Original Article

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Paediatrics Section

Association of Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 (MIS-C) with Co-infections: A Retrospective Cross-sectional Analytical Study from Northern India

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ABSTRACT

Introduction: Multisystem Inflammatory Response Syndrome in Children (MIS-C) temporally associated with Coronavirus Disease 2019 (COVID-19) is characterised by fever, raised inflammatory markers, multisystem involvement with evidence of COVID-19 infection (positive RT-PCR or serology). It occurs concurrently or after 4-6 weeks of acute COVID infection. It has wide range of clinical presentation ranging from mild asymptomatic infection to severe life-threatening illness. Clinical presentation of MIS-C has considerable overlapping features with other tropical infections. During peak wave of COVID-19, when large proportion of population has been affected by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), contracting other infections during and within four weeks of active COVID-19 is inevitable. Despite of this concern, only few researchers have studied co-infection and they explained a complex interaction between COVID-19 and other infections like tuberculosis and dengue. They demonstrated how one infection augments the severity of other. To the best of our knowledge no paediatric population-based study explained the interaction of acute COVID-19 and MIS-C with other infections so far.

Aim: To determine the association of MIS-C with co-infections in SARS-CoV-2 positive children of one month to less than 18 years of age.

Materials and Methods: A retrospective cross-sectional analysis of the medical records of paediatric patients with SARS-CoV-2 infection, treated from September 2020 to February 2021, was performed. All the patients who fulfilled World Health Organisation (WHO) criteria of MIS-C were included. Detailed demographic, clinical, laboratory parameters and associated co-infections were recorded.The severe and non severe MIS-C groups were compared. Sample 't' test, Wilcoxon test and Chi-squared test were used for statistical analysis.

Results: A total of 44 children fulfilled the diagnostic criteria of MIS-C and were included in the study. Out of 44, 20 children (45.4%) had severe disease and 24 had non severe disease. The mean age of children with severe MIS-C was 7.38±5.39 years, as compared to 4.37±4.61 years in the non severe group (p-value=0.044). Males were predominantly affected in both the groups (Male: Female=1.22:1 in severe MIS-C and 2.4:1 in non severe MIS-C). The gastrointestinal system was most commonly affected in both groups. Associated coinfection was noted more in severe MIS-C group (11 vs 1 patient in severe vs non severe group, p-value <0.001). Tuberculosis was found to be associated in three patients, followed by complicated enteric fever, and severe dengue in two patients each. The odds ratio for developing severe MIS-C in the presence of co-infections was 10.5 (CI=2.33-47.27) while in its absence it was 0.10 (0.02-0.43).

Conclusion: The findings of this study support that concurrent infections in COVID-19 can exacerbate the severity of COVID-19 illness and may lead to severe MIS-C.

Keywords: Coronavirus disease-2019, Dengue, Enteric fever, Severe acute respiratory syndrome coronavirus 2 related, Tuberculosis

INTRODUCTION

The emergence of the second wave has hit hard the low and middle-income (LMI) countries like India with daily case counts exceeding 2 00,000 during the peak of second wave [1]. In the year 2020, during the initial stage of the pandemic, the studies on COVID-19 mostly represented adult data. Children were reported to have mild symptoms until April 2020 when reports from United Kingdom described incomplete Kawasaki disease and toxic shock syndrome in association with COVID-19 infection [2,3]. Similar cases were reported across the world which subsequently was termed as multisystem inflammatory response syndrome in children temporally associated with COVID-19 (MIS-C). In May 2020, Centers for Disease Control and Prevention (CDC) and WHO published the case definition for MIS-C [4,5]. The criterion includes fever, elevated inflammatory markers, and signs of multisystem involvement, evidence of SARS-CoV-2 infection or exposure, and exclusion of other potential causes. An increased incidence of such cases usually occurs 4-6 weeks after a peak wave of COVID-19. With the availability of more studies, it is seen that the spectrum of clinical manifestation of COVID-19 is wide and ranges from mild illness to severe life-threatening conditions, causing multiorgan failure leading to significant morbidity and mortality [6,7].

