



Impact of time to diagnosis on the occurrence of cardiogenic shock in MIS-C post-COVID-19 infection

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Received: 3 October 2022 / Accepted: 28 December 2022 / Published online: 6 January 2023
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Abstract

Background In multisystem inflammatory syndrome in children (MIS-C), diagnostic delay could be associated with severity. This study aims to measure the time to diagnosis in MIS-C, assess its impact on the occurrence of cardiogenic shock, and specify its determinants.

Methods A single-center prospective cohort observational study was conducted between May 2020 and July 2022 at a tertiary care hospital. Children meeting the World Health Organization MIS-C criteria were included. A long time to diagnosis was defined as six days or more. Data on time to diagnosis were collected by two independent physicians. The primary outcome was the occurrence of cardiogenic shock. Logistic regression and receiver operating characteristic curve analysis were used for outcomes, and a Cox proportional hazards model was used for determinants.

Results Totally 60 children were assessed for inclusion, and 31 were finally analyzed [52% males, median age 8.8 (5.7–10.7) years]. The median time to diagnosis was 5.3 (4.2–6.2) days. In univariable analysis, age above the median, time to diagnosis, high C-reactive protein, and high N-terminal pro-B-type natriuretic peptide (NT-proBNP) were associated with cardiogenic shock [odds ratio (OR) 6.13 (1.02–36.9), 2.79 (1.15–6.74), 2.08 (1.05–4.12), and 1.70 (1.04–2.78), respectively]. In multivariable analysis, time to diagnosis ≥ 6 days was associated with cardiogenic shock [adjusted OR (aOR) 21.2 (1.98–227)]. Time to diagnosis ≥ 6 days had a sensitivity of 89% and a specificity of 77% in predicting cardiogenic shock; the addition of age > 8 years and NT-proBNP at diagnosis $\geq 11,254$ ng/L increased the specificity to 91%. Independent determinants of short time to diagnosis were age < 8.8 years [aHR 0.34 (0.13–0.88)], short distance to tertiary care hospital [aHR 0.27 (0.08–0.92)], and the late period of the COVID-19 pandemic [aHR 2.48 (1.05–5.85)].

Conclusions Time to diagnosis ≥ 6 days was independently associated with cardiogenic shock in MIS-C. Early diagnosis and treatment are crucial to avoid the use of inotropes and limit morbidity, especially in older children.

Keywords COVID-19 · Delay in diagnosis · Heart failure · MIS-C · SARS-CoV-2

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection is a rare but serious condition [1]. Its cumulative incidence was 7.2 per 100,000 children in France on July 7, 2022 [2]. Two-thirds of patients with MIS-C required critical care support. Complications included cardiogenic shock, extracorporeal membrane oxygenation (ECMO), and death [3]. In high-income countries, deaths are relatively rare, accounting for less than 2% of cases [4].

The diagnosis of MIS-C can be difficult [5]. Early diagnosis would allow rapid treatment. Anti-inflammatory

treatment, including corticosteroids and intravenous immunoglobulins, resulted in rapid recovery and improved outcomes [6]. However, the delayed diagnosis could lead to delayed treatment and an unfavorable outcome. Little is known about the impact of diagnostic delay on the course of MIS-C and its main complication, cardiogenic shock [7].

Depending on the pediatric disease, the prognosis varies with the time to diagnosis. An increased time to diagnosis, defined as more than 10 days from the onset of symptoms, was associated with an increased risk of coronary artery aneurysms in Kawasaki disease [8]. However, a long time to diagnosis of new-onset heart failure was associated with increased survival in pediatric cardiomyopathies and myocarditis [9].

It is unclear whether a diagnostic delay leads to an increased risk of cardiogenic shock in MIS-C. We hypothesized that a prolonged time to diagnosis was associated with an increased occurrence of cardiogenic shock in MIS-C. The aim of the present study was to measure the time to diagnosis, to assess the consequences of a long time to diagnosis on the onset of cardiogenic shock, and to define the determinants of the diagnostic delay.

Methods

Population

A single-center cohort observational study was conducted from May 2020 to July 2022. The period of analysis was divided into two periods: before and after the implementation of the new French therapeutic guidelines on March 18, 2021 [10].

Children with an MIS-C diagnosis meeting the World Health Organization (WHO) criteria hospitalized at the tertiary hospital center were prospectively included [11]. The non-inclusion criteria were duplicates and refusal to participate. Children who had previously been vaccinated against COVID-19 were excluded to ensure that antibody positivity was not related to the vaccine but rather to an actual COVID-19 infection.

The study was registered by the French National Data Protection Commission (*Commission nationale de l'informatique et des libertés, CNIL*, Paris, France) under the reference identifier ID1248 and was validated by the local ethics committee in agreement with French regulations for such observational studies and with the Helsinki Declaration of 1964, as revised in 2000. Informed consent was obtained from children and legal guardians.

