DOI: 10.7860/JCDR/2022/52534.16436

Case Series

Biochemistry Section

Biochemical Investigation of Multisystem Inflammatory Syndrome in Children (MIS-C) with SARS-CoV-2 Infection: A Series of Seven Cases

KAMALAKAR BHAGWAT MANE[1], SWATI DIGAMBAR SAWANT[2]

ABSTRACT

In children, Coronavirus Disease 2019 (COVID-19) is typically mild. However, in rare cases, children are severely affected, and clinical manifestations are differed from adults. The consequence of COVID-19; Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare complication that seems like toxic shock syndrome or Kawasaki Disease (KD). The MIS-C is characterised by an inflammatory response in the body that occurs four weeks after infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Fever, rashes, diarrhoea, red eyes, and vomiting are common early symptoms that can worsen over time. The inflammation can affect the blood vessels, heart, and other organs, leaving children critically ill and in need of immediate medical attention. Many of the children with MIS-C show positive SARS-CoV-2 serology but negative Polymerase Chain Reaction (PCR), supporting the concept that MIS-C is linked to immunological dysregulation that develops after the acute infection has passed. However, some children do have positive PCR testing. A case series of seven critically ill (5 females and 2 males) with MIS-C in sequential order of admission in the Paediatric Intensive Care Unit (PICU) of tertiary care hospital is illustrated. Key findings of this syndrome include fever, epilepsy, diarrhoea, shock and variable presence of rash. In the present case series, the clinical features, laboratory findings and therapies for a cohort of seven children with MIS-C are presented. Laboratory investigations carried out at early stage of disease can be of vital importance to diagnosis of MIS-C.

Keywords: Acute infection, Coronavirus disease-19, Inflammatory markers, Kawasaki disease, Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was initially detected in December 2019 in Wuhan, China. The World Health Organisation (WHO) formally identified this infection, Coronavirus Disease-2019 (COVID-19), and the virus as SARS-CoV-2 on 11th February 2020. On 11th March 2020, the World Health Organisation announced a pandemic [1].

The SARS-CoV-2 typically causes pneumonia in adults and Acute Respiratory Distress Syndrome (ARDS). It is now being identified as a multisystem disorder. Most children, on the other hand, are asymptomatic or have a mild-to-moderate disease. Severe or life-threatening illness is unlikely in children [2]. Children are increasingly being identified with a new condition known as Multisystem Inflammatory Syndrome in Children (MIS-C). Children with MIS-C are sicker, often require intensive care, and could have multisystem involvement and multiorgan dysfunction [3].

CASE SERIES

A case series of seven critically ill children with MIS-C in sequential order of admission in the Paediatric Intensive Care Unit (PICU) of tertiary care hospital is illustrated. Findings observed in this case series were fever, epilepsy, diarrhoea, shock, variable presence of rash and the laboratory findings of Biochemistry, Pathology and Microbiology. Case history including significant clinical features, significant laboratory findings, and therapy given according to standard guidelines for a cohort of seven children with MIS-C is outlined in this case series.

Case 1

A 9-year-old male child presented to Department of Paediatric with fever, convulsion, loose motions, breathlessness and headache since 1 day. There was no significant past medical history or family history. The COVID-19 antibody test was positive. The Rapid Antigen Test (RAT) for COVID-19 was negative.

Patient in delirium state with Glasgow Coma Scale (GCS) 11/15 was admitted to PICU with provisional diagnosis of fever activated epilepsy. On admission, significant laboratory findings were raised inflammatory markers C-reactive Protein (CRP) (157 mg/L), Lactate Dehydrogenase (LDH) (668 U/L) and D-dimer (1140 ng/mL) [Table/Fig-1]. Computed Tomography (CT) brain, fundus examination and 2D Echocardiogram (ECHO) revealed no abnormality. A diagnosis of fever activated epilepsy with MIS-C was made. Patient developed hypotension (blood pressure was-96/50 mmHg). Inotropic support, Intravenous immunoglobulin, anticonvulsants, methylprednisolone and enoxaparin were given. The patient was improved and discharged on 11th day of admission.

