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Original Article

Paediatrics Section

Role of Inflammatory Markers and Clinical Correlate in Children Infected with the Novel SARS-CoV-2: A Prospective Observational Study

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ABSTRACT

Introduction: Inflammatory markers have been used as predictors of adverse outcomes in adults with Coronavirus Disease-2019 (COVID-19) infection. Children mostly have mild infections and raised inflammatory markers have been reported only with severe COVID-19 or Multisystem Inflammatory Disorder (MIS-C). Studies in children showing the role of inflammatory markers in disease prognosis are few, and findings are not conclusive.

Aim: To find out correlation, if any, between the inflammatory markers {Interleukin-6 (IL-6), C-reactive Protein (CRP), procalcitonin, Pro-B-type natriuretic Peptide (Pro-BNP), ferritin, D-dimer} with clinical presentation, prognosis, and outcome in children with acute COVID-19.

Materials and Methods: The hospital-based, prospective observational study was conducted at a tertiary care COVID-19 Paediatric Intensive Care Unit {PICU (Vardhaman Medical College and Hospital, New Delhi)}, Northern India, between September 2020 and December 2020. All children aged less than 12 years, with a positive COVID-19 report were enrolled and investigated. Data was collected for clinical presentation, severity, treatment and outcome. The following variables were recorded: Complete Blood Count (CBC), Kidney Function Test (KFT) and Liver function Test (LFT), Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC), Neutrophil-lymphocyte Ratio (NLR), Platelet Count (PLT), C-reactive Protein (CRP), Procalcitonin (PCT), serum ferritin, Lactate Dehydrogenase (LDH), fibrinogen, and Erythrocyte Sedimentation Rate (ESR) and ProBNP. Coagulation parameters like Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalised Ration (INR), D-dimer were taken. Data was analysed using Statistical Package for the Social Sciences (SPSS) software version 21.0.

Results: A total of 35 children were admitted during the study period. Seventeen children met the criteria for severe disease. Seven children met the criteria for MIS-C. Children presenting with conjunctivitis (n=3) were more likely to have signs of peripheral inflammation hypotension (n=4), tachycardia (n=6), and raised IL-6 levels (pg/mL) as well as the need for inotropic support. IL-6 values were higher in children (Mean±SD=182.47±149.83). Median IL-6 value 199.8 (96.17-275.24) was highest in children with CRP <10 mg/dL (p-value <0.01). Children with raised D-dimer (Mean±SD=1881.94±1265.66 mg/dL) had a longer duration of stay (p-value=0.031).

Conclusion: The study didn't find any correlation between inflammatory markers with clinical presentation and the outcome of COVID-19 infection in children.

Keywords: Coronavirus disease-2019, D-dimer, Interleukin-6, Remdesivir, Severe acute respiratory distress syndrome coronavirus 2

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections, initially thought to be a respiratory illness, causes a spectrum of multisystem involvement and severity (defined by respiratory failure, septic shock, and multiple organ dysfunction) [1]. The overproduction of cytokines caused by aberrant immune activation is known as a cytokine storm and is recognised as a significant cause of disease progression and eventual death [2,3]. The role of Interleukin-6 (IL-6) and, to some extent, IL-10 has been reported as a predictor of COVID-19 severity. Strategies to reduce hypercytokinaemia have shown variable results in patients with severe COVID-19. In this respect, IL-6 inhibitors (tocilizumab), anti-Tumour Necrosis Factor (TNF) α (adalimumab), and anti-IL-1beta (anakinra) have been tried clinically [4].

In the paediatric population, most cases of COVID-19 are reported to have a benign course except few with organ system involvement coinciding with a surge of inflammatory markers specifically termed Multisystem Inflammatory Syndrome (MIS-C) [5-7]. Information on the role of inflammatory markers in paediatric COVID-19 is lacking. Most studies of COVID-19 in the paediatric population have focused on clinical manifestations only. There is limited understanding of the full spectrum of disease in children. Suppression of adaptive immunity and hyperimmune response are seen in adults with severe COVID-19 infection (reflected by inflammatory markers). Although children have been treated with anti-inflammatory treatment, including parenteral immunoglobulin and steroids, high mortality is associated with the condition. It is essential to understand this syndrome, its risk factors, and its causality to delineate treatment alternatives better. There is paucity of data regarding cytokine profiles in Indian patients with moderate to severe COVID-19 age group [8-10]. The studies have reported the role of inflammatory markers in multisystem inflammatory syndrome associated with COVID but their role in acute COVID-19 infection in children is not well documented. Most data or reports are from North America and Europe, which report COVID-19 to be a milder illness in children so the full spectrum of disease is unknown in low-income to middle-income countries [11].