Time to diagnosis measurement

This study was reported in accordance with the Reporting Studies on Time to Diagnosis (REST) guidelines for time-to-diagnosis studies [12].

The period between the first MIS-C symptoms and the date of diagnosis was named the time to diagnosis, expressed in days. This period was divided into two intervals: patients and physicians. The patient interval was defined as the period between the day and hour of the first symptom and the first medical consultation. The physician interval was defined as the period between the day and hour of the first medical consultation and the diagnosis. Time to admission was defined as the period between the first symptom and the first admission to the hospital.

Two physicians specialized in pediatric cardiology independently assessed the time to diagnosis [9]. Potential disagreements were resolved after a third review of the charts. If disagreements persisted, a third experienced physician determined the time to diagnosis. The assessors could access records from initial visits outside of the tertiary hospital when necessary. They were blinded to the primary outcome during the first diagnosis assessment. A long time to diagnosis was defined as six days or more [13].

Patient characteristics

Variables collected were demographic data, symptoms on the first day, biological and ultrasound features, and treatments. The blood biological features were: sodium, platelet, total leucocyte, neutrophil, and lymphocyte counts, blood creatinine, urea, albumin, C reactive protein (CRP), procalcitonin (PCT), D-Dimers, prothrombin time ratio, factor V activity, N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin T, lactate, and pH. Extreme values for each child during hospitalization were collected. The glomerular filtration rate (GFR) was calculated using the Schwartz formula [14]. The ultrasound features were minimal left ventricular ejection fraction (LVEF), presence of coronary dilation and dilated coronary Z score, and presence of arrhythmia or high-grade conduction block [15]. LVEF was considered depressed when below 55%: mildly depressed between 45% and 54%, moderately depressed between 35% and 44%, and severely depressed below 35% [16]. The lowest values of LVEF were used. The only potential immunomodulatory treatments used were intravenous immunoglobulins and corticosteroids. Potential antithrombotic treatments were aspirin and heparin. Data were first presented for all children; they were then compared between children with a short and a long time to diagnosis.

Outcomes

The primary outcome was the presence of cardiogenic shock. Cardiogenic shock was defined by the use of one or more inotropes in the context of signs of shock with

clinical signs of heart failure (hepatomegaly, pulmonary crackles), decreased LVEF and/or increased NT-proBNP [17]. Inotropes included dobutamine, milrinone, epinephrine, and norepinephrine. Other outcomes collected were distributive shock, shock, extracorporeal membrane oxygenation (ECMO), respiratory support, encephalitis, and death. Distributive shock was defined as the need for a fluid bolus greater than 20 mL/kg and/or vasopressor (epinephrine, norepinephrine) [18]. Shock was defined as cardiogenic shock and/or distributive shock [19]. The length of stay in the pediatric intensive care unit (PICU) and/or high-dependency unit (HDU), the total length of stay, and the number of readmissions related to the MIS-C episode were collected. Patients had at least one cardiology visit within three months of discharge.

Determinants

Potential determinants and confounders included age at diagnosis analyzed as a categorical variable, sex, comorbidities, distance from patient's home to tertiary care hospital, number of healthcare visits prior to diagnosis, specialty of the first physician encountered, period before or after the implementation of the new French therapeutic guidelines on March 18, 2021, and existence of Kawasaki clinical criteria [8, 10, 20, 21].

Statistical analysis

For the primary outcome, the linearity of the association with time to diagnosis was tested, and time to diagnosis was transformed into a polynomial and categorized in case of deviance from linearity. Associations between time to diagnosis analyzed as a categorical variable, and the primary outcome were studied by univariable analyses and multivariable analyses using a logistic regression model. The sensitivity and specificity of a long time to diagnosis in predicting cardiogenic shock were defined. Outcomes associated with cardiogenic shock were used to build a predictive score. Age was analyzed as a categorical variable; the median age was utilized to define a practical cutoff. Receiver operating characteristic (ROC) curves were used to define the cutoffs of continuous variables collected at diagnosis. The area under each ROC curve was considered acceptable above 0.8. The sensitivity, specificity, and positive and negative predictive values of this score in predicting cardiogenic shock at diagnosis were defined.

For the determinants, the associations between potential determinants and time to diagnosis, analyzed as a continuous variable, were studied with a Cox proportional hazards

model since time to diagnosis is a censored variable. The hazard ratios (HRs) obtained expressed the instantaneous risk of a diagnosis: the higher the HR, the shorter the time to diagnosis. Adjusted hazard ratios (aHRs) were calculated by multivariable analysis.

