndrome in children (MIS-C) is a rare but severe post-infectious complication of COVID-19, that often requires admission to the Pediatric Intensive Care Unit (PICU). The present study aimed to compare the demographic, clinical and laboratory characteristics between children diagnosed with MIS-C who were admitted to the PICU or did not require PICU admission. **Methods:** Children diagnosed with MIS-C from September 2020 to April 2023 were included in this case-control study. Patient's demographic, clinical and laboratory data, were collected from medical records. **Results:** Fifty children with MIS-C were included in the study [median (IQR) age: 7.5 (4.3, 11.4) years, 28/50 (56%) males]. Twenty-two (22/50, 44%) children required admission to the PICU. In the multivariate regression analysis, hepatic (OR:12.89, 95%CI: 1.35-123.41, p-value=0.03) and cardiological involvement (OR:34.55, 95%CI: 2.2-541.91, p-value=0.01) were significantly associated with hospitalization at the PICU. Regarding the laboratory and imaging parameters during the first 48 hours from admission, D-dimer levels higher than 4μg/mL and decreased Left Ventricular Ejection Fraction were associated with an increased risk of PICU admission (OR:7.95, 95%CI:1.48-42.78, p-value=0.02 and OR=1.28, 95%CI:1.07-1.53, p-value=0.01). Children who were admitted to the PICU were more likely to develop complications during their hospitalization (10/22, 45.5% vs. 3/28, 10.7%, p-value=0.005) and were hospitalized for more days, than children in the pediatric wards (median length of stay (IQR): 20 (15,28) days vs. 8.5 (6, 14) days, p-value<0.001). **Conclusions:** In the present study, cardiovascular, hepatic involvement and increased D-dimer levels in children with MIS-C were associated with admission to the PICU.

Keywords: critical care; MIS-C; PICU; SARS-CoV-2; D-dimer; LVEF

1. Introduction

In spring 2020, a case series of pediatric patients presenting with an hyperinflammatory condition that had similarities with Kawasaki Disease (KD), was described as a post-acute immune response to SARS-CoV-2 infection [1-4]. As more cases were reported globally, the US Centers for Disease Control and Disease Prevention (CDC) and the World Health Organization (WHO) decided to term this clinical entity as Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 [5]. MIS-C typically presents 2-6 weeks after infection with SARS-CoV-2, with a wide range of signs and symptoms, including persistent fever, mucocutaneous lesions, gastrointestinal

 doi:10.20944/preprints202408.2182.v1

symptoms, and cardiac complications along with laboratory evidence of systematic inflammation [6-8].

Although the global incidence of the syndrome remains unclear, MIS-C appears to be a rare sequela of SARS-CoV-2 infection [9,10]. Nevertheless, it is a potentially life-threatening complication of COVID-19, as it could result in severe illness with cardiogenic or distributive shock and multiorgan failure [10-13]. Notably, a significant portion of children with MIS-C present as critically ill, requiring admission to the Pediatric Intensive Care Unit (PICU), with many of them requiring inotropic support and intubation and even in some cases Extracorporeal Membrane Oxygenation [9,14].

While in MIS-C the mortality and the rate of admissions to the PICU are overall higher than in pediatric COVID-19, the long-term effects of the syndrome, are not fully elucidated [15-17]. Additionally, factors associated with increased MIS-C severity and PICU hospitalization are still not well defined [2,8]. The identification of these factors is essential for the prompt recognition and efficient clinical management of children with severe MIS-C [7]. In the present study, we aimed to compare the demographic, clinical and laboratory characteristics between children with MIS-C who were admitted to the PICU or not, and to identify potential factors associated with an increased risk of admission to the PICU.

2. Materials and Methods

2.1. Study Design and Participants

This is a retrospective, case-control study conducted at "Aghia Sophia" Children's Hospital, Athens, Greece. This facility is the largest tertiary care pediatric hospital in the country, with a capacity of 750 beds. Children aged 1 month-16 years old, who were admitted to the hospital from September 2020 to April 2023 and had been diagnosed with MIS-C, were included in the study. The study period covered the following periods, that were categorized by the dominant type of SARS-CoV-2 variant at the same time period in Greece: September 1, 2020 to January 31, 2021 (EU1-B.1.177), February 1, 2021 to July 31, 2021 (Alpha variant), August 1, 2021 to December 31, 2021 (Delta variant) and January 1, 2022 to April 30, 2023 (Omicron variant) [18,19].