Case 2

A 6-year-old female presented to Department of Paediatric with chief complaint of loss of consciousness for 2 hours, unknown bite marks with swelling over lower left foot and discolouration of body for 1 day.

On physical examination, ecchymotic patches over both lower limb and upper limbs were present. With GCS of 3/15, patient was admitted and intubated. The COVID-19 IgG was positive. On admission, significant laboratory findings were, raised inflammatory markers viz. CRP (118 mg/L), LDH (593 U/L), D-dimer (910 ng/mL) and leucocytosis (17.7×103/uL) [Table/Fig-1]. The CT brain, fundus examination and 2D ECHO revealed no abnormality. Patient was provisionally diagnosed as a case of unknown bite but final diagnosis was Multisystem Inflammatory Syndrome in Children (MIS-C). After admission, the patient developed fever. Intravenous immunoglobulin, anticonvulsants, methylprednisolone and enoxaparin were given. Patient condition improved and was discharged on 18th day of admission.

Test parameter	Reference range	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
D-dimer	0-500 ng/mL	1140	910	700	610	559.3	1867	2100
C-reactive protein	0-6 mg/L	157	118	44.1	25.9	30.6	124.58	121
Lactate dehydrogenase	225-450 U/L	668	593	1271	1200	752	1962	1028
Ferritin	30-400 ng/mL	248.5	102.2	33.6	2000	23.13	981.1	93.8
Creatine Kinase-MB	1.7-6.22 ng/mL	6.52	3.22	2.47	15.9	1.43	0.97	37.8
Sodium (Na^+)	135-145 mmol/L	138.4	144.1	131	132	134.7	140	128.5
Potassium (K^+)	3.5-5 mmol/L	3.42	3.06	4.24	3.6	4.04	3.04	4.32
Chloride (Cl^-)	95-105 mmol/L	107.2	107	97	98	102.4	103.8	97.9
Urea	15-40 mg/dL	49	24	34	43	18	9	24
Creatinine	0.7-1.3 mg/dL	1.22	0.27	0.5	0.34	0.27	0.4	0.5
Bilirubin total	0.2-2 mg/dL	0.3	0.5	0.4	4.6	0.3	1	0.8
Bilirubin direct	0.2-0.6 mg/dL	0.2	0.4	0.1	0.7	0.2	0.5	0.2
Bilirubin indirect	0.2-0.4 mg/dL	0.1	0.1	0.3	3.9	0.1	0.5	0.6
Total protein	6-8 gm/dL	5.7	7.5	7.3	4.9	6	6.5	5.5
Albumin	3.5-5 gm/dL	3.5	4.4	4	3.4	3.6	3.3	3.4
Globulin	2.5-3 gm/dL	2.2	3.1	3.3	1.5	2.4	3.2	2.1
Aspartate aminotransferase (AST)	0-35 U/L	29	45	47	149	54	38	110
Alanine aminotransferase (ALT)	0-45 U/L	16	21	13	27	22	11	24
Alkaline phosphatase (ALP)	23-92 U/L	131	203	177	309	97	133	189

[Table/Fig-1]: Biochemical investigations.

Case 3

An 8-year-old female child presented to Department of Paediatric with vomiting, loose stool for 1 day and unconsciousness for 3 hours. Patient was admitted to PICU with GCS of 3/15 with respiratory failure and shock. On admission, significant laboratory findings were noticed like raised CRP (44.1 mg/L), LDH (1271 U/L), D-dimer (700 ng/mL) and leucocytosis (13.59×10^3/uL) [Table/Fig-1]. The COVID-19 antibody test was positive. Cerebrospinal Fluid (CSF) analysis was done. The CT brain, fundus examination and 2D ECHO revealed no abnormality. Patient was provisionally diagnosed as viral encephalitis and finally diagnosed as acute viral encephalitis with MIS-C. Patient was intubated on admission. Patient also developed hypotension for which inotropic support was initiated. Intravenous immunoglobulin, anticonvulsants and methylprednisolone were given. The patient condition was improved and was discharged on 13th day of admission.

