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The Role of Platelets in Multisystem Inflammatory Syndrome in Children (MIS-C) Severity Prediction in PICU, Benha University Hospitals

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) is a cytokine storm syndrome linked to COVID-19. MIS-C is still a diagnostic and clinical problem despite of the numerous suggested diagnostic criteria**.**

Objective: To study the role of platelet in the prediction of MIS-C severity in the Pediatric Intensive Care Unit (PICU), Benha University Hospital.

Methodology: Seventy-one children with MIS-C were included in the retrospective analysis. The included children were categorized into Group A (n=47) and present mild cases of MIS-C severity while group B included severe cases. The composite severity score was used to assess the severity.

The platelet indices were used to predict the severi

Results: The mean age of the included children was 7.3±2.9 and 8.9±3.1 years in groups A and B, respectively, with a male predominance in both groups. No statistically significant different clinical presentation between both groups including gastrointestinal, respiratory, or cardiac presentation. Only shock was evident significant in Group B (P=0.037*). A severe course of MIS-C was predicted by various marker combinations. It was quite clear that PLT, MPV, PCT, and PDW worked together to predict the severity of MIS-C.

Conclusion: PLTs have a predictive role in detecting the severity of MIS-C by describing clinical and laboratory markers linked to MIS-C severity. It may be possible to anticipate the severity of MIS-C by using PLTs measures in standard laboratory procedures.

Keywords: MIS-C, Platelet, severity prediction

INTRODUCTION

Children who suffered from severe acute respiratory syndrome coronavirus (SARS-CoV-2) during the COVID-19 pandemic had and still have a less severe illness than adults. Nevertheless, some kids also experience COVID-19-related aftereffects. MIS-C is one of the cytokine storm syndromes linked to COVID-19 in children, as well as in the majority of patients who partially or completely fit the criteria for Kawasaki disease (KD) [(1)]. Patients with MIS-C were identified with the aid of new, largely overlapping case criteria. The correct diagnosis requires the confirmation of multiple organ involvement, including the neurological, respiratory, renal, gastrointestinal, haematological, cardiac, and mucocutaneous systems, as well as concurrent inflammation in laboratory tests. Establishing a connection between SARS-CoV-2 infection and various alternative illnesses, such as sepsis, KD, or TSS, is crucial [(2)].

Persistent fever, polymorphic rash, gastrointestinal problems, discomfort, conjunctivitis, and peripheral edema are typical indications of MIS-C. Furthermore, some kids have characteristics with those who have KD [(3,4)]. Children with MIS-C also commonly have cardiac involvement, which includes arrhythmia, aneurysm, and coronary dilatation [(5)].

In recent years, MIS-C has been graded based on how serious it is. Some patients are admitted due to minor symptoms and a persistent fever, while others show evidence of heart damage and shock [(6)]. However, as MIS-C seems to be a rare consequence of SARS-CoV-2 (<1%), its incidence is yet unknown [3].

Because it is inexpensive and simple to perform, routine blood testing is the first diagnostic method used in clinical settings. More significantly, the mean platelet volume (MPV), as determined by a complete blood count (CBC), can be utilized as an inflammatory measure since platelets are essential to the inflammatory response. Both acute and chronic conditions typically result in greater levels of IL-6, which may affect the megakaryocyte–platelet axis and encourage higher MPV [7].

Consequently, MPV can offer insights into the diagnosis and prognosis of COVID-19 and sepsis [8]. Additionally, MPV has been proposed as an inflammatory biomarker in severe conditions such as coronary heart disease and pneumonia. There is a dearth of information on the connection between MPV and MIS-C [9].

In patients with severe SARS-CoV-2 infection and MIS-C, coagulation activation is one of the pathogenesis arms that leads to a prothrombotic state [10].

Numerous studies have thoroughly detailed the function of activated PLTs in immune cell activation and their interactions with various pathogens [11]. The Aim of this study was to study the role of platelet in the prediction of MIS-C severity in the Pediatric Intensive Care Unit (PICU), Benha University Hospital.

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PATIENTS AND METHODS

Study design

The current retrospective study is conducted at the Pediatrics Department, Benha University Hospital from January 2021 to May 2023.

Inclusion criteria: All children with World Health Organization (WHO) criteria of MIS-C [12].