For the conduction of a comparative statistical analysis and the identification of potential parameters associated with PICU admission, MIS-C patients were divided into the following groups: patients admitted to the PICU (PICU group), and patients hospitalized exclusively in the Pediatric Ward (Pediatric Ward group).

2.2. Case Definition

The children who were included in the study, met the following CDC 2020 MIS-C case definition criteria: (1) Patient's age <21 years, (2) Clinical severe illness requiring hospitalization, (3) No alternative diagnosis, (4) Fever (≥ 1 day) , (5) Laboratory evidence of inflammation, (6) Evidence of SARS-CoV-2 infection or exposure, (7) Multisystem (≥2) organ involvement (cardiovascular, renal, respiratory, hematologic, gastrointestinal, mucocutaneous, neurologic) [20,21].

2.3. Data Collection

Patients' baseline data including demographics (age, gender) and comorbidities were collected from medical records. Additionally, data regarding COVID-19 including past COVID-19 history, SARS-CoV-2 RT-PCR or antigen test result and SARS-CoV-2 serology, were collected. Clinical data regarding MIS-C course was recorded. The involvement of each system/organ was recorded based on clinical signs, symptoms, laboratory (peak values) and/or imaging findings. Any clinical signs, symptoms and/or imaging findings that were consistent with the KD American Heart Association criteria and the Classification Criteria for Macrophage Activation Syndrome (MAS), were also documented [22,23]. The following laboratory parameters were obtained from medical records during the first 48 hours after admission: Complete Blood Count, biomarkers of inflammation and coagulation, biochemical and cardiac biomarkers. The first recorded measurement of Left Ventricular Ejection Fraction (LVEF) was included in the analysis. Data regarding treatment, management (medications, supportive treatment) and outcomes (PICU admission, days of hospitalization, recovery, complications, mortality) were also collected.

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2.4. Study Approval

The study was carried out in accordance with the Declaration of Helsinki and the study protocol was approved by the scientific and bioethics committee of "Aghia Sophia" Children's Hospital (No 21736).

2.5. Statistical Analysis

The qualitative parameters were described using absolute (n) and relative (%) frequencies. Comparisons of the qualitative parameters between the PICU group vs. the Pediatric Ward group were performed using the Chi-Square test or the Fishers' Exact test. The quantitative parameters were described using Median (IQR). Comparisons of the quantitative parameters between the PICU group vs. the Pediatric Ward group were performed using the Wilcoxon's Rank Sum test. To investigate a possible association between PICU admission and clinical and laboratory parameters, multiple logistic regression analysis was performed. Statistical analysis was performed with the SAS software V9.4 (SAS Institute Inc, North Carolina, USA). The level of statistical significance was set at p-value <0.05.

3. Results

During the study period, 50 children that fulfilled the MIS-C case definition were included in the study. Most of the children were admitted to the hospital during the predominance periods of Delta (16/50, 32%) and Omicron (16/50, 32%) variants. Fourteen out of fifty (28%) children were admitted during Alpha period and 4/50 (8%) during the EU1-B.1.177 period.

The clinical and demographic characteristics of the children are outlined in **Table 1**. The median (IQR) age of the participants was 7.5 (4.3, 11.4) years and 28/50 (56%) children were males. The majority of the children that participated in the study (41/50, 82%) did not have any underlying comorbidity. However, 9/50 (18%) children had (≥1) comorbidities including obesity (5/50, 10%), transfusion-dependent homozygous beta-thalassemia (1/50, 2%), Juvenile Idiopathic Arthritis (JIA) (1/50, 2%), Noonan syndrome (1/50, 2%), postinfectious bronchiolitis obliterans (1/50, 2%), and pulmonary artery stenosis 1/50, 2%).

Table 1. Demographic characteristics and clinical features of 50 children diagnosed with MIS-C and hospitalized at "Aghia Sophia" Children's Hospital, Athens, Greece.

