SYSTEMATIC REVIEW

Multisystem Inflammatory Syndrome Associated With COVID-19 in Children (MIS-C): A Systematic Review of Studies From India

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Background: With wide clinical spectrum, multisystem inflammatory syndrome associated with coronavirus disease 2019 (COVID-19) in children (MIS-C) is a relatively novel condition occurring weeks to months' post SARS-CoV-2 infection. The aim was to systematically review data on clinical features, laboratory parameters and therapeutics of MIS-C from India. **Methods:** This systematic review was done as per the PRISMA guidelines, and quality assessment was done using NIH tool for case-series. A systematic search through databases yielded studies whose data was pooled to calculate the mean frequencies with standard deviation using GraphPad software. **Results:** Screening of 2548 articles published till December, 2021, yielded 11 case-series. World Health Organization case definition was used widely. There was a slight preponderance of males (57%), median (IQR) age was 7 (6,7) years, 63% (*n*=305) required intensive care unit admissions, and mortality rate was 10% (*n*=261). Clinical features included fever, mucocutaneous features (72%), and gastrointestinal problems (62%) in majority. Widely used treatment was corticosteroids (76%) and intravenous immunoglobulin (62%) with other options depending on patient's state. An increased level of inflammatory markers and derangement in other parameters corroborated with disease status. Kawasaki disease like features, not reported in many studies, ranged from 4-76% of patients. **Conclusion:** MIS-C presents with a wide spectrum clinical features, increased inflammatory markers and managed as per the disease course and presentation. Future studies monitoring the long-term effects of MIS-C are recommended.

Keywords: *Clinical features, Laboratory markers, Management*.

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A minority of children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present with multisystem inflammatory syndrome in children (MIS-C), usually 2 to 4 weeks post-infection, the pathophysiology of which is still unclear. The clinical features of this syndrome overlap with Kawasaki disease (KD), toxic shock syndrome (TSS), and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome; although the clinical picture keeps on evolving. The exact incidence is difficult to calculate and this entity is relatively rare, approximately 2 per lakh in children under the age of 21 years [1]. Well-accepted case definitions from various organizations are now available for a clinical diagnosis [2]. Data from India suggests similarity in infectivity rates during both the first and the second waves [3].

The current review addresses the question of clinical manifestations, laboratory profile and therapeutic strategies employed for MIS-C in India. Pooled analyses of all these aspects have been reported from various countries and population groups; however, the aim of current study was to gather data from Indian population and present it in the form of a systematic review.

METHODS

We detailed the following PECO (participants, exposure, comparison and outcome): P: Children with MIS-C, E: coronavirus disease –19 (COVID-19) infection, C: None, O: Types of organ systems involved, common clinical features associated with MIS-C, treatments used, and values of laboratory parameters.

Eligibility criteria for studies: Case series on MIS-C from India published in English till December, 2021 were included. Case definitions as per Centers for Disease Control (CDC), World Health Organization (WHO) and Royal College of Pediatrics and Child Health (RCPCH) criteria were considered. Data related to other coronaviruses were not included and SARS-CoV-2 positivity either by real time-polymerase chain reaction (RT-PCR) or serology was considered essential. Studies on adults (more than 18 years) were excluded.

Search strategy and information sources: The systematic review was conducted as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-

analysis) guidelines updated in 2021. The electronic search was conducted in PubMed, EMBASE and OVID databases. The key terms applied in the databases to search for the relevant studies are listed in **Web Box I.**

Selection process and data collection: Two authors independently did the screening of titles and abstracts. Full text of articles were retrieved, which were further screened by two authors as per the inclusion criteria. Finally, the articles were selected by consensus for inclusion in the review. A structured form to record the details was prepared to extract various parameters from the included studies. The data extraction was done independently by two reviewers, and any conflicts were resolved by discussion or by consulting a third reviewer. Data on age, gender, number of participants, MIS-C case definition, diagnostic criteria, clinical features, treatment regimes, laboratory parameters and features of KD were noted.