1. Age: less than eighteen

2. Fever > 38.0 °C for at least 24 hours, +ve C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin (PCT), D-dimer, Lactate dehydrogenase (LDH), neutrophils, and decreased lymphocytes and albumin. Severe illness involving two or more systems (cardiovascular, respiratory, renal, neurologic, gastrointestinal, and dermatological).

3. A +ve polymerase chain reaction (PCR), a +vee antigen test, a +ve serologic test (IgM, IgG, or IgA), or exposure to COVID-19 case.

4. No other plausible diagnoses.

Exclusion criteria: Incomplete medical records and missing criteria of WHO definition of all MIS-C.

METHODS

All included children have been subjected to the following:

Age, biological sex, residence, medical history, and information about prior COVID-19 infection were among the details gathered from a data system. The +ve COVID-19 sickness in close relatives or connections, was used to determine the day of virus exposure. Additionally, in the data analysis, we included the length of stay (LOS), and the admission to the PICU. Furthermore, **Brisca *et al*.** [13] composite severity score—the Gaslini severity assessment tool (GSATool)—was used to measure the MIS-C severity [13].

Clinical examination: General examination and systemic examination (chest, heart, abdominal, and neurological examination).

Laboratory tests: ESR, procalcitonin (PCT), LDH, albumin, liver and kidney functions, CBC, CRP, cardiac dysfunction markers [troponin I], prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen (FB, and elevated D-dimer (DD) levels], ferritin (FR). The data analysis includes the outcomes of every biomarker that was mentioned.

The included children were categorized into Group A (n=47) and present mild cases of MIS-C severity while group B included severe cases.

Ethical Approval: This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Benha University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis

For statistical analysis, Microsoft Excel and IBM SPSS Statistics version 29.0 (SPSS Inc., Chicago, IL, United States) for Windows were utilized. We used the Shapiro-Wilk test to determine whether the data were normally distributed. Continuous variables were expressed using the median and interquartile range (IQR) or mean ± standard deviation (SD). The qualitative data was presented using both counts and percentages (%), Chi-square test to define significance. An independent samples t-test was used to compare the groups if the data were normally distributed; if not, the Mann-Whitney U test was employed. The cutoff values were determined using Youden's index . A p-value of less than 0.05 was deemed significant.

Youden's index is a measure used to determine the optimal cutoff point for a diagnostic test or predictive model.

RESULTS

The mean age of the included children was 7.3±2.9 and 8.9±3.1 years in groups A and B, respectively, with a male predominance in both groups. Among the 71 included children, 24 matched severe cases and were assigned to Group B. Previous COVID infection was evident in 51% and 29.2 % in groups A and B, respectively. The duration from contact to presentation was 5.2 days in group A and 4.2 days in Group B (P=0.28). 40.4% of children in Group A were admitted to the PICU while 66.7% of children in group B were admitted to the PICU with a statistically significant longer LOS in Group B (P <0.001) **(Table 1)**.

Table **2** reported no statistically significant different clinical presentation between both groups including gastrointestinal, respiratory, or cardiac presentation. Only shock was evident significant in Group B (P=0.037).

Table **3** reported the laboratory findings among both groups. Neutrophil count, CRP, D-dimer, Troponin I, Pro-BNP, Ferritin, LDH, and urea were significantly higher in Group B. Other laboratory investigations were statistically insignificant.

Various marker combinations for MIS-C severity prediction were reported in Table **4**. A severe MIS-C was predicted by all combinations. It was quite clear that PLT, MPV, PCT, and PDW worked together to predict the severity of MIS-C.

Table (1): Sociodemographic data

Variants		Group A (n=47)	Group B (n=24)	P-value
Age (year)	Mean ± SD	7.3±2.9	8.9±3.1	0.038*
Age groups (year): **<5** **5–10** **>10–15** **>15**	N (%)	 14(29.8%) 19(40.4%) 13 (27.7%) 1 (2.12%)	 1(4.1%)) 11(45.8%) 10 (41.6%) 1(4.1%))	 0.43
Gender: **Male** **Female**	N (%)	 33 (70.2%) 14(29.8%)	 16(66.7%) 8 (33.3%)	 0.43
SARS-CoV-2 infection: Positive PCR (%) Not detected (%) No data (%)	N (%)	 5(10.6%) 8 (17.1) 34(72.3%)	 8 (33.3%) 0 (0%) 16(66.7%)	 0.085
COVID contact: Positive (%) Negative (%) No data (%)	N (%)	 24 (51%) 19(40.4%) 4 (8.5%)	 7 (29.2%) 15 (62.5%) 2 (8.3%)	 0.24
Duration from contact to first MIS-C symptoms (day):	Median, IQR	5.2 (3.1–7.3)	4.2 (3–5.4)	0.28
Admitted to PICU:	N (%)	19(40.4%)	16(66.7%))	0.047*
LOS (day):	Median, IQR	9.2 (7.7–10.7)	15.1 (10.7–19.5)	<0.001*
LOS in PICU (day):	Median, IQR	2.3 (1.25–3.35)	3.35(1.6–5.1)	0.54