	Total No of participants	PICU Admission	Pediatric Ward Hospitalization	*p*-value
Total Study Population	50 (100)	22 (44)	28 (56)	n/a
Demographic Characteristics				
Age (years)*	7.5 [4.3, 11.4]	9.1 [4.4, 11.4]	7.2 [4.3, 11]	0.74 [a]
Gender (Males)	28 (56)	12 (54.6)	16 (57.1)	0.85 [b]
Comorbidities	9 (18)	7 (31.8)	2 (7.1)	0.03 [c]
Clinical Presentation				
Fever	50 (100)	22 (100)	28 (100)	n/a
Mucocutaneous manifestations	31 (62)	13 (59.1)	18 (64.3)	0.71 [b]
Cervical Lymphadenitis	12 (24)	5 (22.7)	7 (25)	0.85 [b]
Gastrointestinal Involvement I (Abdominal pain, vomiting, diarrhea)	43 (86)	19 (86.4)	24 (85.7)	>0.99 [c]
Gastrointestinal Involvement II (Hepatic Involvement)	15 (30)	10 (45.5)	5 (17.9)	0.03 [b]
Respiratory Involvement	12 (24)	7 (31.8)	5 (17.9)	0.25 [b]
Kidney Involvement	18 (36)	11 (50)	7 (25)	0.07 [b]
Central Nervous System Involvement	5 (10)	3 (13.6)	2 (7.1)	0.64 [c]
Cardiovascular Involvement	37 (74)	21(95.5)	16 (57.1)	0.002 [b]
LVEF (%)*	65 [60, 70]	60 [55, 65]	68 [65, 71]	0.001 [a]
Myocarditis	32 (64)	18 (81.8)	14 (50)	0.02 [b]
Pericarditis	7 (14)	6 (27.3)	1 (3.6)	0.03 [c]
Coronary Artery Abnormalities	5 (10)	4 (18.2)	1 (3.6)	0.16 [b]

 doi:10.20944/preprints202408.2182.v1

Notes: Values are referred to as absolute frequencies (relative frequencies, %) or *Median [IQR]. *p*-value obtained after: [a] Wilcoxon rank sum test, [b] Chi-Square, [c] Fisher's exact test. Abbreviations: MIS-C; Multisystem inflammatory syndrome in children associated with COVID-19, PICU; Pediatric Intensive Care Unit, n/a; non applicable, LVEF; Left Ventricular Ejection Fraction.

Positive RT-PCR test result for SARS-CoV-2 infection, on admission, was detected in 10/50 (20%) children. SARS-CoV-2 specific antibodies were detected in 39/50 (78%) children. In addition, 31/50 (62%) children had a history of previous SARS-CoV-2 infection and 33/50 (66%) had known previous exposure to SARS-CoV-2.

The most common symptom in children diagnosed with MIS-C was fever (50/50, 100%), followed by gastrointestinal symptoms, (43/50, 86%), cardiac involvement (37/50, 74%) and mucocutaneous manifestations (31/50, 62%). The most common treatment administered in our study population was infusion of Intravenous Immune Globulin (IVIG) (49/50, 98%) (**Table 1**).

Twenty-two out of fifty (44%) participants were admitted to the PICU. During the study period, MIS-C accounted for 3.5% (22/610) of PICU admissions. The main reasons for PICU admission were the following: cardiogenic or vasodilatory shock, respiratory distress, hypoxemic respiratory failure, pulmonary embolism, pulmonary edema and MAS/Hemophagocytic Lymphohistiocytosis (HLH).

The univariate comparisons between clinical and laboratory characteristics of children with MIS-C who were admitted (PICU group) vs. children who were not (Pediatric Ward group) are presented in Tables 1 and 2. More specifically, the PICU group had more frequently underlying comorbidities (7/22, 31.8% vs. 2/28, 7.1% *p*-value=0.03), hepatic involvement (10/22, 45.5% vs. 5/28, 17.9%, *p*-value=0.03) and cardiovascular involvement (21/22, 95.5% vs 16/28, 57.1% *p*-value=0.002) (**Table 1**).