The LMICs are already overburdened with infections like dengue, typhoid, malaria and tuberculosis. Moreover, multiple factors like disruption of routine and preventive healthcare services, overwhelmed healthcare facilities, social stigma, fear, delay in seeking treatment, poor nutrition, and lockdown restrictions causing overcrowding at home may lead to increase in burden of endemic infections [8]. With emergence of COVID-19 pandemic affecting large proportion of population during its peak, it is reasonable to anticipate the increase rate of co-infections and superinfections (SARS-CoV-2 and endemic infections) and they are inevitable. The literature review by Visca D et al.,

explained a complex interaction between COVID -19 and tuberculosis in adults, and how it increases the severity and progression of one another; but no study so far has explained the co-existence of these conditions in the paediatric population [9]. So, this study aimed to evaluate the association between MIS-C and other infections and to evaluate if their co-existence augments the severity of MIS-C.

MATERIALS AND METHODS

A retrospective cross-sectional analytical study was conducted at the Department of Paediatrics, Hamdard Institute of Medical Sciences and Research, Delhi. The study duration was from 1st September 2020 to 28th February 2021. Ethical approval was taken from Jamia Hamdard Institutional Ethics Committee (JHIEC) for conducting the study.

Inclusion criteria: All children, admitted during the study period, who fulfilled criteria for MIS-C including children having co-infections were included in the study [4,5].

Case Definition

According to WHO all the following six criteria must be met to diagnose a child with MIS-C:

1. Children and adolescents 0-19 years of age
2. Fever ≥3 days
3. Clinical signs of multisystem involvement (at least 2 of the following):
   a. Rash or bilateral non purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
   b. Hypotension or shock.
   c. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities {including an Echocardiogram (ECHO) findings or elevated Troponin/N-terminal, protein B-type natriuretic peptide (NT-proBNP)},
   d. Evidence of coagulopathy {by Prothrombin time (PT) test, Partial Thromboplastin Time (PTT), elevated d-Dimers}.
   e. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).
4. Elevated markers of inflammation such as Erythrocyte Sedimentation Rate (ESR), C-reactive protein, or procalcitonin.
5. No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
6. Evidence of COVID-19 {Reverse transcriptase polymerase chain reaction (RT PCR), antigen test or serology positive}, or likely contact with patients with COVID-19.

Exclusion criteria: Children with chronic co-morbidities i.e. immunodeficiency syndrome, cerebral palsy, bronchopulmonary dysplasia, inborn error of metabolism, hematological malignancy, congenital heart disease and connective tissue disorders were excluded from the study.