Case 4

A 2-month-old male child presented to Department of Paediatric with fever, grunting sounds, abdominal distension, hyperpigmented rash all over the body and respiratory distress for 1 day. The RAT for COVID-19 was negative. The COVID-19 antibody IgG was positive. On admission, significant laboratory findings were raised CRP (25.9 mg/L), LDH (1200 U/L), D-dimer (610 ng/mL), Ferritin (2000 ng/mL), CK-MB (15.9 ng/mL) and leucocytosis (11.72×10^3/uL) [Table/Fig-1]. The CSF analysis was suggestive of meningitis revealing nucleated cells, polymorphs, lymphocytes. CSF sugar and CSF protein were 40 mg/dL and 70 gm% respectively. The CT brain, fundus examination and abdominopelvic Ultrasound (USG) revealed no abnormality. He was provisionally diagnosed as a case of meningitis and finally diagnosed as MIS-C with meningitis. The baby was treated with intravenous immunoglobulin, anticonvulsants and methylprednisolone. Patient improved and was discharged on 5th day of discharge.

Case 5

A 2-year-old female child presented to Paediatric Emergency Unit with sudden onset moderate to high grade fever for 1 day was admitted to PICU. The RAT for COVID-19 was negative. Her COVID-19 antibody IgG was found positive. On admission, significant laboratory findings were raised CRP (30.6 mg/L), LDH (752 U/L), D-Dimer (559.3 ng/mL) and leucocytosis (7.2×10^3/uL) [Table/Fig-1]. Her younger sibling was COVID-19 IgG positive. Patient's provisional and final diagnosis was MIS-C. The patient was treated symptomatically and discharged on improvement. The patient was improved and discharged on 7th day of admission.

Case 6

A 5-year-old female child presented to Department of Paediatric with fever, convulsions and unconsciousness for 3 hours. Patient was immediately admitted to PICU. The COVID-19 IgG antibody test was positive. The CT and Magnetic Resonance Imaging (MRI) revealed no abnormality. On admission, significant laboratory findings were raised Ferritin (981.1 ng/mL), CRP (124.58 mg/L), LDH (1962 U/L) and leucocytosis (8.12×10^3/uL) [Table/Fig-1]. Patient was intubated. A diagnosis of MIS-C was made. She was treated with intravenous immunoglobulin, anticonvulsants and methylprednisolone. The patient condition was improved and was discharged on 7th day.

Case 7

A 3.5-year-old female child presented to Department of Paediatric with fever, vomiting for 1 day, convulsions and loss of consciousness for 4 hours. The COVID-19 IgG antibody test was positive. Patient was in hypotensive shock on admission admitted to PICU for inotropic support and mechanical ventilation owing to respiratory distress from cardiac dysfunction. On admission, significant laboratory findings were raised CRP (121 mg/L), LDH (1028 U/L), CK-MB (37.8 ng/mL), SGOT (110 U/L) [Table/Fig-1]. The CT brain revealed acute infract in right Internal Carotid Artery (ICA) territory while fundus examination and 2D-ECHO revealed no abnormality. Provisional diagnosis was status epilepticus and final diagnosis was cardiorespiratory arrest in right ICA territory with status epilepticus and MIS-C. She was treated with methylprednisolone but she succumbed to death on 4th day of admission.

All the details of cases- Biochemistry, Microbiology, CSF examination, haematology and urine examination are provided in [Table/Fig-2].

DISCUSSION

The incidence of SARS-CoV-2 infection was reported 322 per 100,000 in persons under the age of 21, while of MIS-C was reported 2 per 100,000 [4]. A large number of cases were found in Hispanic and Black children, with a modest number of occurrences in Asian children. In three case studies, Black children accounted for 25-45% of cases, Hispanic children for 30 to 40%, White children for 15-25%, and Asian children for 3-28% [4-6].