Cardiovascular involvement included myocarditis, pericarditis, Coronary Artery Abnormalities (CAA) and Pulmonary Embolism and Deep Vein Thrombosis (DVT)-Pulmonary Embolism. Myocarditis (18/22, 81.8% vs. 14/28, 50%, *p*-value=0.02) and pericarditis (6/22 27.3% vs. 1/28, 3.6%, *p*-value =0.03) were more common in the PICU group vs. the Pediatric Ward group. The frequencies of Coronary Artery Abnormalities (CAA) and DVT-Pulmonary Embolism did not differ significantly between the two groups. LVEF was significantly lower in the PICU group than the Pediatric Ward group (*p*-value=0.001) (**Table 1**).

Regarding laboratory parameters, the PICU group had significantly higher levels of D-dimers (*p*-value=0.01). Additionally, serum concentrations of high sensitivity (hs)-Troponin T (*p*-value=0.01), were higher in the PICU group in comparison with the Pediatric Ward group (**Table 2**).

Table 2. Laboratory data of 50 children diagnosed with MIS-C and hospitalized at "Aghia Sophia" Children's Hospital, Athens, Greece.

Laboratory Parameter	Total No of participants	PICU Admission	Pediatric Ward Hospitalization	*p*-value
Complete Blood Count				
Hgb (g/dL)	11.1 [9.8, 12.1]	11 [9.9, 12]	11.4 [9.6, 12.5]	0.42
WBC (×10³/μL)	9.95 [7.2, 15.3]	9.7 [7.3, 13.9]	10 [7.1, 15.8]	0.69
Neutrophils (%)	81.8 [69, 87]	83.4 [74.2, 87]	78.8 [65, 86]	0.33
Lymphocytes (%)	8.9 [6.5, 23.1]	7.4 [6, 15.4]	12.2 [6.9, 23.5]	0.23
Platelets (×10³/μL)	190 [157, 352.5]	187.5 [150, 385]	193 [167, 350]	0.72
Inflammation Biomarkers				
ESR (mm/hr)	70 [32, 95]	65 [25, 80]	79 [35, 100]	0.16
CRP (mg/L)	135 [88.7, 230]	137 [89.7, 229]	129 [87.6, 231]	0.99
PCT (μg/L)	2.29 [1, 7.7]	3.1 [1, 8.6]	2.2 [0.8, 7.6]	0.56
Ferritin (μg/L)	460 [314, 989]	460 [306, 989]	502.5 [329, 1055]	0.84
Coagulation Biomarkers				
D-dimer (μg/mL)	3.1 [2,6]	4.8 [2.7, 6.9]	2.4 [1.5, 4]	**0.01**
INR	1.3 [1.2, 1.4]	1.3 [1.2, 1.5]	1.3 [1.2, 1.4]	0.49
Fibrinogen (μg/mL)	498 [407, 603]	441 [386, 610]	500 [421, 603]	0.52
PT (sec)	15.1 [13.5, 16.4]	15.1 [14, 17.3]	15 [13.3, 16.1]	0.39
APTT (sec)	32.6 [29.8, 36.4]	34.3 [30, 37.2]	31.9 [29.5, 35.4]	0.30
Cardiac Biomarkers				
hs-Troponin T (pg/ml)	8.2 [5.1, 20.2]	11.8 [7.2, 44.8]	5.6 [3.8, 14.6]	**0.01**

 doi:10.20944/preprints202408.2182.v1

NT Pro-BNP (pg/mL)	1987.5 [371.8, 4479.5]	3419 [320.5, 7262]	1727.5 [694, 3295]	0.33
Biochemical Biomarkers				
AST (IU/L)	27 [20, 49]	29 [20, 53]	24 [21, 36]	0.88
ALT(IU/L)	23 [14, 41,5]	26.5 [13, 42]	22 [15, 34]	0.95
Albumin (g/dL)	3.7 [3.5, 4.2]	3.7 [3.5, 3.9]	3.8 [3.5, 4.3]	0.18
Na (mmol/L)	135 [132.5, 136]	134.5 [132, 136]	136 [133, 136]	0.13

Notes: Values are reported as Median [IQR], *p*-values were obtained after Wilcoxon rank sum test. Abbreviations: MIS-C; Multisystem inflammatory syndrome in children associated with COVID-19, PICU; Pediatric Intensive Care Unit, Hgb; Hemoglobulin, WBC; White Blood Cells, ESR; Erythrocyte Sedimentation Rate, CRP; C-Reactive Protein, PCT; Procalcitonin, INR; International Normalized Ratio, PT; Prothrombin Time, APTT; Activated Partial Thromboplastin Time, hs-Troponin T; high sensitivity Troponin T, NT Pro-BNP; , N-terminal prohormone of B-type Natriuretic Peptide, AST; Aspartate Aminotransferase ALT; Alanine Transaminase.