The aim of the present study was to find out correlation, if any, between the inflammatory markers (IL-6, CRP, procalcitonin, Pro-BNP, ferritin, D-dimer) with clinical presentation, prognosis, and outcome in children with acute COVID-19.

MATERIALS AND METHODS

This hospital-based, prospective observational study was conducted at a tertiary care COVID-19 Paediatric Intensive Care Unit {PICU (Vardhaman Medical College and Hospital, New Delhi)}, Northern India, between September 2020 and December 2020. Ethical approval was obtained from the Institutional Ethical Committee (S.No. IEC/VMMC/SJH/Project/2020-08/CC-42 dated 28-08-20).

Inclusion criteria: All children under or equal to 12 years infected with SARS-CoV-2 requiring admission between 1st September, 2020 to 31st December, 2020, were included in the study.

Exclusion criteria: Children with post COVID MIS-C or admitted for long COVID manifestation were excluded from the study.

Study Procedure

All children were positive for COVID-19 on nasopharyngeal swab Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test and Cycle Threshold (CT) value was documented for positive children. Severe disease was considered for children with positive RT-PCR or Rapid Antigen Test positive during the current illness, with clinical features of severity (hypotension/shock) and who had need for hospitalisation because of clinical condition. Clinical profile and laboratory investigations were documented for all the children. All participants were investigated with baseline Complete Blood Count (CBC), Kidney Function Test (KFT) and Liver Function Test (LFT), Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC), Neutrophil-Lymphocyte Ratio (NLR), Platelet Count (PLT), C-Reactive Protein (CRP), Procalcitonin (PCT), serum ferritin, Lactate Dehydrogenase (LDH), fibrinogen, Erythrocyte Sedimentation Rate (ESR) and PRO-B type Natriuretic Peptide (proBNP) and coagulation parameters like Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalised Ration (INR), D-dimer. Biochemical tests were done using institutional automated analysers and other markers by Enzyme-linked Immunosorbent Assay (ELISA) kit-based test in the Department of Haematology. Standard institutional protocol for management based on clinical and laboratory parameters was followed in all children. The severity classification was based on World Heath Organisation (WHO) (Clinical management of COVID-19: interim guidance, 27 May 2020) case definition. Clinical features and need for fluid resuscitation, electrolyte management, antibiotics, use of steroids (dexamethasone/methylprednisolone), Intravenous Immune Globulin (IVIG), remdesivir, oxygen support, mechanical ventilation requirement and duration of stay was documented for all the children.

STATISTICAL ANALYSIS

All data were recorded in a predesigned case recording form to facilitate entry in a Microsoft excel spreadsheet. Categorical variables were analysed by rate, ratio, proportion, and continuous variables by mean {Standard Deviation (SD)}, median {Inter Quartile Range (IQR)}. The association of variables was analysed by Student t-test, Chi-square test wherever applicable. For correlation between two continuous variables: Pearson's product-moment Correlation (if normally distributed) and Spearman Rank Correlation (if normally distributed) and Spearman Rank Correlation (if not normally distributed) were used. For correlation between a continuous and a categorical variable: Point Biserial Correlation was used. For correlation between two categorical variables: Cramer's V was used. Data was analysed using Statistical Package for the Social Sciences (SPSS) software version 21.0.