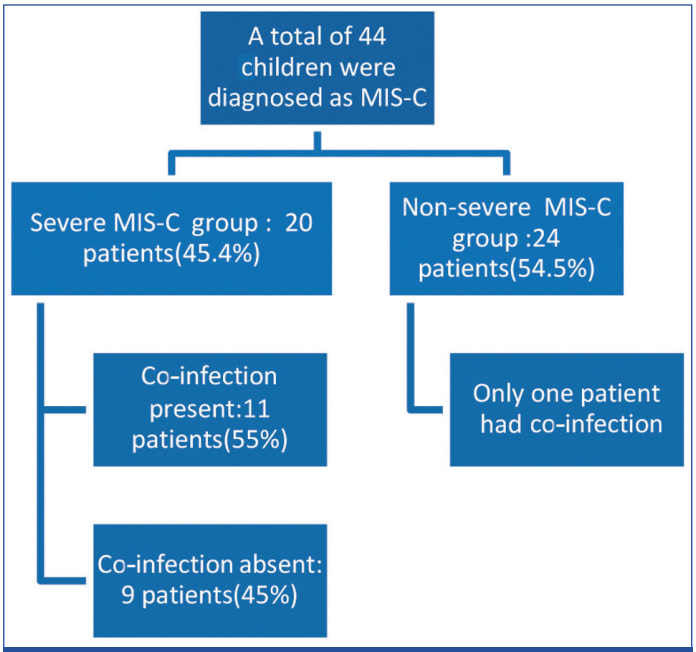
Study Procedure

The data was extracted from records, which included demographic profile, detailed clinical presentation, presence of other co-infections (tuberculosis, dengue, enteric fever etc.). The following laboratory parameters were recorded- complete blood count, absolute lymphocyte count, hepatic function tests, renal function tests, C-reactive protein (CRP), Erythrocyte sedimentation rate (ERP), serum ferritin, D-dimer, coagulation profile, creatinine phosphokinase-MB (CPK-MB) and lactate dehydrogenase (LDH). Any clinically significant finding on Chest X-ray and other radiological imaging were recorded. Qualitative COVID-19 RT PCR was performed by using COVIWOK COVID-19 test kit and SARS-CoV-2 quantitative antibodies were detected in serum by the LIAISON® SARS-CoV-2 S1/S2 IgG test which uses indirect Chemiluminescence Immunoassay (CLIA) technology for the quantitative determination of anti S1 and anti S2 specific IgG antibodies.

These patients were further divided into two groups on the basis of severity [10,11] [Table/Fig-1].

- Severe MIS-C: Patients with shock, cardiac dysfunction, severe respiratory distress, respiratory failure, altered sensorium, thromboembolism, markedly raised inflammatory markers (CRP >10 mg/dL, Serum Ferritin >500 mcg/L, raised cardiac Troponin I >0.5 ng/mL)
- Non severe MIS-C: Children with persistent fevers and mild symptoms(Diarrhoea,headache, fatigue etc). Inflammatory markers may be elevated but without signs of severe multisystem involvement.

Both the groups (Severe MIS-C and Non severe MIS-C) were further subdivided into two, on the basis of presence or absence of co-infections [Table/Fig-1] and were compared. Further patients within severe MIS-C group, with and without co-infections were compared, to determine if presence of co-infections affects the disease severity.



[Table/Fig-1]: Flowchart showing the distribution of study population.

STATISTICAL ANALYSIS

Data were coded and recorded in MS Excel spreadsheet and transferred to Statistical Package for Social Sciences (SPSS) software version 23.0 (IBM Corp.). Group comparisons for continuously distributed data were made using Independent sample 't' test when comparing two groups. If data were found to be non normally distributed, appropriate non parametric tests in the form of Wilcoxon test were used. Chi-squared test was used for group comparisons for categorical data. In case the expected frequency in the contingency tables were found to be <5 for >25% of the cells, Fisher's exact test was used instead. Statistical significance was kept at $p \leq 0.05$.

RESULTS

Total of 44 paediatric patients fulfilled the inclusion criteria (MIS-C), and were included in the study. Out of them, 20 patients were found to have severe MIS-C (45.4%), and the remaining 24 (54.5%) were classified in the non severe MIS-C group. Among 20, 11 patients (55%) in severe MIS-C group had co-infections as compared to only 1 patient in non severe MIS-C. [Table/Fig-1].

Severe MISC vs Non severe MISC [Table/Fig-2,3]: The children in the severe MIS-C group were relatively older (7.38±5.39 years in MIS-C vs 4.37±4.61 years in non severe, p-value <0.05). There was no difference in age distribution in the severe MIS-C group. In the

non severe MIS-C group, majority (70.8%) were less than five years of age. Males were predominantly affected in both the groups (Male: Female=1.22:1 in severe MIS-C and 2.4:1 in non severe MIS-C).