Critical appraisal: The quality of case-series was evaluated using the NIH quality assessment tool. Two authors independently did the quality assessment, which was further confirmed by a third author.

Effect measures and synthesis methods: Data on age, gender, SARS-CoV-2 infection confirmation by RT-PCR or serology, intensive care unit (ICU) admissions and mortality was collected from the case-series. Data on clinical manifestations, laboratory parameters and management were also collected. The findings from individual studies were summarized in summary tables, and data for these variables were pooled as relative frequencies and presented as mean and standard deviation. Data analysis and graphical plotting was done using Graph Pad Software (version 5.0, GraphPad Software Inc).

RESULTS

Database search and screening process is depicted in **Fig. 1**. A total of 2548 articles (Pubmed, 238; Scopus, 294 and EMBASE, 2016) were identified in accordance with the key terms from the published literature. Of these, 246 articles were removed due to duplication, and the remaining 2,302 articles were further screened by their title and abstract. Finally, 11 case series were identified for this review. The results of the critical appraisal of the included studies are presented in **Web Table I**.

Out of all the included studies, majority (*n*=6) used the WHO clinical definition for MIS-C; two studies each used the CDC and RCPCH definitions. The details of included case-series are depicted in **Table I.** The data were obtained from different cities across the country (**Web Fig. 1**). Majority of the studies are from the state of Maharashtra followed by Tamil Nadu and West Bengal. The cumulative demographic data comprising of age, gender, SARS-CoV-2

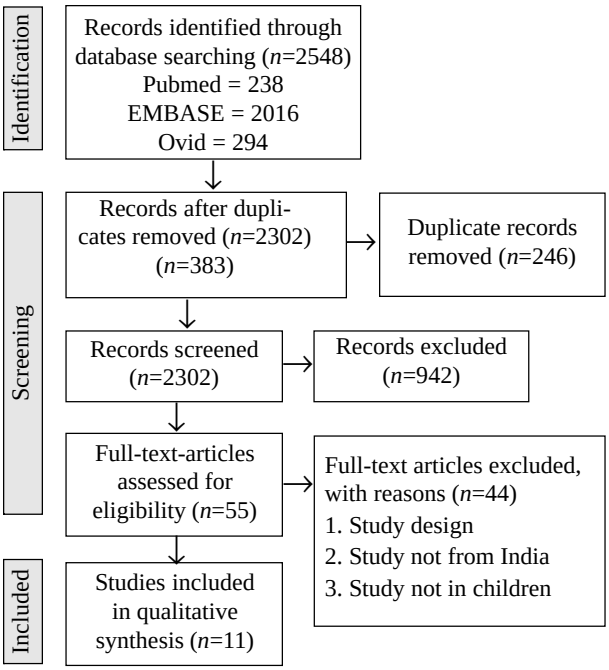

Fig. 1 Flowchart for screening and selection of studies.

positivity (RT-PCR and serology), ICU admissions and mortality on 305 children from different studies is shown in **Fig. 2**. Majority of children were males (57.42%), with median (range) age of 7 year (2 month-16 year). SARS-CoV-2 positivity was confirmed by serology in 71.5%, while rest had a positive RT-PCT. ICU admission was needed in 63.2%, with a mortality rate of 10.8%.

Clinical Manifestations

All children presented with high grade fever with median (IQR) duration of 6.1 (5.2, 7.9) days. The clinical features are presented in **Fig. 3.** The pooled data from all patients (*n*=313) from Indian case-series revealed predominance of mucocutaneous features (72%), with rash (53.5%), conjunctivitis (54.3%) and oral cavity changes (27%) being the most common findings. This was followed by gastrointestinal manifestations in around 62% of cases, including abdominal pain (54.7%) and diarrhea/vomiting (51%). SARS-CoV-2 induces multiple cardiovascular complexi-ties with manifestations in a significant percentage of children (54%). As expected, majority of studies reported complications of the respiratory system (42%) with cough and respiratory insufficiency being the main features. Not all studies reported neurological complications, accounting for around 32% in the remaining studies, which reported headache, seizures and/or altered sensorium being the main features. Features of KD fulfilling the classical definition were reported in six studies ranging from 4-76%. Based on these studies, the median (IQR) age of MIS-C children exhibiting KD like features was found to