The multivariate regression model (model 1) regarding clinical parameters associated with PICU admission in MIS-C is presented in Table 3. More specifically, hepatic (OR:12.89, 95%CI: 1.35-123.41, *p*-value=0.03) and cardiovascular involvement (OR:34.55, 95%CI: 2.2-541.91, *p*-value=0.01) were significantly more common in the PICU group vs. the Pediatric Ward group (model 1, **Table 3**).

Table 3. Multiple logistic derived Odds Ratios (OR) with 95% Confidence Intervals (95%CI) for admission to the PICU by clinical (model 1) and laboratory and echocardiographic measurements at presentation (model 2) of children diagnosed with MIS-C.

Variable	Category or increment	OR	95% CI		*p*-value
Model 1 (Clinical parameters)					
Comorbidities	yes vs no	7.52	0.83	67.80	0.07
Hepatic Involvement	yes vs no	12.89	1.35	123.41	**0.03**
Kidney Involvement	yes vs no	1.60	0.34	7.49	0.55
Cardiovascular Involvement	yes vs no	34.55	2.20	541.91	**0.01**
Model 2 (Laboratory and echocardiographic measurements at presentation)					
D-dimer	4+ vs 4 μg/mL	7.95	1.48	42.78	**0.02**
hs-Troponin T	one (pg/ml) more	1.00	0.99	1.02	0.76
LVEF	one % less	1.28	1.07	1.53	**0.01**

Abbreviations: PICU; Pediatric Intensive Care Unit, MIS-C; Multisystem inflammatory syndrome in children associated with COVID-19, hs-Troponin T; high sensitivity Troponin T, LVEF; Left Ventricular Ejection Fraction.

In a separate multivariate regression model, regarding the laboratory measurements obtained during the first 48 hours from admission and initial LVEF, children with D-dimer levels higher than 4μg/mL had an increased risk to be admitted to the PICU (OR:7.95, 95%CI: 1.48-42.78, *p*-value=0.02) (model 2, **Table 3**). Additionally, decreased LVEF was associated (OR=1.28, 95%CI: 1.07-1.53, *p*-value=0.01) with an increased risk of admission to the PICU (model 2, **Table 3**).

Concerning management and treatment, statistically significant differences in the PICU group vs. the Pediatric Ward group were noted in the administration of supplementary oxygen (9/22, 40.9% vs. 0/25, 0%, *p*-value<0.000), pulse glucocorticoid therapy (11/22, 50% vs.4/28, 14.3% *p*-value=0.01), Low Molecular Weight Heparin (16/22, 72.7% vs. 8/28, 28.6%, *p*-value=0.002), and receptor antagonist of IL-1 (anakinra) (9/22 40.9% vs. 0/28, 0%, *p*-value<0.001) (Table 1). Regarding the patients hospitalized in the PICU, 11/22 (50%) children received inotropes and 11/22 (50%) received vasopressors. Half of the children admitted to the PICU needed hemodynamic support for [median (IQR)]: 3 (2, 5) days and 7/22 (31.8%) children required mechanical ventilation for [median (IQR)]: 5 (4, 6) days. Additionally, one child (1/22, 4.5%) received Continuous Renal Replacement Therapy (CRRT) (**Supplementary Table S1**).