Parameters	Severe MIS-C (n=20)	Non severe MIS-C (n=24)	p-value
Age (years)	7.38±5.39	4.37±4.61	0.044
Age group			
<5 years	7 (35.0%)	17 (70.8%)	0.059
5-10 years	6 (30.0%)	3 (12.5%)	
>10 years	7 (35.0%)	4 (16.7%)	
Gender			
Male	11 (55.0%)	17 (70.8%)	0.277
Female	9 (45.0%)	7 (29.2%)	
Duration of stay (Days)	13.55±7.65	4.88±1.90	<0.001
Co-infection (Present)	11 (55%)	1 (4%)	<0.001
Predominant system involve			
Gastrointestinal	8 (40%)	17 (70.8%)	0.010
Lungs	6 (30%)	1 (4.2%)	
Central nervous system	2 (10%)	4 (16.7%)	
Musculoskeleton	0	2 (8.3%)	
Vascular	1 (5%)	0	
Multisystem	3 (15%)	0	
Clinical presentation			
Cough and coryza	11 (55%)	6 (25.0%)	0.042
Sore throat	6 (30%)	1 (4.2%)	0.035
Abdominal pain	12 (60%)	10 (41.7%)	0.226
Diarrhoea	7 (35%)	18 (75.0%)	0.008
Vomiting	10 (50%)	16 (66.7%)	0.263
Rash	5 (25%)	3 (12.5%)	0.436
Mucous membrane changes	13 (65%)	8 (33.3%)	0.036
Swollen hands and feet	13 (65%)	2 (8.3%)	<0.001
Confusion/Irritability	8 (40%)	10 (41.7%)	0.911
Seizures	3 (15%)	4 (16.7%)	1.000
Shock	9 (45%)	0	<0.001
Toxic shock syndrome	2 (10%)	0	0.201
Kidney involvement	8 (40%)	0	<0.001

[Table/Fig-2]: Clinical and Demographic features of MIS-C patients.
The following parameters had significant difference in between two groups (p<0.05): Age, presence of co-infections, predominant system involvement, mucosal involvement, oedema, shock, renal failure and duration of stay

The most commonly involved system in both the groups was gastrointestinal (80% in severe and 83% in non severe), followed by the respiratory system (75%) in severe MIS-C and central nervous system including non specific signs like irritability and confusion (62%) in non severe MIS-C group. All the patients in severe MIS-C group, and majority in non severe MIS-C group (91.7%) had fever. Respiratory symptoms, mucous membrane changes, swollen hands and feet, shock and oliguria were found to be significantly higher in severe MIS-C group (p-value <0.05), whereas diarrhoea was more common in non severe MIS-C population (p-value=0.008).

Co-infections [Table/Fig-4]: Total of 12 (34.1%) patients among cohort had other co-infections. Further 11 (55%) patients in severe MIS-C group had non SARS-CoV-2 infections which was significantly higher than the non severe MIS-C group (4.2 %) (p-value <0.001). The 11 patients in the MIS-C group with co-infections included tuberculosis in three patients, two with dengue fever, two with complicated enteric fever, one each with viral hepatitis A, viral hepatitis E, measles and amoebic dysentry. In the non severe MIS-C group only one patient was diagnosed with co-infection who had tuberculosis. The odds ratio for developing severe MIS-C in the presence of co-infections, was 10.5 (CI=2.33-47.27).