RESULTS

A total of 35 children were admitted during the study period. The mean age was 4.61±4 years, of which 11 (31.4%) participants were less than one year of age. Eighteen (51.4%) of the participants were males. Fever was the predominant symptom (97.1%) and rash was present in 8 (22.9%) children. Only a subset (12.9 %) of children were completely asymptomatic. Four children were found to have a culture positive bacterial infection in addition to COVID-19 infection. The summary of the clinical presentation is shown in [Table/Fig-1]. Four (11.4%) of the participants had respiratory distress. Three (8.6%) of the participants had a neurological presentation.

Presentation	n (%)
Fever	34 (97.1)
Rash	8 (22.9)
Conjunctivitis	3 (8.6)
Oral mucosal inflammation	1 (2.9)
Peripheral inflammation	2 (5.7)
Hypotension	4 (11.4)
Tachycardia	6 (17.1)
Reduced urine output	2 (5.7)
Chest pain	1 (2.9)
Cough/Tachypnea	5 (14.3)
Respiratory distress	4 (11.4)
Abdominal pain/Distension	5 (14.3)
Diarrhoea	3 (8.6)
Vomiting	6 (17.1)
Altered sensorium/Lethargy	2 (5.7)
Seizures	3 (8.6)
Reduced oral acceptance	14 (40.0)
Joint pain/Restriction/Swelling	2 (5.7)

[Table/Fig-1]: Summary of clinical presentation.

The details of lab values are shown in [Table/Fig-2]. The mean CT Values were 27.16±5.37. The mean IL-6 Levels (pg/mL) were 182.47±149.83. The mean CRP (mg/L) was 17.52±34.71 and 20 (73.5%) of the participants had CRP ≤10 mg/L. Twenty-six (74.3%) of the participants had ESR: >20 mm/hour and only 3 (8.6%) children were positive for Troponin-T. Nearly 23 percent of the children had serum fibrinogen >400 mg/dL, the majority 23 (65.7%) of the participants had serum procalcitonin ≤0.5 ng/mL and 25 (71.4%) of the participants had LDH >250 mg/dL. Six of the children had TLC <4000/cumm, mean±SD neutrophils was 48.64±19.73%. The mean±SD lymphocytes was 42.47±18.02%. The mean±SD eosinophils (%) was 2.23±1.87 and mean±SD NLR was 1.54±1.10. Eight (22.9%) of the participants had eosinopaenia. Seventeen (48.6%) children had thrombocytopenia. For 10 (28.6%) children urea >30 mg/dL at time of admission, mean±SD serum creatinine was 0.56±1.02 mg/dL and mean±SD sodium was 134.31±6.31 mEq/L.

The mean±SD SGPT (U/L) and SGOT were 66.15±83.54 and 47.29±47.80, respectively. The mean duration of stay was 12.20±5.85 days and 10 (28.6%) of the participants had duration of stay >14 Days. Seven (20%) children received IVIG. Seventeen (48.6%) of the participants were treated with steroids, four (11.4%) children received remdesivir and five (14.3%) participants required Inotrope support and mechanical ventilation

The correlation of laboratory values with clinical features and outcome is shown in [Table/Fig-3]. Children presenting with pain abdomen had raised serum urea levels compared to those without pain abdomen (p-value <0.05). Children presenting with respiratory distress were more likely to receive steroids, antiviral, and higher hemodynamic instability chances. Children who required mechanical ventilation were significantly associated (p-value <0.05) with the variable ALP (U/L): SGPT, total bilirubin (mg/dL). Children presenting with conjunctivitis were more likely to have signs of peripheral Inflammation, hypotension, tachycardia, raised IL-6 Levels (pg/mL), need for inotropes. Children with predominantly respiratory symptoms like cough/tachypnea had higher serum procalcitonin (ng/mL), LDH levels. Raised CRP was a surrogate for