N, number; IQR, interquartile range; SD, SD: standard deviation; *: Significant.

Table (2): Symptoms and clinical features in both groups

Variants		Group A (n=47)	Group B (n=24)	P-value
Vomiting	N (%)	23 (49%)	13 (54.2%)	0.54
Abdominal pain	N (%)	24 (51%)	17 (70.8%)	0.31
Diarrhea	N (%)	15 (31.9%)	11(45.8%)	0.41
Obstipation	N (%)	3 (6.4%)	1(4.1%)	0.64
Lymphadenopathy	N (%)	8(17%)	4 (16.7%)	0.91
Conjunctivitis,	N (%)	24 (51%)	15 (62.5%)	0.62
Rash	N (%)	34(72.3%)	16(66.7%)	0.39
Sole desquamation	N (%)	5(10.6%)	2(8.3%)	0.76
Raspberry lips, tongue	N (%)	19(40.4%)	11(45.8%)	0.81
Pneumonia	N (%)	10 (21.3%)	10 (41.6%)	0.23
Pleuritis	N (%)	5(10.6%)	4 (16.7%)	0.67
Bronchitis	N (%)	5(10.6%)	9 (37.5%)	0.06
Coronary injury	N (%)	1 (2.2%)	7 (29.2%)	0.21
Other symptoms (neurological, nephrological, and articular)	N (%)	9 (19.15%)	7 (29.2%)	0.34
Shock	N (%)	1 (2.12%)	7 (29.2%)	0.037*

N, number; IQR, interquartile range; SD, SD: standard deviation; *: Significant.

Table (3): Laboratory test results in both groups

Variants		Group A (n=47)	Group B (n=24)	P-Value
WBC, 10^9 cells/L	Median, IQR	9.6 (7.7–10.9)	12.4 (8.7–15.7)	0.068
Neu ($\times10^9$ cells/L)	Median, IQR	6.7 (5.3–8.1)	10.7(7.3–13.1)	0.012*
Lymph ($\times10^9$ cells/L)	Median, IQR	1.7 (1.2–2.2)	1.1 (0.65–1.45)	0.24
Hgb (g/L)	Median, IQR	113 (110–116)	119 (111–127)	0.35
PLT ($\times10^9$ cells/L)	Median, IQR	231 (171–291)	217 (126–308)	0.63
MPV (fl)	Median, IQR	8 (7.5–8.5)	8.5 (7.9–9.1)	0.187
PCT (%)	Median, IQR	0.17 (013–0.21)	0.22 (0.14–0.30)	0.423
PDW (%)	Median, IQR	16.3 (15.12–17.18)	16.7 (16.3- 17.1)	0.14
CRP (mg/L)	Median, IQR	132 (101–163)	182(133–231)	0.022*
ESR (mm/h)	Median, IQR	29 (19–39)	34 (21–47)	0.335
PCT (ng/ml)	Median, IQR	4.6(1.05–8.15)	12.1 (4.6–17.6)	0.082
PT (%)	Median, IQR	29 (22–35)	36 (23–49)	0.24
APTT (s)	Median, IQR	34 (29–45)	37.5 (32.7–42.3)	0.38
INR	Median, IQR	1.12(1.03–1.21)	1.2 (1.1–1.3)	0.34
D-dimers (ng/ml)	Median, IQR	3.1 (2.1–4.1)	4.9 (3.3–6.5)	0.031*
Fibrinogen (g/L)	Median, IQR	3.3 (2.33–4.27)	4.65 (3.23–6.07)	0.083
Troponin I (ng/ml)	Median, IQR	0.12 (0.01–0.23)	4.3 (1.2–7.4)	<0.001*
Pro-BNP	Median, IQR	82 (41–121)	465 (28–902)	<0.001*
Ferritin (mcg/L)	Median, IQR	146(98–194)	397 (181–613)	<0.001*
LDH (U/L)	Median, IQR	171(121–221)	271(182–360)	<0.001*
Albumin (g/L)	Median, IQR	18.7(12.1–23.3)	19.9 (11.8-29)	0.71
Creatine (µmol/L)	Median, IQR	38 (31–45)	45 (32–58)	0.33
Urea (U/L)	Median, IQR	3.6 (3.1–4.1)	4.95 (3.42–6.48)	0.026*
ALT (IU/L)	Median, IQR	33(22–44)	31 (22- 40)	0.46
AST (U/L)	Median, IQR	38 (30-46)	41.5 (33–50)	0.75
GGT (IU/L)	Median, IQR	30.5 (15.2–45.8)	37 (17–57)	0.12