Investigation	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Microbiology							
Malaria	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Dengue	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Widal	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Cerebrospinal Fluid (CSF) examination							
Appearance	Clear	Clear	Opalescent	Opalescent	Clear	Clear	Clear
Colour	Colourless	Colourless	Colourless	Reddish	Colourless	Colourless	Colourless
Clots	No	No	No	No	No	No	No
Cobweb	No	No	No	No	No	No	No
Nucleated cells/mm^3	20	No	No	25-30	No	No	No
Polymorphs/mm^3	90	No	No	90	No	No	No
Lymphocytes/mm^3	10	No	No	10	No	No	No
CSF Sugar mg/dL	155	50	114	40	50	40	70
CSF Protein mg/dL	30	40	600	70	40	44	50
Complete blood count							
White Blood Cell (WBC) count 10^3/µL	6.43	17.7	13.598	11.72	7.2	8.12	10
Red Blood Cell (RBC) count 10^6/µL	4.51	4.8	3.94	3.48	3.5	4	4.2
Platelets 10^3/µL	167	178	213	148	115	125	138
Lymphocytes %	17.9	5	9.3	22	22	18	14
Neutrophils %	80	93	89.2	74.2	75	80	84
Prothrombin time in seconds	21.04	19.7	31.5	18	20	19.5	22.5
International normalised ratio	1.56	1.4	2.3	1.4	1.51	1.23	1.8
Urine examination-routine							
Albumin mg/g	Nil	+	Trace	+	Nil	Nil	+
Sugar mg/dL	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Epithelial cells/High power field	1 to 2	1 to 2	4 to 5	1 to 2	Nil	Nil	1 to 2
Pus cells/High power field	4 to 5	2 to 3	55 to 60	14 to16	Nil	Nil	2 to 3
RBC/High power field	Occasional	15 to 20	Plenty	Occasional	Nil	Nil	Occasional

[Table/Fig-2]: Microbiology, Cerebrospinal Fluid (CSF) Examination, Haematology and Urine examination investigations.

Many affected children's Polymerase Chain Reaction (PCR) for SARS-CoV-2 tests were negative but had positive serological tests. This data supports the concept that MIS-C is linked to immunological dysregulation following acute infection [5,7].

In MIS-C and severe acute COVID-19, clinical characteristics are overlapped. The MIS-C can be distinguished from severe acute COVID-19 infection by different patterns of organ system involvement and clinical presentation. Prominent feature in severe acute COVID-19 is severe pulmonary involvement (i.e., pneumonia, acute respiratory distress syndrome). Respiratory symptoms are common in MIS-C patients, although they are a result of shock or impaired cardiac function. Gastrointestinal symptoms (mostly abdominal pain) are also more common in MIS-C than in severe acute COVID-19 infection [8].

The MIS-C shows greater levels of inflammatory markers (CRP, D-dimer, and ferritin) than severe acute COVID-19, and lymphopenia and thrombocytopenia are more prevalent with MIS-C [8].

The timing of appearance of symptoms in MIS-C is variable. The time between acute infection and the appearance of MIS-C symptoms in children with a known history of COVID-19 is usually two to six weeks in children with a known history of COVID-19. Rare cases of MIS-C have been recorded that occurred more than 6 weeks after the acute SARS-CoV-2 infection [9].

In the prognosis, diagnosis, and management of children with MIS-C, laboratory biomarkers play an integral role. Apart from these additional clinical signs, fever is an ubiquitous indicator that occurs in a variable percentage of patients. As a result, biomarkers are a vital adjunct in prompt diagnosis and therapy, which can save life. There have been several diagnostic criteria proposed [10]. Authors have followed unique diagnostic criteria of MIS-C put up by the Centre for Disease Control and Prevention (CDC) case definition for MIS-C [11].

To rule out the common endemic causes of fever, authors had done a rapid malarial antigen test, peripheral smear for malaria, dengue NS1/NS2, and Widal test. All seven cases were tested negative for malaria, dengue and typhoid.