Variables with a *P* value less than 0.05 for the primary outcome and 0.24 for determinants were retained for the multivariable analyses with a maximum of two models. The significant variables with the highest odds ratios (ORs) were chosen for the two models for outcome. A *P* value less than 0.05 was considered statistically significant.

For a two-tailed test with an alpha risk of 5% and a beta risk of 10%, the estimated minimum sample size was 20 patients, with at least 10 in each group [22, 23].

Statistical analyses were performed with Stata v13 (Statacorp, College Station, TX, USA). The results are presented as numbers (percentages), medians [interquartile ranges (IQR)], ORs or HRs with 95% confidence intervals (95% CIs). For categorical variables, Fisher's exact test was used. For quantitative variables, a Shapiro-Wilk normality test was used to verify the normal distribution. With unpaired data, an unpaired *t* test or a Mann-Whitney test was used. With paired data, a paired *t* test or a Wilcoxon matched-pairs signed rank test was used.

Results

Patient characteristics

Figure 1 shows the flow chart. Totally 28 children (90%) had a positive SARS CoV-2 test: serology (24, 77%) and/or polymerase chain reaction (PCR) (8, 26%) with a previous contact at least two weeks before the onset of symptoms. All the other children (3, 10%) had contact with a patient infected with COVID-19 two to six weeks before the first symptoms.

The characteristics of the children are presented in Table 1. All children had elevated CRP and NT-proBNP levels. Three (10%) had coronary dilation. The dilation was moderate (+2.8, +3.3 and +3.9 standard deviations) and completely resolved in all cases before discharge. One (3%) had a high-grade atrioventricular block that resolved completely before discharge.

Time to diagnosis and outcomes are presented in Table 2. Records from initial visits outside of the tertiary hospital were needed for one child. The mean (\pm standard deviation) time to diagnosis was 5.3 (\pm 1.6) days, and the mean difference between short and long time to diagnosis was 2.4 days. The time to diagnosis was not significantly different from the time to treatment for all children (Table 2, *P*=0.753). The time to diagnosis was significantly longer than the time to admission for all children (Table 2, *P*<0.001).

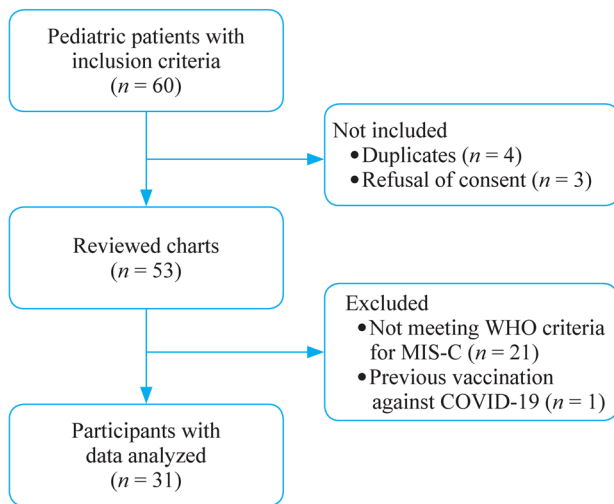


Fig. 1 Flow chart of the study. MIS-C multisystem inflammatory syndrome in children

Among analyzed children, 21 (68%) were treated after the implementation of the new therapeutic guidelines: they were all treated with intravenous immunoglobulins and corticosteroids, apart from one who was only treated with corticosteroids. Among the 10 children (32%) treated before, they all received intravenous immunoglobulins. Eight children (80%) had corticosteroids before the new guidelines, vs. 21 (100%) after ($P=0.097$).

Nine children (29%) had aspirin, including three treated at a low dose for coronary dilatation. Six children (60%) received aspirin before the new guidelines, vs. 3 (14%) after ($P=0.015$).

Outcomes

Excluding children with encephalitis, children with a long time to diagnosis had a longer PICU and/or HDU length of stay [3 (2–4) vs. 2 (0.5–3) days, $P=0.025$, $n=22$]. They also had a longer total length of stay [7 (6.5–7.5) vs. 6 (5–6) days, $P=0.048$, $n=21$] before discharge from the tertiary care hospital.

Table 3 shows the factors associated with cardiogenic shock. One child (3%) received only norepinephrine. In univariable analysis, age greater than eight years, high levels of CRP and NT-proBNP, and a long time to diagnosis were associated with the use of inotropes. In multivariable analysis, a time to diagnosis equal to or greater than six days was associated with the use of inotropes, regardless of age or CRP level. Figure 2 reveals the probability of the onset of cardiogenic shock as a function of time to diagnosis.