Investigations	Mean±Standard deviation || Median (Inter quartile range) || Minimum-Maximum || n (%)
Cycle threshold values	27.16±5.37 || 26.97 (24.07-31.57) || 15.88 - 35.04
Interleukin-6 levels (pg/mL)	182.47±149.83 || 149.10 (68.71-254.97) || 1.98 - 666.00
C-reactive protein (mg/L)	17.52±34.71 || 4.40 (0.60-9.40) || 0.60 - 139.00
C-reactive protein	
≤10 mg/L	25 (73.5)
>10 mg/L	9 (26.5)
Erythrocyte sedimentation rate (mm/Hr)	34.37±17.68 || 36.00 (21.00-45.50) || 5.00 - 72.00
Erythrocyte sedimentation rate	
≤20 mm/Hr	9 (25.7)
>20 mm/Hr	26 (74.3)
N-terminal proB brain natriuretic peptide (pg/mL)	1441.46±4310.39 || 151.00 (100.00-802.50) || 0.19 - 25000.00
Trop-T (Positive)	3 (8.6)
D-dimer (ng/mL)	1881.94±1265.66 || 1639.00 (1012.00-2721.50) || 64.00 - 4614.00
D-dimer	
≤500 ng/mL	5 (14.3)
>500 ng/mL	30 (85.7)
Serum ferritin (ng/mL)	904.08±2924.17 || 314.00 (203.00-693.96) || 31.94 - 17637.00
Serum ferritin	
≤300 ng/mL	16 (45.7)
>300 ng/mL	19 (54.3)
Serum fibrinogen (mg/dL)	328.94±95.70 || 347.00 (278.50-392.00) || 111.00 - 548.00
Serum fibrinogen	
<200 mg/dL	4 (11.4)
200-400 mg/dL	23 (65.7)
>400 mg/dL	8 (22.9)
Serum procalcitonin (ng/mL)	10.83±21.93 || 0.10 (0.10-9.99) || 0.10 - 100.70
Serum procalcitonin	
≤0.5 ng/mL	23 (65.7)
>0.5 ng/mL	12 (34.3)
Lactate dehydrogenase (mg/dL)	380.80±185.95 || 336.00 (239.00-448.00) || 128.00 - 884.00
Lactate dehydrogenase	
≤250 mg/dL	10 (28.6)
>250 mg/dL	25 (71.4)
Haemoglobin (g/dL) haemoglobin	10.03±2.23 || 10.30 (8.70-11.25) || 5.80 - 15.00
<12 g/dL	28 (80.0)
≥12 g/dL	7 (20.0)
Total leucocyte count (cells/cu.mm)	11679.43±9478.00 || 9600.00 (5950.00-12900.00) || 2100.00 - 42000.00
Total leucocyte count	
<4000/cu.mm	6 (17.1)
4000-11000/cu.mm	19 (54.3)
>11000/cu.mm	10 (28.6)
Neutrophils (%)	48.64±19.73 || 52.00 (38.00-63.50) || 7.00 - 78.00
Lymphocytes (%)	42.47±18.02 || 38.00 (31.50-52.00) || 17.00 - 88.00
Monocytes (%)	6.38±4.65 || 5.50 (2.50-9.50) || 1.00 - 19.00
Eosinophils (%)	2.23±1.87 || 2.00 (1.00-3.10) || 0.00 - 6.00
Neutrophil-lymphocyte ratio	1.54±1.10 || 1.42 (0.76-2.03) || 0.08 - 4.59
Eosinopaenia (Present)	8 (22.9)
Platelets (/cu.mm)	198914.29±144513.86 || 150000.00 (94500.00-281500.00) || 18000.00 - 500000.00
Platelets	
Low	17 (48.6)
Within normal limits	18 (51.4)
Urea (mg/dL)	30.80±27.81 || 22.00 (14.00-34.00) || 3.00 - 111.00
Urea	
≤30 mg/dL	25 (71.4)
>30 mg/dL	10 (28.6)
Serum creatinine (mg/dL)	0.56±1.02 || 0.30 (0.20-0.40) || 0.10 - 5.60

