Mortality and its correlation with diagnostic tests and treatment modalities in multisystem inflammatory syndrome in children admitted in tertiary care hospital of North India

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ABSTRACT

Background: The present study aimed to describe mortality and its correlation with diagnostic tests and treatment modalities among children admitted as a case multisystem inflammatory syndrome in children (MIS-C) in Indira Gandhi Medical College, Shimla. **Materials and Methods:** We conducted a cross-sectional study for MIS-C from January to July 2021, in the pediatric ward of a tertiary care hospital in North India. All children admitted with the diagnosis of MIS-C were included in the study. Data regarding sociodemographic factors and mortality were extracted and analyzed using Epi Info V7 software. **Results:** In the present study, a total of 31 children admitted as a case of MIS-C were included in the study. Of these, 23 (74.2%) were discharged after full recovery, 5 (16.1%) died during treatment, and 3 (9.7%) left the hospital against medical advice. Children presenting with severe illness, acidosis, azotemia, Hb<10gm%, Leukocytosis, abnormal RFTs, lipid profile, thrombocytopenia, deranged coagulogram, abnormal ECG, required pediatric intensive care, inotropic support, IVIG, Aspirin, LMWH, had a shorter hospital stay and a higher mortality. Statistical significance was seen with deranged renal function, thrombocytopenia, abnormal ECG, use of LMWH, and respiratory support. **Conclusion:** Mortality was significantly higher in children having shorter hospital stay <1 week, presenting with severe illness and deranged RFTs, thrombocytopenia, abnormal ECG, and requiring respiratory support, ventilatory support, and taking LMWH.

Key words: *Correlation, Diagnostic tests, Mortality, Multisystem inflammatory syndrome in children, Treatment modalities*

Thousands of cases of children and adolescents with hyperinflammatory responses such as Kawasaki disease have been reported across the world amid the coronavirus disease 2019 (COVID-19) pandemic, leading to the coining of the new term COVID-19-associated MIS-C [1].

Children with MIS-C present with fever and inflammation of various organ systems and are confirmed by laboratory investigations, such as blood and urine tests for clinical assessment and abnormal inflammatory markers. Once the diagnosis of MIS-C is confirmed, children need to be followed up with laboratory tests to assess the progression of the illness by assessing inflammatory markers, coagulation profile, liver, renal, cardiac function, and other aspects [2,3].

Detailed workup for inflammatory markers, cardiac imaging, and serological testing in cases compatible with MIS-C, with negative RT-PCR test, is warranted, be appropriately managed and followed up, and continuous upgradation of guidelines regarding the management of MIS-C cases is required [4].

Physicians treat the case using intra venous immunoglobulins, steroids, and other anti-inflammatory drugs to reduce inflammation and protect the heart, kidneys, and other organ systems from damage [5,6].

Children with MIS-C need in-hospital care and some children even require intensive care. Characterizing the epidemiology, spectrum of illness, clinical course, treatments, and prognosis of MIS-C cases are a key for reducing morbidity and mortality [7,8].

There is a paucity of data regarding mortality and its correlation with diagnostic tests and treatment modalities of MIS-C in this hilly region of North India. Against this backdrop, this study was conducted to describe mortality and its correlation with diagnostic tests and treatment modalities among children admitted as a case of MIS-C in a tertiary teaching hospital in North India.

Aims and Objectives

The aims of the study were to evaluate the mortality and its correlation with diagnostic tests and treatment modalities associated with MIS-C.

MATERIALS AND METHODS

We conducted a ross-sectional, descriptive, and institution-based study, from January 2021 to July 2021, in the department

of pediatrics, at a tertiary care hospital in North India (Indira Gandhi Medical College, Shimla, Himachal Pradesh). All children diagnosed and admitted as cases of MIS-C, as per the WHO operational definition was included in the study. Ethical clearance was obtained from the concerned authorities of the institution. Data were collected from the record files of admitted children, compiled and entered into MS Excel, and analyzed using appropriate statistical tools in software Epi Info V7 by applying the appropriate statistical tests in terms of frequencies and percentage.

Operational Definition for a Case of MIS-C [8]

Children and adolescents 0–19 years of age with fever >3 days AND two of the following:

a. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet).
b. Hypotension or shock.
c. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP),
d. Evidence of coagulopathy (by PT, PTT, and elevated D-dimers).
e. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test, or serology positive) or likely contact with patients with COVID-19.