Table 4 shows the sensitivity, specificity, and positive and negative predictive values of time to diagnosis, age and NT-proBNP in predicting cardiogenic shock. Figure 3 shows the

ROC curves of NT-proBNP and CRP levels at diagnosis. The area under the ROC curve was considered acceptable for NT-proBNP but not for CRP. A new score including time to diagnosis ≥ 6 days, age > 8 years, and NT-proBNP at diagnosis $\geq 11,254$ ng/L (1 point for each) was built. The sensitivity, specificity, and positive and negative predictive values of a score equal to three points are described in Table 4.

Shock was associated with age ≥ 8.8 years [OR 10.50 (1.72–63.91), $P=0.011$], signs of encephalitis during hospitalization, including psychomotor slowing, behavior changes, and/or confusion [confirmed secondarily by electroencephalogram, OR 7.50 (1.14–49.26), $P=0.036$], and neck pain before or at the time of diagnosis [OR 10.86 (1.03–114.58), $P=0.047$]. Distributive shock was associated with neck pain before or at the time of diagnosis [OR 11.50 (1.33–99.33), $P=0.026$].

None of the children required invasive ventilation, dialysis, or ECMO. All children recovered completely from clinical cardiological and neurological impairment at a median follow-up of 72 (55–412) days. One (3%) was readmitted for isolated recurrence of fever two weeks after discharge with a decrease in CRP, and corticosteroids were tapered for six weeks instead of three without recurrence.

Determinants

The determinants of short time to diagnosis are presented in Table 5. No child aged 10 or older (9 (29%)) met the clinical Kawasaki criteria.

Discussion

This study was the first to assess the time to diagnosis in MIS-C. The median time to diagnosis of MIS-C was 5.3 days in our tertiary care hospital. More than a third had a long time to diagnosis. High age, CRP and NT-proBNP were associated with cardiogenic shock. A long time to diagnosis was independently associated with cardiogenic shock. A predictive score including time to diagnosis ≥ 6 days, age > 8 years and NT-proBNP at diagnosis $\geq 11,254$ ng/L had a sensitivity of 89% and a specificity of 91% for cardiogenic shock. Independent determinants of diagnostic delay were older age, a long distance from tertiary care hospital, and the early pandemic period. Treatment within six days of symptom onset reduced morbidity, including cardiac, respiratory, and renal dysfunction, and was further associated with a reduced length of stay.

The median age, sex ratio and comorbidities of our patients with MIS-C were consistent with previous reports [19]. The rate of gastrointestinal symptoms was lower, but data collection in our study was limited to the first day of

Table 1 Patient characteristics

Variables	All children	Time to diagnosis < 6 d (n = 18)	Time to diagnosis ≥ 6 d (n = 13)	P
Males	16 (52)	10 (56)	6 (46)	0.722
Age (y)	8.8 (5.7–10.7)	7.8 (5.1–9.8)	10.5 (8.5–11.8)	0.026
Weight (kg)	29 (21–43)	24 (19–37)	38 (27–53)	0.020
Past medical history	8 (26)	4 (22)	4 (31)	0.689
Asthma	5 (16)	3 (17)	2 (15)	1
Obesity ^a	4 (13)	1 (6)	3 (23)	0.284
CNS malformation	1 (3)	1 (6)	0 (0)	1
Kidney malformation	1 (3)	1 (6)	0 (0)	1
Symptoms on the first day				
Fever	27 (87)	17 (94)	10 (77)	0.284
Digestive signs ^b	15 (48)	8 (44)	7 (54)	0.722
Asthenia	11 (35)	4 (22)	7 (54)	0.128
Headache	5 (24)	5 (28)	0 (0)	0.058
Neck pain	3 (10)	1 (6)	2 (15)	0.558
Sore throat	3 (10)	1 (6)	2 (15)	0.558
Others ^c	4 (13)	1 (6)	3 (23)	0.284
Blood biological features				
Sodium (mmol/L)	131 (126–133)	132 (127–134)	129 (126–133)	0.410
Platelets (10 ⁹ /L)	126 (101–266)	124 (97–202)	149 (96–290)	0.400
Leucocytes (10 ⁹ /L)	14.9 (8.3–18.6)	10.0 (7.8–17.8)	17.5 (12.5–26.4)	0.012
Lymphocytes (10 ⁹ /L)	0.8 (0.5–1.1)	0.8 (0.5–1.6)	0.8 (0.4–1.1)	0.409
Neutrophils (10 ⁹ /L)	10.9 (5.7–15.1)	6.8 (5.5–11.2)	14.0 (9.4–22.0)	0.032
CRP (mg/L)	208 (125–294)	201 (108–254)	269 (166–414)	0.075
Procalcitonin (ng/ml) ^d	17 (9.5–32)	15 (8–19)	24 (10–95)	0.165
Albumin (g/L) ^e	25 (22–30)	25 (23–30)	24 (21–29)	0.240
D-Dimers (μg/L) ^f	4000 (2800–6200)	4050 (2875–5600)	3700 (2330–7000)	0.835
Urea (g/L)	0.43 (0.32–0.59)	0.36 (0.29–0.45)	0.59 (0.40–1.20)	0.003
GFR (ml/min/1.73m ²)	115 (87–138)	128 (104–148)	91 (35–128)	0.012
Prothrombin time ratio (%) ^g	75 (66–86)	80 (70–88)	67 (51–79)	0.014
Lactates (mmol/L)	2.5 (1.6–3.6)	1.9 (1.5–3.2)	3.2 (1.7–4.6)	0.103
Acidosis ^h	5 (16)	1 (7)	4 (31)	0.134
NT-proBNP (ng/L)	10,012 (3527–22,304)	5555 (2384–10,227)	22,304 (13,859–47,889)	<0.001
Troponin T (ng/L)	58 (29–166)	32 (16–60)	141 (63–316)	0.001
LVEF (%)	45 (40–52.5)	45 (45–56)	40 (30–50)	0.021
Normal	7 (23)	5 (28)	2 (15)	0.667
45–54	12 (39)	10 (56)	2 (15)	0.032
35–44	8 (26)	3 (17)	5 (38)	0.229
<35	4 (13)	0 (0)	4 (31)	0.023