Finally, concerning disease outcomes, the following complications were recorded in our study: persisting myocardial dysfunction, persisting CAA, DVT-Pulmonary Embolism, pleural effusion, MAS, gastrointestinal bleeding and acute renal failure requiring CRRT. The development of complications during the hospitalization and the persistence of the complications at the time of discharge from the hospital were more frequent in the PICU group than in the Pediatric Ward group

 doi:10.20944/preprints202408.2182.v1

(10/22, 45.5% vs 3/28, 10.7%, *p*-value=0.005 and 8/22, 36.4% vs. 3/28, 10.7% *p*-value=0.04, respectively) (Table 1). Furthermore, children in the PICU were hospitalized for more days than children in the Pediatric Wards [median LOS (IQR): 20 (15,28) days vs. 8.5 (6, 14) days, *p*-value<0.001]. For the PICU group, the median (IQR) LOS at the PICU was 4.5 (3, 7.25) days and the median (IQR) duration of hospitalization at the general pediatric department after PICU discharge was 10.5 (7.75, 18) days. All children were discharged, and no death was recorded in our study population (**Supplementary Table S1**).

4. Discussion

In the present study, we compared the characteristics of children diagnosed with MIS-C who needed admission to the PICU with those hospitalized in the Pediatric Wards. Among these 50 patients, various clinical and laboratory parameters associated with PICU admission were identified.

In our setting, a substantial proportion (44%) of the children with MIS-C required admission to the PICU. In other studies, the rates of PICU admission vary from 14% to 80% [2,12,24,25]. This variability may be a result of differences in the diagnostic and management protocols, in the timing of treatment's administration, and in the capacity of the PICU of each hospital [2,24]. It could be also attributed to differences in the study periods, as the severity and incidence of the syndrome varies according to the circulating SARS-CoV-2 strain [18,26,27]. Notably, evidence from different studies suggest that the risk and the severity of MIS-C during the Omicron wave were decreased compared to the Alpha or Delta waves [26-28].

Regarding baseline demographic parameters, while children requiring PICU admission were older than children hospitalized in the pediatric ward, we did not find any significant association between age and need for PICU hospitalization. By contrast, other studies have reported that older age is associated with PICU admission in MIS-C [2,7,25,29]. In the study by Abrams et al, PICU admission was more likely in children ≥6 years old [7]. Furthermore, in a case series of 183 MIS-C patients, children presenting with shock were significantly older than the children without shock [2,30].

In our study population, most children with MIS-C (74%) had cardiac manifestations, which were more prevalent in children admitted to PICU (95.5%). The cardiac involvement in MIS-C ranges from mild manifestations to severe cardiac complications and includes arrythmias, pericardial effusion, CAA and myocarditis [31]. In our study, specifically, pericarditis and myocarditis were significantly more frequent in critically ill children. In line with our findings, according to previous reports, cardiac involvement in MIS-C occurs in up to 80% of patients [32,33]. Moreover, a multi-center study of 166 MIS-C patients reported that hypotension, shock and myocardial involvement were much more common in children with severe MIS-C [33].

Additionally, the concentrations of hs-Troponin T were significantly higher in the PICU group, as described by other studies [7,33]. In contrast with other reported data, in our study while the first measurements of N-Terminal prohormone of B-type Natriuretic Peptide (NT-proBNP) were higher in the PICU group, there was not a significant difference between the two groups [7]. In the multivariate model for quantitative parameters, lower LVEF values were identified as a potential risk factor for PICU admission. Decreased LVEF has been associated with severe disease course in MIS-C in other studies [31,34,35]. Beaver et al., reported that lower LVEF at admission was associated with the need of vasoactive medication and Tran et al. reported that LVEF (<60%) was associated to the risk for developing shock and PICU admission, in MIS-C patients [31,34]. These findings underline the importance of close echocardiographic monitoring of children with MIS-C.

According to our findings, during the MIS-C course, hepatic involvement (peak liver enzymes and/or imaging findings) was significantly more common in the PICU group. In line with this finding, in a multi-center study of MIS-C patients, hepatomegaly was associated with PICU admission [33]. In MIS-C, the immense release of pro-inflammatory cytokines leads to organ dysfunction, including liver damage [36]. Hence, the higher frequency of hepatic involvement in the PICU group, may be secondary to the shock and the more profound organ dysfunction that is observed in these patients [37].