Table I Details of Case-Series Included in the Review

Study ID	*City, No. of participants*	*Disease definition*	*Age (y)*	*Males no. (%)*	*SARS-COV-2*		*ICU admissions (%)*	*Mortality*	*KD like features no. (%)*
					RT-PCR	*Sero-logy (%)*			
Jain, et al. [8]	Mumbai, 23	WHO	7.2 (0.8 to 14)	11 (48)	39.1	30.4	-	4.30	1 (4.3)
Dhanalakshmi, et al. [9]	Chennai, 19	RCPCH	6 (1.1 to 16)	8 (42)	27	53	100	0	7 (36.8)
Shobhavat, et al. [10]	Mumbai, 21	WHO	7 (1.9 to 12)	10 (48)	38	76	100	14	NR
Gupta, et al. [4]	New Delhi, 20	CDC	1 to 12	12 (60)	98	Not done	65	60	4 (20)
Venkataraman, et al. [33]	Chennai, 44	RCPCH	7 (0.5 to 14)	19 (43)	23	100	53	0	NR
Sugunan, et al. [34]	Thiruvananthapuram, 32	CDC	7.5(5 to 9.5)	21 (66)	31	78	94	0	NR
Balagurunathan, et al. [5]	Coimbatore, 21	WHO	6.9 (4)) mean (sd)	15 (71.4)	4.8	90.4	52.4	0	16 (76.2)
Maheshwari, et al. [6]	Delhi, 29	WHO	4.1	18 (62)	82.7%	27.6	27.6	34.5	-
Angurana, et al. [7]	Chandigarh, 40	WHO	7	26 (65)	10	66.7	85	5	25
Kashyap, et al. [35]	Faridabad, 12	-	6.5	9 (75)	8.33	92	100	25	-
Nathella, et al. [36]	Chennai, 44	WHO	7	19 (43)	0	100	52.7	-	-

WHO: World Health Organization [https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19]; RCPCH: Royal College of Pediatrics and Child Health [https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance]; CDC: Centers for Disease Control [https://www.cdc.gov/mis/mis-c/hcp/index.html]. - indicates 'data not provided'.

be 6.9 (5.5, 7.3) year. In one of such case-series, around 35% MIS-C cases presented with acute encephalitis-like illness [4] and 20% had signs and symptoms of severe dengue-like illness.

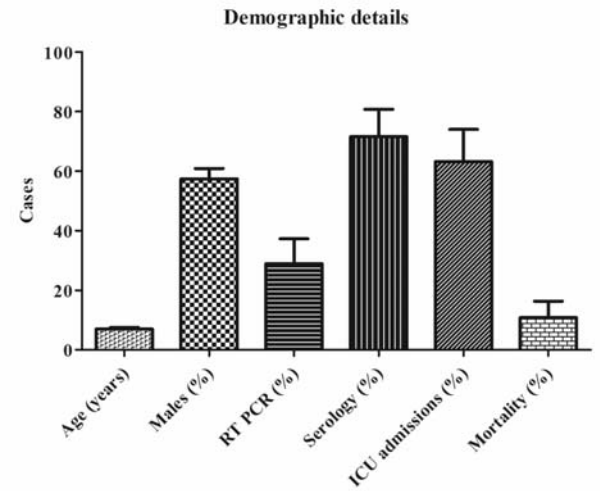

Fig. 2 Demographic characteristics of MISC children from included studies (*Data is presented as mean with standard error*).