Results were expressed as number (%) or median (IQR). Significant *P* values < 0.05 were indicated in bold

CNS central nervous system, *CRP* C-reactive protein, *GFR* Glomerular Filtration Rate, *IQR* interquartile range, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *LVEF* ultrasound left ventricular ejection fraction, *MIS-C* multisystem inflammatory syndrome in children

^aObesity was defined as a body mass index above the International Obesity Task Force curve depending on age, reaching the value of 30 at 18 years old

^bDigestive signs included vomiting, abdominal pain and diarrhea

^cOther symptoms on the first day included myalgia and dysgeusia (same patient), arthralgia and rash (same patient), cough, and hypotonia (*n* = 1, 3% for each)

^d*n* = 25 with available data

^e*n* = 29 with available data

^f*n* = 15 with available data

^gChildren with low prothrombin time had normal factor V activity (above 60%)

Table 1 (continued)^hAcidosis was defined as pH below 7.37 for arterial or capillary samples and below 7.33 for venous samples**Table 2** Time to diagnosis and outcomes

Variables	All children	Time to diagnosis < 6 d (n = 18)	Time to diagnosis ≥ 6 d (n = 13)	P
First consulted physician				
General practitioner	21 (68)	12 (67)	9 (69)	1
Hospital emergency	10 (32)	6 (33)	4 (31)	1
Number of healthcare visits before diagnosis	3 (2–4)	3 (2–3.3)	3 (3–4)	0.221
Patient interval	2.0 (1.0–3.0)	1.5 (1.0–3.0)	2.2 (1.2–3.5)	0.377
Medical interval	3.1 (2.0–4.4)	2.7 (1.0–3.2)	4.4 (3.6–5.6)	0.001
Time to diagnosis	5.3 (4.2–6.2)	4.7 (3.3–5.1)	6.3 (6.1–7.2)	< 0.001
Time to treatment	5.3 (4.3–6.3)	4.7 (3.6–5.1)	6.3 (6.1–7.3)	< 0.001
Time to admission	4.0 (3.0–5.0)	4.0 (2.8–4.2)	5.0 (3.0–6.0)	0.071
Admission ward				
PICU	22 (71)	11 (61)	11 (85)	0.237
HDU	6 (19)	4 (22)	2 (15)	1
Pediatric cardiology	3 (10)	3 (17)	0	0.245
Non-invasive positive airway pressure support ^a	5 (16)	0 (0)	5 (38)	0.008
Shock	11 (35)	3 (17)	8 (62)	0.021
Cardiogenic shock	9 (29)	1 (8)	8 (62)	0.001
Distributive shock	6 (19)	3 (17)	3 (23)	0.676
Inotropes				
None	22 (71)	17 (94)	5 (38)	0.001
Dobutamine	7 (23)	0 (0)	7 (54)	< 0.001
Norepinephrine	4 (13)	1 (6)	3 (23)	0.284
Epinephrine	2 (6)	0 (0)	2 (15)	0.168
Milrinone	2 (6)	0 (0)	2 (15)	0.168
Heparin ^b	7 (23)	1 (6)	6 (46)	0.012
Encephalitis	9 (29)	5 (28)	4 (31)	1
Death	0 (0)			

Results were expressed as number (%) or median (IQR). Significant *P* values < 0.05 were indicated in bold. *HDU* high-dependency unit, *IQR* interquartile range, *MIS-C* multisystem inflammatory syndrome in children, *PICU* pediatric intensive care unit

^aFour children were treated with high-flow nasal cannula and one with non-invasive ventilation

^bFour children had a preventive dose and three curative.