RESULTS

During the study period, 31 children were diagnosed and admitted as MIS-C in the pediatric ward between January 2021 and July 2021.

The mean age of the children diagnosed with MIS-C was 7.12±4.78 years. About 38.7% (n=12) were in the age group of 5–10 years, 32.3% (n=10) 6–10 years, 25.8% (n=8) 11–15 years, and 3.2% (n=1) 15–19 years age group. Of them, 51.6% (n=16) were male while 48.4% (n=15) were female. About 93.5% (n=29) were from rural area while 6.5% (n=2) from urban area.

The mean duration of hospital stay was 9.19±5.24 days. About 41.9% (n=13) had a hospital stay of <7 days, 38.7% (n=12) for 1–2 weeks, and 19.4% (n=6) for ≥2 weeks. Of the 31 children, 23 (74.2%) were discharged after full recovery, 5 (16.1%) died during treatment, and 3 (9.7%) left the hospital against medical advice (LAMA) (Table 1).

Mortality was higher in children having a hospital stay <1 week, but it is not statistically significant (Table 2).

Acidosis, azotemia, Hb <10 g%, leukocytosis, neutrophilic predominance, higher creatine and urea levels, deranged lipid profile, dyselectrolytemia, and abnormal glycemic levels were associated with all the children who died and had a shorter hospital stay but there is no statistical difference except for deranged urea and creatinine levels (Table 3), suggesting that children presenting with more severe laboratory derangements and had a shorter hospital stays and higher mortality rates.

Mortality was higher in children with thrombocytopenia and a deranged coagulation profile, but not significant, other than with thrombocytopenia (Table 4).

Children having markedly raised inflammatory markers such as higher levels of erythrocyte sedimentation rate (ESR), ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), and high D-dimer were associated with greater mortality, but it was not statistically significant (Table 5).

In this study, mortality was greater in children having abnormal ECG, despite normal echo and troponin I levels, abnormal ECG finding was statistically significant (Table 6).

Children requiring pediatric intensive care, ventilatory support for pARDS, shock requiring inotropic support, deranged coagulogram, requiring treatment with methylprednisolone, intravenous immunoglobulin (IVIG), aspirin, and low-molecular-weight heparin (LMWH) were associated with higher mortality (Table 7).

DISCUSSION

A high index of suspicion for MIS-C in severe critical cases in this time of pandemic is the need of the hour [9].

Table 1: Duration of stay and outcome of MIS-C patients

Characteristics	Frequency	Percentage
Duration of stay		
≤1 week	13	41.9
1–2 weeks	12	38.7
≥2 weeks	6	19.4
Mean duration of stay	9.19±5.24 days	
Outcome		
Discharged	23	74.2
Death	5	16.1
LAMA (left against medical advice)	3	9.7
Total	31	100.0

Table 2: Association of the duration of stay with mortality

Hospital Stay	Outcome		Total	p-value
	Discharge/LAMA	Death		
Duration of stay				
<1 week				
Count	10	3	13	0.341
%	76.9%	23.1%	100.0%	
>1 week				
Count	16	2	18	
%	88.9%	11.1%	100.0%	

Table 3: Association of various biochemical tests with mortality

Investigations	Outcome		Total	p-value
	Discharge/ LAMA	Death		
Acidosis				
No				
Count	11	1	12	0.342
%	91.7%	8.3%	100.0%	
Yes				
Count	15	4	19	
%	78.9%	21.1%	100.0%	
Azotemia				
No				
Count	9	1	10	0.472
%	90.0%	10.0%	100.0%	
Yes				
Count	17	4	21	
%	81.0%	19.0%	100.0%	
Hemoglobin				
>10 g%				
Count	7	1	8	0.888
%	87.5%	12.5%	100.0%	
<10 g%				
Count	19	4	23	
%	82.6%	17.4%	100.0%	
Total leukocyte count				
Normal for age				
Count	13	0	13	0.116
%	100.0%	0.0%	100.0%	
Increase for age				
Count	13	5	18	
%	72.2%	27.8%	100.0%	
Neutrophilic %				
Normal for age				
Count	5	0	5	0.564
%	100.0%	0.0%	100.0%	
Increase for age				
Count	21	5	26	
%	80.8%	19.2%	100.0%	
Creatine				
Normal				
Count	23	2	25	0.012
%	92.0%	8.0%	100.0%	
High				
Count	3	3	6	
%	50.0%	50.0%	100.0%	
Urea				
Normal				
Count	23	2	25	0.012
%	92.0%	8.0%	100.0%	
High				
Count	3	3	6	
%	50.0%	50.0%	100.0%	

(Contd...)