Serum creatinine	
≤1 mg/dL	31 (88.6)
>1 mg/dL	4 (11.4)
Serum sodium (mEq/L)	134.31±6.31 || 134.00 (131.00-136.50) || 123.00 - 152.00
Serum sodium	
<135 mEq/L	23 (65.7)
≥135 mEq/L	12 (34.3)
Serum potassium (mEq/L)	4.43±0.80 || 4.30 (3.80-4.80) || 3.10 - 6.20
Serum potassium	
≤5.5 mEq/L	30 (85.7)
>5.5 mEq/L	5 (14.3)
Serum Glutamic-pyruvic Transaminase (SGPT) (U/L)	66.15±83.54 || 44.00 (30.50-68.00) || 11.40 - 489.00
Serum Glutamic-pyruvic Transaminase (SGPT)	
≤40 U/L	15 (42.9)
>40 U/L	20 (57.1)
Serum Glutamic-oxalacetic Transaminase (SGOT) (U/L)	47.29±47.80 || 31.00 (18.00-54.00) || 7.00 - 242.00
Serum Glutamic-oxalacetic Transaminase (SGOT)	
≤40 U/L	21 (60.0)
>40 U/L	14 (40.0)
Alkaline Phosphatase (ALP) (U/L)	156.83±101.78 || 132.00 (106.00-210.50) || 18.00 - 486.00
Total bilirubin (mg/dL)	0.69±0.79 || 0.40 (0.20-0.75) || 0.10 - 3.40
Total bilirubin	
≤1 mg/dL	28 (80.0)
>1 mg/dL	7 (20.0)

[Table/Fig-2]: Summary of investigations.

Variables	CT Values	IL-6 levels (pg/mL)	CRP (mg/L)	ESR (mm/Hr)	NT-PRO-BNP (pg/mL)	Troponin-T	D-dimer (ng/mL)	Serum ferritin (ng/mL)	Serum fibrinogen (mg/dL)	Serum procalcitonin (ng/mL)	LDH (mg/dL)
Age (Years)	0.489**	-0.334*	-0.128	-0.153	-0.361*	-0.166	-0.052	-0.294	0.084	-0.295	0.006
Gender	-0.309	-0.19	0.239	0.155	0.162	0	0.157	0.166	0.15	0.106	0.142
Fever	-0.178	0.135	0.083	0.24	0.041	0	-0.17	0.045	-0.035	-0.311	0.143
Rash	0.249	0.196	-0.104	0.145	0.346	0.544**	0.383	0.318	-0.127	0.262	0.062
Conjunctivitis	0.07	0.533	-0.125*	0.064	0.05	0.621*	-0.055	-0.04	-0.023	-0.064	0.127
Oral mucosal inflammation	0.049	0.562	-0.065	-0.171	-0.053	0	-0.078	-0.031	-0.164	-0.085	0.139
Peripheral inflammation	0.049	0.443	-0.095*	-0.069	0.028	0.326	-0.011	-0.033	0	-0.017	0.22***
Hypotension	0.207	0.317	0.008	0.003	-0.033	0.124	0.168	-0.073	-0.194	-0.177	-0.057
Tachycardia	0.318*	0.323	-0.058	0.051	-0.012	0.369	0.185	-0.072	-0.187	-0.16	0.207
Reduced urine output	-0.099	0.103)	-0.019	0.023	-0.058	0	0.013	-0.017	0.311	-0.122**	-0.106
Chest pain	0.178	-0.135	-0.083	-0.24	-0.041	0	0.17	-0.045	0.035	0.311	-0.143
Cough/Tachypnea	0.13	-0.058	-0.195*	-0.173	-0.121	0	0.153	-0.084	-0.054	0.282	-0.112
Respiratory distress	0.057	0.014	-0.16*	0.178	0.466	0.511*	0.128	0.482	-0.188	0.356	0.078
Abdominal pain/ Distension	0.164	-0.226	-0.088	0.305	0.05	0	-0.104	-0.084	0.218	-0.13	0.314
Diarrhoea	-0.077	-0.02	-0.051	0.157	0.082	0	-0.138	-0.043	0.396	-0.061	-0.105
Vomiting	0.171	-0.042	-0.193*	-0.049	-0.096	0	-0.044	-0.092	-0.199	-0.223**	-0.316*
Altered Sensorium/ Lethargy	-0.057	-0.202	0.284	0.284***	-0.078	0	-0.002	-0.02	-0.201	-0.122**	0.145
Seizures	-0.057	-0.134	0.195	0.281*	-0.01	0.213	0.036	-0.025	-0.069	-0.065	0.22
Reduced oral acceptance	-0.217	0.084	0.04	0.(093	-0.034	0	-0.026	-0.132	-0.178	-0.222	0.184
Joint pain/Restriction/ Swelling	-	0.156	0.002	0.214	-0.041	0	0.041	-0.065	0.061	0.075	0.023
Duration of stay >10 days	-0.294	-0.018	-0.14	0.286	0.228	0	0.258	0.186	0.146	0.286	0.11