Medical interval: time from first medical consultation to diagnosis; patient interval: time from the first symptom to first medical consultation

symptoms. Here, all children had an increase in NT-proBNP and CRP, as described in the literature [24]. The rates of hospitalization in the PICU, shock, and use of inotropes were similar to those of other studies [4, 25].

This study demonstrated for the first time that diagnostic delay was associated with cardiogenic shock. NT-proBNP and CRP levels were also associated with cardiogenic shock in univariable analysis. NT-proBNP has been shown to be the key cardiac marker to differentiate between serious and non-serious conditions related to SARS-CoV-2 [26]. In the

studies by Whittaker et al. and Abrams et al., inflammatory markers were higher in children with shock [19, 27]. In addition, the association between troponin and severity has remained controversial [26, 27]. Troponin was not associated with cardiogenic shock in our study, although it may have been underpowered.

In the study by Bautista-Rodriguez et al., where the patients included had a relatively low mean age of seven years and a low rate of positive SARS-CoV-2 tests of 62.3%, a shorter time to admission was associated with ECMO and

Table 3 Factors associated with cardiogenic shock

Variables	Univariable analysis		Multivariable analysis			
	OR (95% CI)	P	Model 1 aOR (95% CI)	P	Model 2 aOR (95% CI)	P
Age ≥ 8.8 y	6.13 (1.02–36.89)	0.048	3.56 (0.43–29.65)	0.240		
CRP ^a	2.08 (1.05–4.12)	0.035			1.75 (0.79–3.84)	0.165
NT-proBNP ^b	1.70 (1.04–2.78)	0.035				
Troponin T ^c	1.05 (0.99–1.12)	0.120				
Time to diagnosis (d)	2.79 (1.15–6.74)	0.023				
Time to diagnosis ≥ 6 d	27.20 (2.71–272.83)	0.005	21.01 (2.00–220.81)	0.011	21.21 (1.98–227.05)	0.012

Data with significant P values < 0.05 were indicated in bold

aOR adjusted odds ratio, CRP C-reactive protein, MIS-C multisystem inflammatory syndrome in children, NT-proBNP N-terminal pro-B-type natriuretic peptide, OR odds ratio, 95% CI 95% confidence interval

^aCRP values were analyzed as (value in mg/L)/100

^bNT-proBNP values were analyzed as (value in ng/L)/10000

^cTroponin T values were analyzed as (value in ng/L)/10

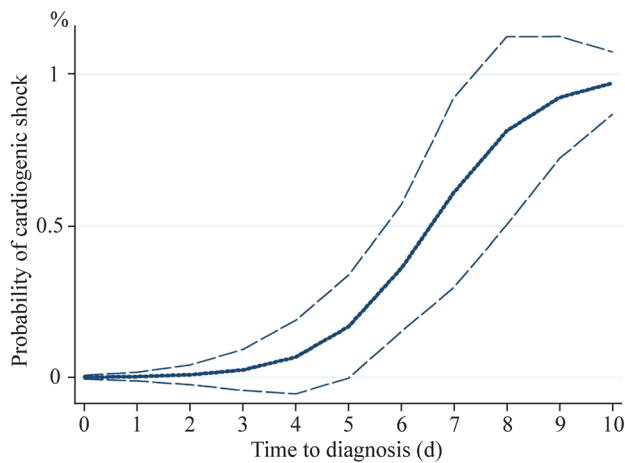


Fig. 2 Probability of cardiogenic shock depending on time to diagnosis. The mean is indicated by the solid line and the 95% confidence interval by the dotted lines

Table 4 Sensitivity, specificity, and positive and negative predictive values of time to diagnosis, age and NT-proBNP in predicting cardiogenic shock at diagnosis of MIS-C

Variables	Se (%)	Sp (%)	PPV (%)	NPV (%)
Time to diagnosis ≥ 6 d (1 point)	89	77	62	94
Age > 8 y (1 point)	89	50	42	92
NT-proBNP at diagnosis ≥ 11,254 ng/L (1 point)	89	68	53	94
Predictive score^a = 3 points	89	91	80	95

MIS-C multisystem inflammatory syndrome in children, NPV negative predictive value, NT-proBNP N-terminal pro-B-type natriuretic peptide, PPV positive predictive value, Se sensitivity, Sp specificity

^aThe predictive score, indicated in bold, was defined as the addition of each of the three items

death in MIS-C [22]. Here, a shorter time to diagnosis was associated with a lower occurrence of cardiogenic shock in MIS-C, which seemed paradoxical. First, it was shown that the time to diagnosis was significantly different from the time to admission. Second, here, the rate of distributive shock, also called vasoplegic shock, did not differ by time to diagnosis in MIS-C [28]. In the study by Zhang et al., this has also been found in Kawasaki disease shock syndrome [29]. Additionally, in the study by Grimaud et al., vasoplegic features were frequently associated with cardiogenic shock in MIS-C, as found here [30].