Parameters	Severe MIS-C (n=20)	Non severe MIS-C (n=24)	p-value
COVID RT-PCR (Positive)	1 (5.0%)	3 (12.5%)	0.614
COVID antibody (AU/mL)	75.92±75.66	98.40±84.10	0.316
Haemoglobin (g/dL)	9.82±2.62	10.58±1.89	0.291
TLC (10^3/cumm)	13.04±8.75	11.93±6.44	0.860
Polymorphs (%)	63.88±21.77	51.00±19.31	0.015
Lymphocytes (%)	29.27±21.60	39.08±18.74	0.036
Absolute lymphocyte count (thousands/cumm)	3457.25±3963.41	4483.08±3146.47	0.067
Platelet count (Lacs/cumm)	1.96±1.34	3.67±1.28	<0.001
C-reactive protein (mg/dL)	17.60±44.88	3.02±3.45	0.007
ESR (mm/Hr)	65.94±47.12	34.07±23.51	0.030
S. Ferritin (ng/mL)	2313.54±6892.98	121.07±165.42	<0.001
LDH (U/L)	639.67±362.79	43.00±0	0.500
AST (U/L)	196.20±324.86	41.65±21.10	0.104
ALT (U/L)	417.25±1077.50	40.40±56.26	0.176
S. Albumin (g/dL)	2.96±0.56	3.91±0.48	<0.001
Blood urea (mg/dL)	40.87±27.98	25.98±22.44	0.054
S. Creatinine (mg/dL)	0.57±0.37	0.37±0.18	0.024
Urine R/M			
RBCs	4 (20%)	0	0.109
WNL	16 (80.0%)	17 (100.0%)	
Stool R/M			
E.histolytica growth	1 (25%)	0	0.225
Pus Cells (per hpf)	0 (0.0%)	4 (26.7%)	
WNL	3 (75.0%)	11 (73.3%)	
CPK MB	-	45.00±24.04	-
Troponin	1.50±0.88	2.70±0	0.468
Fibrinogen (mg/dL)	80.00±0	-	-
D-Dimer (FEU/L)	4.97±2.86	1.44±2.03	<0.001
Prothrombin time (seconds)	15.75±1.98	16.35±0.92	0.386
INR	1.18±0.14	1.22±0.07	0.387
Chest X-ray			
Normal	5 (31.2%)	6 (85.7%)	
Abnormal	11 (68.8%)	1 (14.3%)	
CECT chest			
Normal	1 (16.7%)	0	1.000
Abnormal	5 (83.3%)	1 (100%)	
Echocardiography			
Normal	9 (75.0%)	3 (100%)	1.000
Abnormal	3 (25.0%)	0	

[Table/Fig-3]: Laboratory parameters.
g/dL: Grams per decilitre; mg/dL: Milligrams per decilitres; TLC: Total leucocyte count; cmm: Cubic millimeter; DLC: Differential leucocyte count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; FEU/L: Fibrinogen equivalents unit per litre; INR: International normalised ratio; RT PCR: Reverse transcriptase polymerase chain reaction; AU/mL: Absorbance units per millilitres. The following parameters had significant difference in between the two groups (p<0.05): Differential leucocyte count (Polymorphs % and lymphocyte %); serum albumin; serum ferritn; serum creatinine and D-dimer levels

Co-infections in severe MIS-C group	Number of patients	Details
Tuberculosis	3	2- Disseminated tuberculosis, 1- Miliary tuberculosis
Dengue fever	2	Both were critically ill and one patient developed HLH
Complicated enteric fever	2	One presented with MERS*
Acute Viral hepatitis	2	
Amoebic dysentry	1	
Measles	1	

[Table/Fig-4]: Details of co-infections in Severe MIS-C group.
MERS: Mild encephalopathy with reversible splenial changes; HLH : Haemophagocytic lymphohistiocytosis

On comparing the patients with and without co-infections within severe MIS-C cohort, no significant difference was found in terms of clinical presentation, severity of illness (requirement of oxygen, ionotropic, ventilator support etc.), laboratory parameters and duration of stay.

DISCUSSION

Since the emergence of COVID-19 pandemic, the deleterious effect of co-morbidities like diabetes, hypertension and congenital heart diseases on the severity of the infection have been explained. Limited studies have explored the association of SARS-CoV-2 with non SARS-CoV-2 infections, especially prevalent in LMIC like tuberculosis (TB) and other tropical infections including dengue and malaria. [8,12,13]. Though many researchers have tried to provide a vision to foresee the increased burden of co-infections (concurrent infections with SARS-CoV-2 and other organisms), yet no population-based study described them in detail [14-16]. Some authors attempted to estimate the effect of COVID-19 pandemic on HIV, tuberculosis and malaria in LMIC[8]. With the aid of a modelling study researchers have raised concerns that due to disruption of routine health services, there could be a significant increase in mortality over next five years due to non SARS-CoV-2 infections [13].