[Table/Fig-3]: Correlation between laboratory parameters and clinical presentation.
CT: Cycle threshold; IL-6: Interleukin-6; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NT-PRO-BNP: N-terminal proB brain natriuretic peptide; LDH: Lactate Dehydrogenase.
*For correlation between two continuous variables: Pearson's product moment correlation (if normally distributed), and Spearman Rank correlation (if not normally distributed), **For correlation between a continuous and a categorical variable: Point Biserial correlation, ***For correlation between 2 categorical variables: Cramer's V

raised IL-6 Levels (pg/mL), CRP, and raised D-dimer values. Raised D-dimer level correlated with NLR and duration of stay. Children with elevated serum creatinine at presentation had a longer duration of stay. IL-6 was elevated in all children presenting with conjunctivitis. Thrombocytopenia was significantly associated with eosinopaenia.

DISCUSSION

This study didn't find a single laboratory parameter that correlated with illness severity at admission. IL-6 levels were very high irrespective of clinical presentation in children requiring admission. Elevated D-dimer, pain abdomen and deranged renal function were associated with a prolonged course of illness. CRP correlated with raised IL-6 and D-dimer levels. There was no death in the study group. High CRP values were reported by Graff K et al., as predictors of severe disease in children [12]. Elevated CRP has been identified as a risk factor for children requiring critical care. The present study study did not find CRP to be associated with severe illness or ventilatory or inotrope support [13-15].

In a study by Qiu H et al. from China, higher levels of procalcitonin and creatine kinase-MB (myocardial band), and increased D-dimer levels were reported in mild cases [16]. Laboratory data from eight severe paediatric patients from the same country showed normal or increased leucocyte count and high levels of CRP, PCT and LDH [17]. In a study of 67 children from the United States, admission to an ICU was associated with higher levels of CRP, procalcitonin, and pro-B-type natriuretic peptide and an increased platelet count [14]. Although values of inflammatory markers were high, they did not correlate significantly with the severity of the disease.

Henry BM et al., explained milder disease in children by the absence of lymphopaenia [18]. Procalcitonin level was increased in 80% of Chinese paediatric patients in the study of Xia and Shao, and, in that series, 40% of the children had a co-infection. The study did find blood culture positive bacterial infection in 4 patients, but their laboratory parameters were not different from those without co-infection [19].

In a meta-analysis on the risk profile of severe illness in children with COVID-19, five clinical characteristics or biomarkers were found to have an independent association with COVID-19 severity [20,21]. The analysis showed 12.9% of children were completely asymptomatic, in agreement with a previous report [22]. In the present study, no laboratory markers were consistently associated with severity or outcome of COVID-19.

There was no death in the study group, which is consistent with the findings of other studies. Children tend to have milder diseases [23]. Children infected with COVID-19 having an exaggerated inflammatory response against the virus are not commonly described [24,25].

Similar to the present study, CT values have been reported to be similar in mild and hospitalised children [26]. This study found no correlation between CT values and clinical severity or laboratory parameters.

The present study, one of the few prospective studies available from low-income and medium-income countries, points to the need for a clinical symptom-based algorithm for early identification and management of COVID-19 in children.

Limitation(s)

The small sample size and lack of serial biomarkers are some of the limitations. A large multicentre study to clearly define the role of laboratory markers and appropriate time for repeating the biomarkers is required.

CONCLUSION(S)

The present study did not find any single laboratory parameters that correlated with the severity of COVID-19 infection in children. As children remain more susceptible to COVID-19 infection due to lack of vaccination, there is a need for a clinical symptom-based algorithm to be implemented especially in a low-resource setting. The majority of children have mild manifestations but elevated inflammatory markers as shown in our study point towards similar pathophysiology of COVID-19 infection in children and adults.

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