All the cases did not have underlying comorbidities. In all seven cases, laboratory findings were significant elevation of inflammatory markers, such as D-dimer, C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), Erythrocyte Sedimentation Rate (ESR), Procalcitonin (PCT). Raised ferritin was found in case 4. Other findings were hyponatraemia in cases 3, 4 and 7, raised urea in cases 1 and 4 suggestive of kidney injury, hypoalbuminemia in cases 1, 4, 6 and 7 and elevated Creatine Kinase-MB or CK-MB in cases 1, 4 and 7 suggesting myocardial impairment and heart failure.

Case 4 showed an increased serum ferritin level. Studies on ferritin levels in COVID-19 patients have revealed equivocal findings. It is unclear whether that was a bystander effect or an actual illness manifestation [12]. One study and a meta-analysis showed ferritin levels could predict severe disease and mortality [13,14]. One retrospective study showed that ferritin played only a minimal role in deciding Intensive Care Unit (ICU) admission and the need for ventilation, as well as failure to predict mortality [15].

In all cases, there was elevated CRP showing higher than 25 mg/dL. While in cases 1, 4, 6, and 7 CRP levels were >100 mg/dL. Similar to the present study results, few studies showed, the majority of patients had elevated CRP and values greater than 100 mg/dL were common; CRP is a plausible, beneficial initial laboratory investigation for screening MIS-C patients as well as monitoring them after therapy [16,17]. When compared to non severe disease, children with severe respiratory disease and MIS-C had significantly higher serum CRP, PCT, platelet count, and sodium levels. [18,19].

Authors found neutrophilic leucocytosis in all the cases. Neutrophils play an important role in the innate immune response. The formation of Neutrophil Extracellular Traps (NETs) is one of their functional mechanisms [20].

CSF findings in all cases were consistent with aseptic meningitis, as has been described in KD. Cases 3, 4, and 7 all had hyponatraemia, which has been reported in Kawasaki disease and may be pertaining to more severe inflammation and Kawasaki shock syndrome [21].

Biochemical markers of MIS-C include serum D-dimer, PCT, creatine kinase, and IL-6 [22]. Some studies observed commonly reported abnormal laboratory parameters in children were leucocytosis, increased creatine kinase, elevated D-dimer, CRP, AST and ALT [22,23].

Authors found abnormal microscopic and biochemical parameters in urine routine examination in five cases, which is similar to what was found in one study where urine biochemical parameters were studied to predict disease severity. Positive urine protein and urine glucose results were more common in severe and critical patients. The severity was not related to urine occult blood and specific gravity [24].

Intravenous Immunoglobulin (IVIG) and methylprednisolone were administered to the children in this case series, both of which have been shown to be effective in the treatment of Kawasaki disease. This was highly effective in most patients in reducing systemic inflammation, as indicated by fever resolution and improved cardiac function over days.

Six children were discharged from the hospital after their inflammatory laboratory markers recovered; they are normotensive, afebrile, and properly hydrated, and they do not require oxygen therapy. Despite treatment, case 7 succumbed to death as a result of severe MIS-C. The COVID-19 complications, such as MIS-C, can present in a wide variety of ways and should be considered in any severe acute febrile illness.

Laboratory studies of the disease's biochemical, pathophysiological, and immunological processes are essential to provide understanding and prognostic indications into potential therapeutic targets, as well as to support vaccine development strategies.

CONCLUSION(S)

Early laboratory investigations of inflammatory markers correlating with the diagnostic clinical features is an ultimate key to diagnose MIS-C. Laboratory investigations are helpful for early detection and timely management of MIS-C cases.

REFERENCES

[1] Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current status of epidemiology, diagnosis, therapeutics, and vaccines for novel Coronavirus Disease 2019 (COVID-19). J Microbiol Biotechnol. 2020;30(3):313-24.

[2] Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021;93(2):1057-69.