Preliminary studies have shown that SARS-CoV-2 infected patients with latent TB have increased risk of disease progression and TB patients are at 2.1-fold increased risk of developing severe disease [17,18]. In addition to the socio-economic factors and logistic issues, a complex interplay of various pathophysiological mechanisms has been responsible. Impaired lung function due to pre-existing respiratory infection and shared immune dysregulation are contributory. [9,18]. They are presumed to augment the severity of each other. This hypothesis could explain the development of MIS-C and progression to severe disease in these patients. In the present cohort, four patients had TB co-infection, of which three had disseminated TB and MIS-C; all were adolescents and received Bacille Calmette-Guerin (BCG) vaccine. Few adult population-based studies have been published on TB and COVID-19 co-infection, but there is no paediatric data, except three cases reports by Gupta S et al. [19]. To understand the interaction between tuberculosis and COVID-19, a global study coordinated by Global Tuberculosis Network (GTN) and supported by WHO is ongoing [20]. Preliminary results that suggest that COVID-19 is contributory in TB pathogenesis cannot be ruled out or confirmed at present and larger studies are required [21].

Tropical infections like dengue, malaria and scrub typhus occur in post monsoon period [23]. If an epidemic of COVID-19 hits a tropical country like India during this time then there can be an increase rate of these co-infections. Moreover, tropical infections and COVID-19 have similar clinical presentation; Yan et al has shown that the presentation of COVID-19 can overlap with dengue leading to misdiagnosis [22]. Increased mortality and morbidity have been seen in adults infected with COVID-19 and dengue co-infection. Few cases of dengue and scrub typhus with COVID-19 in children have been reported. All had associated MIS-C and were critically ill [24-27]. An adolescent with scrub typhus was reported to develop macrophage activation syndrome (MAS) [27]. Similar findings were observed in this study. Two critically ill patients were diagnosed with MIS-C and dengue co-infection (diagnosed by NS1 antigen detection) of which one developed secondary hemophagocytosislymphohistiocytosis (HLH). Though dengue virus is a known etiological agent, studies have also suggested SARS-CoV-2 as potential trigger for causing HLH but here the role of either could not be confirmed. One recent study has recommended HLH investigation in severe COVID-19 patients with suggestive laboratory parameters. [28]. The increased severity in such co-infections could be explained with cross reactivity of immune responses. Certain studies have suggested that SARS-CoV-2 and dengue virus (DENV) interaction could lead to antibody dependent enhancement in SARS-CoV-2 infection [29,30]. However, detailed studies are required to draw conclusion on their exact pathogenesis and to determine if their role is bidirectional in disease progression or amplification.

Unlike vector-borne diseases, the transmission of water-borne infections like enteric fever, viral hepatitis and diarrhoea occurs throughout the year with seasonal outbreaks. The peak incidence of enteric fever in India occurs post monsoon period (May-October) [31]. In this study, two patients each had enteric co-infection and viral hepatitis and one had amoebic dysentery. Till now only a single case of enteric co-infection has been reported in an adolescent male [32]. Here, two patients of MIS-C with enteric co-infections (positive blood cultures) were reported. Both had a complicated course with one presenting as encephalopathy showing splenial changes on Contrast-Enhanced Magnetic Resonance Imaging (CE-MRI) of brain. Mild encephalopathy with reversible splenial changes (MERS) is a rare finding in *Salmonella typhi* infection though few cases due to SARS-CoV-2 has been reported [33,34]. Cerebrospinal fluid sample was negative for COVID RT PCR and other viral and bacterial etiology. Identifying and treating such cases keeping in mind a broad differential diagnosis is crucial for the timely management.