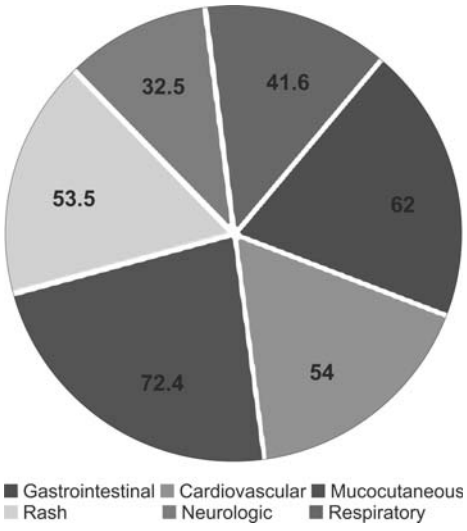

Fig. 3 Clinical manifestations of multisystem inflammatory syndrome associated with COVID-19 (MIS-C) from Indian case series (*N*=313).

Laboratory Parameters

Due to a lack of uniformity in the reporting format, laboratory investigations of individual studies could not be pooled and are presented in a tabular format (**Table II**). An increase in inflammatory markers, particularly C-reactive protein (CRP) was reported in more than 93% of patients, with values ranging from 96 to 473 mg/L (values reported in only a few studies). Another marker consistently high in studies was IL-6, with median values ranging from 43-527 pg/mL; although, only few case-series reported this marker. The most common hematological abnormalities reported were lymphopenia (44% of patients) and neutrophilia (75% patients, range 99.2-148.8×10^9/L) with few studies also reporting leuko-cytosis. Thrombo-cytopenia was also reported in 43% of patients (6 studies). Around 85% of patients had high values of D-dimer (ranging from 1469-10,000 ng/mL). Anemia was also reported in most of the children.

Biomarkers of cardiac dysfunction, troponin and pro-Brain natriuretic peptide (pro-BNP) were also reported to be deranged in many studies [5-7]. Around 82% of affected children had high pro-BNP values (median (range) 8202 (202- 29562) pg/mL), while 34% reported high troponin values (median value (range) 81 (33-348) pg/mL). Sufficient information regarding other para-meters such as creatinine and glutamic pyruvic trans-aminase was not provided in most of the studies. In studies where echocardiography was performed [6,8], left ventricular systolic dysfunction (41%) and coronary dilation (28%) were the most common findings. Arrhy-thmia and pericardial effusion was also seen in a few patients; however, reported only by two studies [7,9].

Management

The treatment approach followed in the included case-series has been summarized in **Fig. 4**. The data from 10 (*n*=233) studies is presented. Corticosteroids were the most commonly administered therapy (76%) followed by intravenous immunoglobulin (IVIG, 62%). Inotropic and vasoactive support was given to 49% patients. Four studies [5,7,9,10] used anti-coagulative drugs such as heparin and aspirin in 69% of patients. Not all studies have reported the use of antibiotics, but where needed, it was given to around 90% of the cases. Mechanical ventilation was provided to around 29% of patients to manage the respiratory insuffi-ciency. Immunomodula-tory agents such as tocilizumab and infliximab were used in around 8% of cases. One study [10] has also mentioned the use of adrenaline or noradrenaline in more than 80% of their patient cohort.

DISCUSSION

Majority of the children reported were aged around 7 years with a slight preponderance of males. A previous meta-analysis of 56 studies revealed an association of male gender with poor prognosis in COVID-19 in children [11], which has also been reported in adults [12]. A recent systematic review, in contrast, reported mean age of children to be around 9 years [13]. The mortality rate in our analysis was found to be more than 10%, which is much higher than <2% mortality rate reported in a few studies [32,35]. Owing to severe heart failure, cardiac arrest, and refractory hypotension, a higher number of deaths (6.7%) were observed in another study of children with COVID-19. KD-like features were more commonly associated with male gender [14]. A poor prognosis in males could be explained by ACE2 expression, the transmembrane protease, *serine-type 2 (TMPRSS2)* gene, and hyper-inflammatory immunological response in general in males [15].