Table 3: ***(Continued)***

Investigations	Outcome		Total	p-value
	Discharge/ LAMA	Death		
Lipid profile				
Normal				
Count	9	0	9	0.302
%	100.0%	0.0%	100.0%	
High				
Count	17	5	22	
%			100.0%	
Potassium				
Normal				
Count	24	4	28	0.376
%	85.7%	14.3%	100.0%	
Deranged				
Count	2	1	3	
%	66.7%	33.3%	100.0%	
Sodium				
Normal				
Count	24	4	28	0.367
%	85.7%	14.3%	100.0%	
Deranged				
Count	2	1	3	
%	66.7%	33.3%	100.0%	
Glycemic control				
Normal				
Count	25	5	30	0.839
%	83.3%	16.7%	100.0%	
Deranged				
Count	1	0	1	
%	100.0%	0.0%	100.0%	
Total				
Count	26	5	31	
%	83.9%	16.1%	100.0%	

Table 4: Association of various hematological parameters with mortality

Investigations	Outcome		Total	p-value
	Discharge/LAMA	Death		
Platelets				
Normal				
Count	8	0	8	0.003
%	100.0%	0.0%	100.0%	
Low				
Count	18	5	23	
%	78.3%	21.7%	100.0%	
Prothrombin time				
Normal				
Count	11	0	11	0.363
%	100.0%	0.0%	100.0%	
High				
Count	17	5	22	

(Contd...)

Table 4: *(Continued)*

Investigations	Outcome		Total	p-value
	Discharge/LAMA	Death		
%	77.3%	22.7%	100.0%	
INR				
Normal				
Count	16	2	18	0.506
%	88.9%	11.1%	100.0%	
High				
Count	12	3	15	
%	80.0%	20.0%	100.0%	
Activated partial thromboplastin time				
Normal				
Count	15	2	17	0.639
%	88.2%	11.8%	100.0%	
High				
Count	11	3	14	
%	78.6%	21.4%	100.0%	
Total				
Count	26	5	31	
%	83.9%	16.1%	100.0%	

Table 5: Association of various inflammatory markers with mortality

Investigations	Outcome		Total	p-value
	Discharge/ LAMA	Death		
Absolute neutrophilic count				
Normal for age				
Count	16	3	19	0.647
%	84.2%	15.8%	100.0%	
Increase for age				
Count	10	2	12	
%	83.3%	16.7%	100.0%	
ESR				
Normal				
Count	2	1	3	0.741
%	66.7%	33.3%	100.0%	
High				
Count	24	4	28	
%	85.7%	14.3%	100.0%	
Ferritin				
Normal				
Count	3	0	3	0.206
%	100.0%	0.0%	100.0%	
High				
Count	23	5	28	
%	82.1%	17.9%	100.0%	
LDH				
Normal				
Count	3	0	3	0.206
%	100.0%	0.0%	100.0%	
High				
Count	23	5	28	
%	82.1%	17.9%	100.0%	
D-dimer				
Normal				
Count	5	0	5	0.363
%	100.0%	0.0%	100.0%	
High				
Count	21	5	26	
%	80.8%	19.2%	100.0%	
CRP				
Normal				
Count	1	0	1	0.354
%	100.0%	0.0%	100.0%	
High				
Count	25	5	30	
%	83.3%	16.7%	100.0%	
Total				
Count	26	5	31	
%	83.9%	16.1%	100.0%	

Table 6: Association of various cardiac markers with mortality

Investigations	Outcome		Total	p-value
	Discharge/ LAMA	Death		
Troponin-1				
Normal				
Count	22	3	25	0.498
%	88.0%	12.0%	100.0%	
High				
Count	4	2	6	
%	66.7%	33.3%	100.0%	
ECG				
Normal				
Count	23	2	25	0.014
%	92.0%	8.0%	100.0%	
Abnormal				
Count	3	3	6	
%	50.0%	50.0%	100.0%	
Echo				
Normal				
Count	20	3	23	0.445
%	87.0%	13.0%	100.0%	
Abnormal				
Count	6	2	8	
%	75.0%	25.0%	100.0%	
Total				
Count	26	5	31	
%	83.9%	16.1%	100.0%	