Limitation(s)

There are various limitations of study. Major limitation was its retrospective design and absence of detailed immunopathological markers.

CONCLUSION(S)

In conclusion, this study suggests that patient with recent SARS-CoV-2 infection, if superinfected has increased susceptibility for developing MIS-C; and SARS-CoV-2 infection increases the possibility of progression of latent TB. These results are not confirmatory and well-designed prospective studies should be designed to be able to answer many questions regarding the burden of co-infections. Further questions that need answers are- whether concurrent COVID-19 infection increases the severity of other infectious diseases, do immunopathological mechanisms cause bi-directional amplification of disease and if any superinfections post COVID-19 facilitates the development of MIS-C.

Till then, a broad differential diagnosis along with well-planned out laboratory investigations can help in early diagnosis and management.

REFERENCES

[1] World Health Organization. WHO coronavirus disease (COVID-19) dashboard [Internet]. Geneva: World Health Organization; 2020. Available from: https://covid19.who.int/. (Last accessed on 8th October, 2021).

[2] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020. Epub 2020/05/11.

[3] DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe COVID-19 in Children and Young Adults in the Washington, DC Metropolitan Region. J Pediatr. 2020;223:199-203.e1. Doi: 10.1016/j.jpeds.2020.05.007.

[4] Centers for Disease Control and Prevention Health Alert Network (HAN). Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp. (Accessed on 11th April 2021).

[5] World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19: Scientific Brief. 2020. https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. (Accessed on 11th April 2021).

[6] Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021;56:837-48.

[7] Baradaran A, Malek A, Moazzen N, Shaye ZA. COVID-19 associated multisystem inflammatory syndrome: A systematic review and meta-analysis. Iran J Allergy Asthma Immunol. 2020;19:570-88.

[8] Hogan AB, Jewell BL, Sherrard-Smith E, Vesga JF, Watson OJ, Whittaker C, et al. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: A modelling study. Lancet Glob Health. 2020;8:e1132-41.

[9] Visca D, Ong CWM, Tiberi S, Centis R, D'Ambrosio L, Chen B. Tuberculosis and COVID-19 interaction: A review of biological, clinical and public health effects. Pulmonology. 2021;27:151-65.