Fever lasting for an average of 6 days was seen, corroborating with other systematic reviews [16]. As compared to other febrile conditions, children with MIS-C had a higher reported temperature (40°C vs 38.9°C) and a greater duration of fever [17]. We found a preponderance of mucocutaneous features, with less common respiratory features. Respiratory symptoms in children, as compared to adults, were less prevalent, as reported in other studies as well [18]. Evidence regarding oral manifestations in MIS-C has recently come up in a systematic review [19]. These authors reported oral manifestations to appear even earlier than systemic changes [41].

Acute abdomen is the characteristic feature of MIS-C, mostly due to non-surgical intestinal inflammatory pathology. Similar to our findings, gastrointestinal symptoms were observed in around 61% of patients in a recently published systematic review [20]. Another review of 1415 patients from 31 studies across the globe reported predominance of gastrointestinal symptoms and a lesser frequency of patients experiencing respiratory symptoms [21]. This could be explained by a lower expression of ACE-2 receptor gene among children as compared to adults. Another report by Dhar, et al. [22] documented a very high incidence of gastrointestinal symptoms (84%), followed by myocarditis and neurological involvement. More than 50% of children in our review reported cardiovascular changes, corroborating with previous reports [21]. Such symptoms occur concurrently with the peak of cytokine storm with levels of IL-6 correlating with coronary artery dilatation. Cardiac injury could also be caused by a direct viral infection of cardiomyocytes via the ACE2 receptor causing acute myocarditis [23].

A cytokine driven hyper-inflammatory state is postulated to disrupt the blood-brain barrier without direct viral invasion of central nervous system [24]. Another

Table II Laboratory Markers of MIS-C Patients from Different Case-Series (*N*=305)

Study	*CRP mg/dL*	*Ferritin (ng/mL)*	*Leukocytes (x109)*	*Lympho-cytes %,*	*Neutro-phils %,*	*Hb gm/dL*	*Platelet x109*	*Creatini-ne (mg/dL)*	*D-dimer (ng/mL)*	*ESR*	*IL-6 (pg/mL)*	*NT-Pro BNP (pg/mL)*	*Troponin (ng/mL)*	*Hepatic dysfunction*
Jain, et al. [8]	96.6	596.8 (282.2-1473.5)[a]	15%	14.3%	80	10.4 (2.2)	236.8 (155.9)	0.47 0.35-(0.6)[a]	4090 (1824.9-9958.7)[a]	NR	230.2 (95.5-498.7)[a]	410 (205.5-21277)[a]	33.4 (5.7-185)[a]	–
Dhanalakshmi, et al. [9]	100%	238 (220-1230)a, 21.4%	–	36.8%	68.4%	31.5%	15.7%	NR	92.8%	81.8%	-	75%	16.6%	–
Shobhavat, et al. [10]	98 (89-119)[a]	710 (422-1609)[a]	9.8 (2.8-14.15)	80%	NR	9.6 (9-11.1)	71%	NR	2664 (1469.5-6510)	NR	215 (43-527)	NR	53.5 (21.75-367.9) pg/mL	–
Gupta, et al. [4]	99%	99%	15%	30%	NR	NR	25%	5%	50%	NA	15%	NA	NA	60%
Venkataraman, et al. [33]	169 (39-473)	NR	NR	1386 (330-2200) /mm3	11658 (9918-14878) / mm3	NR (62-110)	110	NR	NR	NR	NR	NR	NR	NR
Sugunan, et al. [34]	94%	NR	NR	NR	NR	NR	59.3%	NR	100%	47%	NR	87.5%	–	56/50%
Balagurunathan, et al. [5]	100%	42.9%	NR	47.6%	76.2 %	19%	38%	NR	95.2%	85%	90.5%	80%	30.8%	35/29
Maheshwari, et al. [6]	101 mg/L	335, 28.6%	NR NR	38%	NR	61.9%	127000 /mL	NR	80.9%	45 mm/h		NR	NR	23.8%
Angurana, et al. [7]	95%	90%	NR	65%	NR	NR	50%	NR	92.5%	NR	NR	100%	65%	47.5%
Kashyap, et al. [37]	100%	66.7%	NR	NR	NR	NR	NR	NR	83.3%	NR	NR	66.6%	NR	NR
Kumar, et al. [36]	169 (39-473)	605 (38-2571)[a]	NR	1386 (330-2200)	11 658 (9918-14 878)	-	110 (62-210) ×109/L	NR	4890 (2446-10 000)[a]	NR	NR	NR	NR	NR