Three clinical patterns of MIS-C have already been defined in the study by Whittaker et al., namely, children in shock, children with Kawasaki criteria, and children without shock or Kawasaki criteria. Children in shock were older, had signs of heart failure, high NT-proBNP, and reduced LVEF [19, 22]. In the study by Theocharis et al., their LVEF course has been described in agreement with our definition of a long time to diagnosis: children were frequently admitted on day 5 from the onset of symptoms, and the lowest LVEF was on day 7 [13]. Cardiogenic shock often appeared after six days in children in shock, while in others, cardiogenic shock never occurred. In the study by Bautista-Rodriguez et al., signs of severity were associated with a shorter time to admission [22]. On the one hand, in a population where the time to admission was long, as in the literature, children in shock were admitted on day 7 because of signs of severity, whereas children without shock were admitted later. On the other hand, in a population where the time to admission was short, as in the present study, most children were treated before the onset of severity [median time to treatment (IQR) 5.3 (4.3–6.3) days]. In the current study, the time to admission was indeed short

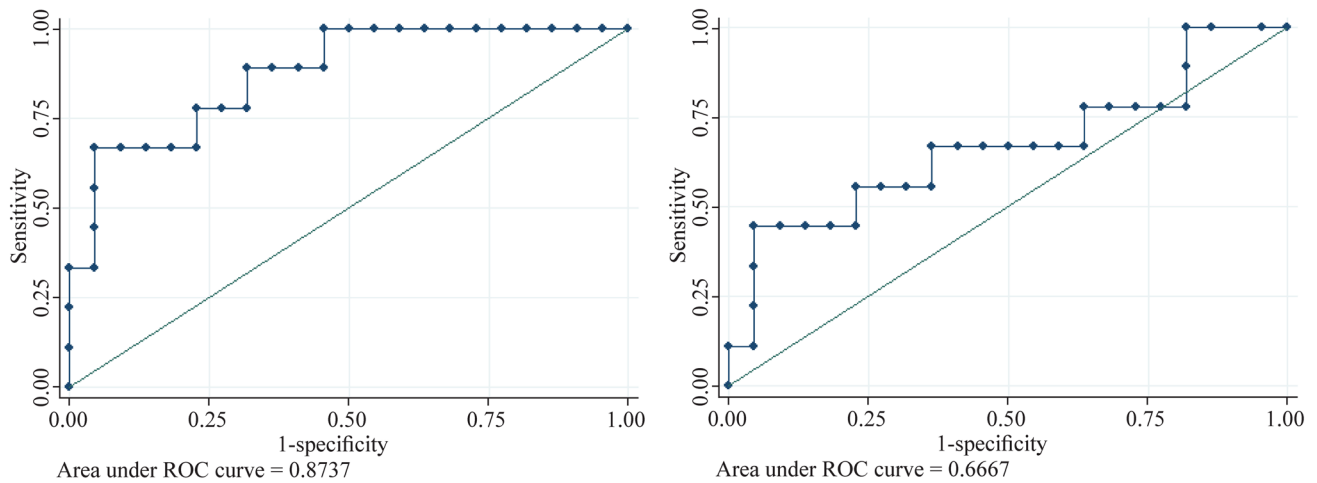


Fig. 3 Receiver operating characteristic (ROC) curves of NT-proBNP (left graph) and CRP (right graph) at diagnosis of MIS-C to predict cardiogenic shock. Laboratory parameters were collected on the day

of diagnosis or within 12.5 h before or after diagnosis. *CRP* C-reactive protein, *MIS-C* multisystem inflammatory syndrome in children, *NT-proBNP* N-terminal pro-B-type natriuretic peptide

Table 5 Determinants of short time to diagnosis

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age at diagnosis, y [vs. 1st half (2.6–8.8)]				
2nd half (8.8–15.3)	0.31 (0.13–0.76)	0.011	0.34 (0.13–0.88)	0.026
Sex (female)	0.91 (0.44–1.88)	0.800		
Comorbidity ^a	1.44 (0.64–3.28)	0.380		
Distance from the tertiary care hospital ^b	0.49 (0.16–1.52)	0.219	0.27 (0.08–0.92)	0.036
Number of healthcare visits before diagnosis	0.77 (0.49–1.20)	0.249		
GP as the first consulted physician ^c	1.30 (0.59–2.90)	0.517		
Late period ^d	1.62 (0.74–3.56)	0.232	2.48 (1.05–5.85)	0.038
Children with clinical Kawasaki criteria	1.89 (0.76–4.67)	0.171	1.89 (0.70–5.11)	0.210

Data with significant *P* values < 0.05 were indicated in bold

aHR adjusted hazard ratio, *GP* general practitioner, *HR* hazard ratio, *MIS-C* multisystem inflammatory syndrome in children, *95% CI* 95% confidence interval

^aAt least one comorbidity including asthma, obesity or organ malformation

^bDistance was analyzed as (value in km)/100

^cVs. emergency physician

^dThe late period was defined as the period after the implementation of the new French therapeutic guidelines on March 18, 2021

(mean ± standard deviation 3.8 ± 1.7 days) compared to the literature (5 ± 3 days) [22, 23].