Table 7: Association of various biochemical tests with mortality

Treatment	Outcome		Total	p-value
	Discharged/ LAMA	Death		
Respiratory support				
Yes				
Count	11	5	16	0.026
%	68.8%	31.2%	100.0%	
No				
Count	15	0	15	
%	100.0%	0.0%	100.0%	
Ventilatory support				
Yes				
Count	21	3	24	0.312
%	87.5%	12.5%	100.0%	
No				
Count	5	2	7	
%	71.4%	28.6%	100.0%	
Inotropic support				
Yes				
Count	13	5	18	0.050
%	72.2%	27.8%	100.0%	
No				
Count	13	0	13	
%	100.0%	0.0%	100.0%	
IVIG				
Yes				
Count	19	5	24	0.250
%	79.2%	20.8%	100.0%	
No				
Count	7	0	7	
%	100.0%	0.0%	100.0%	
Methylprednisolone				
Normal				
Count	8	2	10	0.218
%	80.0%	20.0%	100.0%	
Low/High				
Count	18	3	21	
%	85.7%	14.3%	100.0%	
LMWH				
Yes				
Count	12	5	17	0.036
%	70.6%	29.4%	100.0%	
No				
Count	14	0	14	
%	100.0%	0.0%	100.0%	
Aspirin				
Yes				
Count	18	5	23	0.198
%	78.3%	21.7%	100.0%	
No				
Count	8	0	8	
%	100.0%	0.0%	100.0%	

The mean age of the children diagnosed with MIS-C was 7.12±4.78 years. About 38.7% (n=12) were in the age group of 5–10 years, 32.3% (n=10) 6–10 years, 25.8% (n=8) 11–15 years, and 3.2% (n=1) 15–19 years age group. Among them, 51.6% were male while 48.4% were female. About 93.5% were from the rural area while 6.5% were from urban areas, showing that the COVID-19 pandemic and its complicating illness have pervaded to even the most rural backgrounds of this hilly state, even areas with poor connectivity. Similar types of results have been observed in the studies done by Hoste *et al*. [10], Fouriki *et al*. [11], Leora *et al*. [12], and Ahmed *et al*. [13], but none of the studies have studied the rural/urban disparity of the MIS-C cases.

Out of 31 children of MIS-C, 23 (74.2%) were discharged after full recovery, 5 (16.1%) died during treatment, while 3 (9.7%) left the hospital against medical advice. Mortality was higher in children with hospital stay <1 week but was not statistically significant.

Acidosis, azotemia, Hb <10 g%, leukocytosis, neutrophilic predominance, higher creatine and urea, deranged lipid profile, dyselectrolytemia, and abnormal glycemic levels were associated with higher mortality, but were not significant, except for deranged renal function. Likewise, mortality was higher in children with thrombocytopenia and a deranged coagulation profile, but only thrombocytopenia was significant.

Markedly raised ESR, ferritin, LDH, D-dimer, and CRP were also associated with greater mortality, but no statistical difference. Mortality was more in children having abnormal ECG findings and it was statistically significant.

Children requiring pediatric intensive care, ventilatory support for pARDS, shock requiring inotropic support, deranged coagulogram, necessitating treatment with methylprednisolone, IVIG, aspirin, and low-molecular-weight heparin were associated with higher mortality. Hoste *et al*. [10] and Fouriki *et al*. [11] showed similar findings, but with a lower mortality rate as compared to our study, Leora *et al*. [12] also corroborated our findings of greater mortality in patients with deranged coagulogram and higher levels of inflammatory markers, but the mortality was quite low compared to our center. Ahmed *et al*. [13] and Kwak *et al*. [1] also had similar findings in their studies.

This study signifies that MIS-C children who had a hospital stay of <7 days and also had elevated creatinine and urea, thrombocytopenia, abnormal ECG findings, requiring ventilatory and inotropic support, and receiving IVIG and LMWH among other treatment modalities had a severe illness at presentation, and they are significant predictors of mortality.

Since our study was carried out in a resource-limited setting, in the hilly terrain with poor access to health-care resources, it could be that patients presented with greater severity of illness, and thus, we had a higher mortality rate as compared to studies in developed countries.

More detailed workup for inflammatory markers, imaging in required cases, and immunoglobulin testing in cases compatible with MIS-C presenting late with negative RTPCR are required

to understand and form guidelines regarding the management of MIS-C cases [4,7,8].

CONCLUSION

Mortality was significantly more in children having shorter hospital stays <1 week, presenting with severe illness and deranged RFTs, thrombocytopenia, abnormal ECG, and requiring respiratory support, ventilatory support, and taking LMWH.

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