Regarding laboratory findings, children diagnosed with MIS-C that had D-dimer levels above a specific threshold (>4μg/mL) at presentation had an increased risk to be admitted to the PICU. The role of D-dimers has already been underscored in MIS-C as evidence suggest that the syndrome is

 doi:10.20944/preprints202408.2182.v1

characterized by a prothrombotic inflammatory state [35,38,39]. An association between D-dimer levels and PICU admission has also been observed in other studies [8,33,40]. In children with severe COVID-19, including MIS-C, D-dimer levels were associated with a higher risk not only of PICU admission, but also for intubation, myocardial dysfunction, and development of sequelae [38]. As D-dimer measurements are easy to obtain through routine blood testing, serial measurements should be included in the routine laboratory evaluation in children with MIS-C [38].

Other laboratory markers obtained in the acute phase of MIS-C have been associated with PICU admission, like elevated ESR (>30 mm/h), CRP (>5 mg/dL), ferritin, PCT, prothrombin time, thrombocytopenia, lymphopenia, hyponatremia and decreased serum albumin levels [8,24,25,29,31,41,42]. Significant differences in the above biomarkers were not detected in our population, possibly due to the limited number of participants. Still, altogether the above findings emphasize the importance of obtaining repeated laboratory measurements in these children [7].

Concerning treatment, a subset of children did not respond to the initial infusion of IVIG and needed a second infusion of IVIG (30%), pulsed glucocorticoids (30%) or administration of IL-1 receptor antagonist (anakinra) (18%). The administration of pulsed glucocorticoids and anakinra were more common in the PICU group.

A significant number of children developed complications during their hospitalization, with complications being more prevalent in critically ill children. In our study population, CAA were detected in 10% of the children. In accordance with our findings, the prevalence of CAA in MIS-C is estimated approximately at 8-26% [43,44]. The incidence of MAS/HLH in our study was lower (4%) than that reported in previous studies (18–76%) [33]. Markedly, two children presented with clinical features similar to acute appendicitis. Similar cases have been reported in literature and suggest that MIS-C could either mimic the disease or presents together with complicated forms of acute appendicitis [45].

Finally, in our study, all children were discharged from hospital and no deaths were recorded. Other studies have also reported a rather low mortality rate in MIS-C, estimated approximately at 1.9% [46,47]. As it has been described in other reports, in a subset of the children, especially in those with critical illness, complications including residual myocardial dysfunction, did not fully resolve at the time of discharge [47]. However, in a three-month multidisciplinary follow-up, these complications resolved, suggesting that MIS-C has an overall favorable outcome in children that had received appropriate treatments.

Our study has some limitations. The major limitation of this study is the relatively small number of participants. Due to the small sample size, we may have not been able to detect significant differences in some of the clinical features that were less frequently observed in our study groups. However, MIS-C appears to be a rare complication of SARS-CoV-2 infection, with an initially estimated incidence of 45-54 cases/100.000 infected children <15 years old [48]. Also, given that its incidence has further declined during the Omicron wave, we believe that data from similar series are important [48]. Additionally, in our study we have included children diagnosed with MIS-C during the predominance periods of several different SARS-CoV-2 variants (EU1-B.1.177, Alpha, Delta, Omicron), in Greece. Moreover, although our center is the largest tertiary care pediatric hospital in the country, another limitation of the present study is its single-center study design.

5. Conclusions

The findings of our study suggest that cardiovascular and hepatic involvement are associated with hospitalization at the PICU. In addition, D-dimer levels above a specific threshold could possibly aid in predicting which child with MIS-C will require admission to the PICU, while decreased LVEF was recognized as a potential risk factor for PICU admission. The findings highlight the importance of specific laboratory and echocardiographic measurements in children with MIS-C, for the early identification of high-risk patients.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Treatment and disease outcomes of 50 children diagnosed with MIS-C and hospitalized at "Aghia Sophia" Children's Hospital, Athens, Greece.

Author Contributions: Conceptualization, A.M.; methodology, M.-M.D., E.M. and A.M.; validation, M.-M.D.; formal analysis, N.D.; investigation, M.-M.D., E.M. E.-B.T and C.T.; resources, E.M.; data curation, M.-M.D. and

E.M.; writing—original draft preparation, M.-M.D. and E.M.; writing—review and editing, E.-B.T., C.T., C.B., N.D. and A.M.; supervision, C.B. and A.M.; project administration, A.M.;. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the by the scientific and ethics committee of "Aghia Sophia" Children's Hospital, Athens, Greece (No 21736, 11/2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author (A.M.) upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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