To clarify the factors that could explain the diagnostic delay, we showed that children over 8.8 years of age were three times more likely to have a delayed diagnosis, as in heart failure [9]. Older age was then an independent determinant of diagnostic delay but also a predictor of severe MIS-C, as in the study by Karunakar et al. [25]. Moreover, in MIS-C, the specialty of the first consulted physician was not a determinant of the diagnostic delay, unlike congenital heart diseases [9]. In the current study, in MIS-C, the number

of healthcare visits before diagnosis was not a determinant either, unlike Kawasaki disease [8]. However, in MIS-C, children living far from our tertiary center were diagnosed significantly later, as previously described in Kawasaki disease, possibly as a result of a delay in physician recognition of MIS-C [8]. Medical knowledge about this disease needs to be deepened, although it has probably improved since the start of the COVID-19 pandemic because the time to diagnosis was shorter in the second half of our study period.

MIS-C diagnosis is challenging, and a differential diagnosis is often evoked. Time is often needed to rule out

diagnoses such as bacterial infection or hematological cancer. We suggest prompt treatment when the time to diagnosis is equal to or greater than six days, with all the WHO criteria. When the time to diagnosis is less than six days, the probability of cardiogenic shock seems low, and time may be granted to collect the results of the differential diagnostic tests. High inflammation and increased NT-proBNP have proven their diagnostic value in increasing the likelihood of MIS-C [31]. Echocardiography within 24 hours of admission is advised as LVEF and other more sensitive parameters, including global longitudinal strain, could help to guide the diagnosis [32]. Echocardiography should then initially be repeated daily until a probable diagnosis is found [13].

At the time of diagnosis, predicting shock could improve triage and impact monitoring and care. We described for the first time a three-point score to predict cardiogenic shock, including a cutoff for NT-proBNP. In the study by Ganguly et al., NT-proBNP > 935 ng/L had a sensitivity of 70% and a specificity of 77.5% in diagnosing MIS-C [31]. In the present study, the association of time to diagnosis ≥ 6 days, age > 8 years and NT-proBNP at diagnosis $\geq 11,254$ ng/L had a sensitivity of 89% and a specificity of 91% in predicting cardiogenic shock in MIS-C. Treatment could then be intensified.

Our study has several limitations. First, although 21 children (35%) were excluded because they were misclassified, a small proportion of children were not included for refusal of consent. However, the databases used were comprehensive for our tertiary center, as children with SARS-CoV-2-related conditions were prospectively included. Second, although two physicians assessed the time points independently to limit measurement bias, these data were collected retrospectively. Third, our study only included children admitted to our tertiary care hospital. Milder cases admitted to secondary care centers could then have been omitted. Indeed, the rate of cardiac systolic dysfunction (77%) was high in our study, although the same proportions as in the literature of mildly, moderately and severely depressed LVEF were found [16]. Finally, this study was monocentric with a limited number of patients and hence of analyzable variables on multivariable logistic regression, and the predictive score needs external validation.

In conclusion, for MIS-C, children with a time to diagnosis of at least six days had a higher risk of developing cardiogenic shock, especially children over eight years of age, with an NT-proBNP at diagnosis $\geq 11,254$ ng/L. Although the time to diagnosis has improved during the last period of the COVID-19 pandemic, a long distance from the tertiary care center was a risk factor for the diagnostic delay. High NT-proBNP and low LVEF could help to diagnose MIS-C in cases of prolonged fever with signs of severity to initiate urgent treatment and limit morbidity. Distributive shock was

not associated with time to diagnosis. Larger multicentric studies are needed to better describe this condition.

Acknowledgements The authors thank Dr Florence Flamein for her help in study design.

Author contributions SB: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing—original draft, writing—review & editing. MB: data curation, investigation, resources, and writing—review & editing. MR, JS, FD, SL, AH, FG: resources, validation, and writing—review & editing. M-EL, J-BB, HR, OD, TR, AD: resources, and writing—review & editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding No funding was secured for this study.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Ethical approval This study was validated by the local ethics committee (Univ. Lille, CHU Lille) with the reference identifier ID1248, in agreement with French regulations for such observational studies. Informed consent to participate in the study has been obtained from participants and their parent or legal guardian.

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