[3] Singh-Grewal D, Lucas R, McCarthy K, Cheng AC, Wood N, Ostring G, et al. Update on the COVID-19-associated inflammatory syndrome in children and adolescents; paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2. J Paediatr Child Health. 2020;56(8):1173-77.

[4] Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347-58.

[5] Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383(4):334-46.

[6] Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: A multicentre observational study. Lancet Child Adolesc Health. 2020;4(9):669-67.

[7] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259-69.

[8] Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H, et al. Characteristics and outcomes of US children and adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) compared with severe acute COVID-19. JAMA. 2021;325(11):1074-87.

[9] Cirks BT, Rowe SJ, Jiang SY, Brooks RM, Mulreany MP, Hoffner W, et al. Sixteen weeks later: Expanding the risk period for multisystem inflammatory syndrome in children. J Pediatric Infect Dis Soc. 2021;10(5):686-90.

[10] Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: A comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180(2):307-22.

[11] CDC Health Alert Network. Mulitsystem Inflammatory Syndrome in Children (MIS-C) associated with Coronavirus Disease 2019 (COVID-19). [Available from: "https://emergency.cdc.gov/han/2020/han00432.asp".

[12] Kappert K, Jahić A, Tauber. Assessment of serum ferritin as a biomarker in COVID-19: Bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020;25(8):616-25.

[13] Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther Adv Respir Dis. 2020;14:1753466620937175.

[14] Lin Z, Long F, Yang Y, Chen X, Xu L, Yang M. Serum ferritin as an independent risk factor for severity in COVID-19 patients. J Infect. 2020;81(4):647-79.

[15] Bellmann-Weiler R, Lanser L, Barket R, Rangger L, Schapfl A, Schaber M, et al. Prevalence and predictive value of anemia and dysregulated iron homeostasis in patients with COVID-19 Infection. J Clin Med. 2020;9(8):2429.

[16] Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev. 2021;38:51-57.

[17] Wahezi DM, Lo MS, Rubinstein TB, Ringold S, Ardoin SP, Downes KJ, et al. American College of Rheumatology Guidance for the Management of Pediatric Rheumatic Disease during the COVID-19 Pandemic: Version 1. Arthritis Rheumatol. 2020;72(11):1809-19.

[18] Fernandes DM, Oliveira CR, Guerguis S, Eisenberg R, Choi J, Kim M, et al. Severe Acute Respiratory Syndrome Coronavirus 2 clinical syndromes and predictors of disease severity in hospitalized children and youth. J Pediatr. 2021;230:23-31.e10.

[19] Pierce CA, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med. 2020;12(564):eabd5487.

[20] Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, et al. Novel cell death program leads to neutrophil extracellular traps. The Journal of Cell Biology. 2007;176(2):231-41.

[21] Schuster JE, Palac HL, Innocentini N, Rowley AH, Young LT, Shulman ST. Hyponatremia is a feature of kawasaki disease shock syndrome: A case-control study. J Pediatric Infect Dis Soc. 2017;6(4):386-88.

[22] Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine. 2020;24:100433.

[23] Ma X, Liu S, Chen L, Zhuang L, Zhang J, Xin Y. The clinical characteristics of pediatric inpatients with SARS-CoV-2 infection: A meta-analysis and systematic review. J Med Virol. 2021;93(1):234-40.

[24] Liu R, Ma Q, Han H, Su H, Liu F, Wu K, et al. The value of urine biochemical parameters in the prediction of the severity of coronavirus disease 2019. Clin Chem Lab Med. 2020;58(7):1121-24.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra, India.
2. Assistant Professor, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Swati Digambar Sawant,
Assistant Professor, Department of Biochemistry, Dr. Vaishampayan Memorial Government Medical College, Solapur, Maharashtra, India.
E-mail: drswatitalekar@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Dec 04, 2021
- Manual Googling: Mar 09, 2022
- iThenticate Software: Apr 13, 2022 (15%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Sep 22, 2021**
Date of Peer Review: **Dec 04, 2021**
Date of Acceptance: **Mar 15, 2022**
Date of Publishing: **Jun 01, 2022**