N, number; IQR, interquartile range; SD, SD: standard deviation; *: Significant.

Table (4): Predictors of MIS-C severity

Laboratory parameters	Cutoff value	Youden's index	P-value
Laboratory parameters Predictors			
CRP + Neu	0.834	0.523	<0.001
CRP + Neu + PCT	0.768	0.494	0.006
CRP + Neu + PCT + DD	0.623	0.47	<0.001
CRP + Neu + PCT + DD + FB	0.552	0.614	<0.001
CRP + Neu + PCT + DD + FB + pro-BNP	0.774	0.69	<0.001
CRP + Neu + PCT + DD + FB + pro-BNP + FR	0.807	0.773	<0.001
CRP + Neu + PCT + DD + FB + pro-BNP + FR + LDH	0.613	0.861	<0.001
CRP + Neu + PCT + DD + FB + pro-BNP + FR + LDH + U	0.500	1	<0.001
CRP + Neu + Lymph + FR + pro-BNP + PCT	0.836	0.75	<0.001
Platelet marker combinations in MIS-C severity prediction.			
PLT + MPV + PCT + PDW	0.716	0.725	<0.001
PLT + MPV + PCT + CRP	0.810	0.615	<0.001
PLT + MPV + PCT + PCT	0.687	0.773	<0.001
PLT + MPV + PCT + PDW + pro-BNP	0.667	0.71	<0.001
PLT + MPV + PCT + PDW + FR	0.759	0.87	<0.001
PLT + MPV + PCT + PDW + LDH	0.642	0.83	<0.001
PLT + MPV + PCT + PDW + U	0.788	0.75	<0.001
PLT + MPV + PCT + PDW + FB	0.616	0.697	<0.001
PLT + MPV + PCT + PDW + LDH + FR	0.567	0.814	<0.001
PLT + MPV + PCT + PDW + LDH + pro-BNP	0.500	1	<0.001

DISCUSSION

In extreme situations, MIS-C, a disorder brought on by cytokine storms, needs to be treated quickly and aggressively. 71 children with MIS-C who had no prior comorbidities were admitted and treated for this study. More than half of the children who presented with a range of symptoms needed PICU treatment. The combination of PLT indices has the capacity to predict MIS-C severity, even when a single PLT biomarker was not significant.

The transmission of several SARS-CoV-2 viral strains affects the risk of MIS-C. Numerous investigations have revealed that [14]. Our analysis shows that after the first wave of COVID-19, 51% and 29.2% of the MIS-C cases in groups A and B, respectively, appeared. Prior to establishing MIS-C, the majority of our patients did perform PCR testing for SARS-CoV-2. We therefore depended on epidemiological anamnesis of the close contacts verified COVID-19 disease. The majority of prior investigations have documented MIS-C outbreaks, and the median duration to beginning was around 4 weeks (27.5 days) [15,16].

Fever, severe systemic inflammation, hypotension, and heart failure are the hallmarks of MIS-C. According to a recent research, the condition's severity can be mild or may present with shock [17].

The current study's age of approximately 8 years and male gender predominance were consistent with the findings of the majority of MIS-C investigations [18,19]. Additionally, rash, gastrointestinal problems, and conjunctivitis were the most common clinical signs of MIS-C. Overall, all clinical indications were in line with case reports of cardiovascular involvement, rash, and prominent stomach symptoms from earlier MIS-C studies [20,21]. According to a variety of data, between 30% and 60% of patients arrive in the PICU with signs of shock and require therapy [22]. In our instance, eight kids exhibited signs of shock.