[10] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical Characteristics of 58 Children With a Paediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020;324(3):259-69.
[11] Center for Disease Control and Prevention, Center for Preparedness and Response: Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19), Clinician Outreach and Communication (COCA) Webinar. Available at: https://emergency.cdc.gov/coca/calls/2020/callinfo_051920.asp?deliveryName=USCDC_1052-DM28623.
[12] Wu Q, Xing Y, Shi L, Li W, Gao Y, Pan S, et al. Coinfection and other clinical characteristics of COVID-19 in children. Paediatrics. 2020;146:e20200961. Doi: 10.1542/peds.2020-0961.
[13] Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: A retrospective cohort study. Clin Microbiol Infect 2021;27:83-88.
[14] Marimuthu Y, Nagappa B, Sharma N, Basu S, Chopra KK. COVID-19 and tuberculosis: A mathematical model based forecasting in Delhi, India. Indian J Tuberc. 2020;67:177-81.
[15] Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: Potentially lethal and unexplored in COVID-19. Lancet Microbe. 2020;1:e11. https://doi.org/10.1016/S2666-5247(20)30009-4.
[16] Gupta U, Prakash A, Sachdeva S, Pangtey GS, Khosla A, Aggarwal R, et al. COVID-19 and Tuberculosis: A Meeting of Two Pandemics! J Assoc Physicians India 2020;68:69-72.
[17] Chen Y, Wang Y, Fleming J, Yu Y, Gu Y, Liu C, et al. Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. [Internet] Infectious Diseases (except HIV/AIDS) 2020. http://medrxiv.org/lookup/doi/10.1101/2020.03.10.20033795 Mar [cited 2020 May 22].
[18] Gao Y, Liu M, Chen Y, Shi S, Geng J, Tian J. Association between tuberculosis and COVID-19 severity and mortality: A rapid systematic review and meta-analysis. J Med Virol. 2021;93:194-96.
[19] Gupta S, Chopra N, Singh A, Gera R, Chellani H, Pandey R, et al. Unusual clinical manifestations and outcome of multisystem inflammatory syndrome in children (MIS-C) in a tertiary care hospital of North India. J Trop Pediatr. 2021;67(1):fmaa127. Doi: 10.1093/tropej/fmaa127.
[20] Casco N, Jorge AL, Palmero D, Alffenaar JW, Fox G, Ezz W, et al. TB and COVID-19 co-infection: Rationale and aims of a global study. Int J Tuberc Lung Dis. 2021;25:78-80. Doi: 10.5588/ijtld.20.0786. PMID: 33384052.
[21] Tadolini M, Codecasa LR, García-García JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: First cohort of 49 cases. Eur Respir J. 2020;56:2001398. https://doi.org/10.1183/13993003.01398-2020.
[22] Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: A review of the literature. Southeast Asian J Trop Med Public Health. 2014;45:719-26.
[23] Yan G, Lee CK, Lam LT, Yan B, Chua YX, Lim AY, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis. 2020;20:536.
[24] Ratageri VH, Pawar GR, Nikhil G, George SS. Co-Infection of Dengue fever with COVID-19 in a child with MIS-C. Indian J Pediatr. 2021;88:485.
[25] Alam A, Sudarwati S, Hakim DDL, Mahdiani S. Case Report: Severe COVID-19 and dengue in an Indonesian Infant. Am J Trop Med Hyg. 2021;104:1456-60.
[26] Somasetia DH, Malahayati TT, Andriyani FM, Setiabudi D, Nataprawira HM. A fatal course of multiple inflammatory syndrome in children coinfection with dengue. A case report from Indonesia. IDCases. 2020;22:e01002. Doi: 10.1016/j.idcr.2020.e01002.
[27] Gupta A, Gill A. Multisystem Inflammatory Syndrome in a Child with Scrub Typhus and Macrophage Activation Syndrome. J Trop Pediatr. 2021;67:fmab021. Doi: 10.1093/tropej/fmab021.
[28] Retamozo S, Brito-Zerón P, Sisó-Almirall A, Flores-Chávez A, Soto-Cárdenas MJ, Ramos-Casals M. Haemophagocytic syndrome and COVID-19. Clin Rheumatol. 2021;40:1233-44.
[29] Harapan H, Ryan M, Yohan B, Abidin RS, Nainu F, Rakib A, et al. Covid-19 and dengue: Double punches for dengue-endemic countries in Asia. Rev Med Virol. 2021;31:e2161. Doi: 10.1002/rmv.2161.
[30] Ulrich H, Pillat MM, Tárnok A. Dengue Fever, COVID-19 (SARS-CoV-2), and Antibody-Dependent Enhancement (ADE): A Perspective. Cytometry A. 2020;97:662-67.
[31] Saad NJ, Lynch VD, Antillón M, Yang C, Crump JA, Pitzer VE. Seasonal dynamics of typhoid and paratyphoid fever. Sci Rep. 2018;8:6870. Doi: 10.1038/s41598-018-25234-w.
[32] Ayoubzadeh SI, Isabel S, Coomes EA, Morris SK. Enteric fever and COVID-19 co-infection in a teenager returning from Pakistan. J Travel Med. 2021;28:taab019. Doi: 10.1093/jtm/taab019.
[33] Ka A, Britton P, Troedson C, Webster R, Procopis P, Ging J, et al. Mild encephalopathy with reversible splenial lesion: An important differential of encephalitis. Eur J Paediatr Neurol. 2015;19:377-82.
[34] Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. JAMA Neurol. 2020;77:1440-45.

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