In this investigation, the **Brisca *et al.*** [13] suggested composite severity score (also known as GSATool). The researchers used an intensive therapy approach and the multistep early risk evaluation (GSATool) to show that. With the exception of evidence of shock ($p = 0.037$), the majority of our examined MIS-C patients were in classes I and II, and most of the cases did not differ in clinical presentation.

PICU admission is important in detecting the MIS-C severity. According to systematic evaluations by **Hoste *et al.*** [10] and **Radia *et al.*** [17]; 56.3%–77% of MIS-C patients were in shock, and roughly 68%–74% of them require therapy in the intensive care unit. The necessity for inotropic medication was the primary reason for the transfer of another group of patients to the PICU as their condition worsened over time [23].

According to the GSATool, children in the current study who had more PICU treatment had higher scores, and this difference was statistically significant. It's interesting to note that 40.4% of Group A patients were admitted to the PICU even though they didn't require respiratory or cardiovascular support. This shows that doctor-perceived referrals to the PICU may be influenced by the lack of prognostic factors in the early stages.

In a retrospective analysis, **Kaidar *et al.*** [23] observed similar findings, with 1/3 of the cases managed in the PICU without the use of vasopressors or inotropic drugs. According to the researchers' hypothesis, the best outcome measure for MIS-C severity might not be PICU hospitalization.

However, the median hospital stay in the majority of the studies is less than 10 days, indicating that recovery from the severe illness is very quick [24,25]. In line with the current findings, the PICU had a short length of stay (median of 3 days), and the hospital's overall LOS was a median of 2 weeks. The severity group and PICU admission had the biggest effects on the overall length of stay.

All patients completed a biomarker screening panel in accordance with current guidelines for the range of presentation indicators of MIS-C. High neutrophil counts and elevated levels of CRP, DD, FR, and pro-BNP were identified in the current investigation as risk factors for severe MIS-C.

Abrams *et al.* [16] reported that the probabilities of severe MIS-C increased two times with higher CRP, FR, and DD levels, and 5 times in high pro-BNP.

Kaidar *et al.* [23] found that when pro-BNP levels exceeded 8,000 ng/L, severity risk increased by 8.4 times. Numerous investigations reported cardiac biomarkers in the early detection of MIS-C in young COVID-19 [26,27]. A rise in troponin I was more specific than a pro-BNP value of 282 ng/L or higher alone, although it was less sensitive (60%) according to **Gullu *et al.*** [28].

Hb%, lymphocyte, and PLT counts did not correlate with the various severity groups in the current investigation, contrary to previous reports [16,24]. The current study was undoubtedly small, and other studies have looked at a larger number of people.

However, in contrast to younger patients, we found that older patients in our study had more severe MIS-C characteristics. As anticipated, the severity of MIS-C could be predicted by all of the standard inflammatory markers used for diagnosis.

The MIS-C diagnostic panel appears to offer a more accurate diagnosis when all of the biomarkers are combined. Nevertheless, MIS-C biomarkers are not publicly accessible in small regional hospitals or primary care settings [29]. Therefore, a more straightforward and accessible prediction method would allow for the timely prescription of a particular treatment.

The need for novel biomarkers has raised interest in PLTs' function [11]. **Barrett *et al.*** [30] discovered that in SARS-CoV-2 infection, immaturity, greater size, and reticulated PLT count were linked to more severe illness.

Alkan *et al.* [19] demonstrated that MPV was higher in the severe cases in analysis of 64 MIS-C patients. Other metrics, such as PCT and PDW, were unable to distinguish between severity groups, nevertheless. None of the PLT indices by itself showed any differences between the severity groups in the current investigation. Patients with more severe illness had greater MPV and PDW, although the difference was not statistically significant. Remarkably, a combination of PLT, MPV, PCT, and PDW can predict MIS-C.

CONCLUSION

Our investigation highlights the important role of PLTs in the pathophysiology and severity of MIS-C by describing clinical and laboratory markers linked to MIS-C severity. It may be possible to anticipate the severity of MIS-C by using PLTs and PLT index measures in standard laboratory procedures.

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