Values in mean (SD) or [a]median (IQR). % indicates percentage of patients having abnormal values. MIS-C –multisystem inflammatory syndrome in children, NR – Not reported. [b]Defined as *(AST>50U/I) (ALT>50 U/I).*

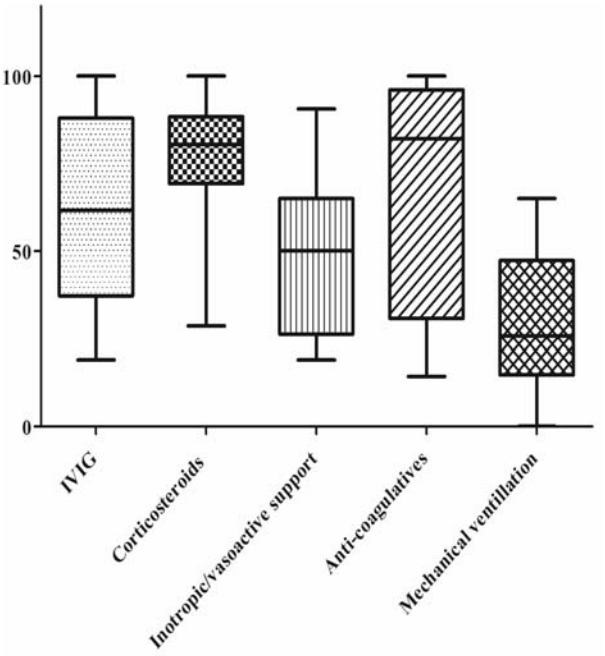

Fig. 4 Therapeutic approaches used for clinical management of multisystem inflammatory syndrome in children (MIS-C) (*N*=233) in Indian case-series.

mechanism could be an induction of autoimmune response owing to a mimicry of viral antigens with self-antigens which occurs following a latent period post-infection [25]. The most commonly observed symptoms include strokes, encephalopathy and seizures. We found only 32% of children manifesting with features of headache, seizures, and altered senso-rium. Similarly, another review reported 38% of the cases with neurologic manifestations [26]. The pathophysiological mechanisms behind such complications during MIS-C remain unclear. Another study found neurologic symptoms to be relatively rare [48]. Adults, on the other hand, have quite a high prevalence of such neurological features [27].

The treatment is partly dependent on the presenting condition of patient, and has been evolving with the availability of a wide range of therapeutic options. A recently published review reported frequent use of IVIG and other anti-inflammatory medicines including aspirin, corticosteroids, inotropes and anticoagulation therapies [28]. Unlike adults, the use of antivirals and convalescent plasma therapy was infrequent, as reported in other reviews as well [29]. A better clinical efficacy reported to be achieved with treatment with IVIG together with methylprednisolone as compared to IVIG alone [30].

Higher than normal BNP levels were found in our review, as reported in a meta-analysis of cardiac markers in MIS-C patients as compared to mild or moderate COVID-19 cases [31]; although, troponin and aspartate aminotransferase were not different between these two patient groups.

MIS-C remains a multi-faceted disease and hence poses a difficulty for the treating clinician to decide on the course of its management. New guidelines keep on emerging as the disease evolves over time and as the data on long term effects of MIS-C becomes available. Therefore, we have attempted a compilation of all clinical aspects of MIS-C in the Indian population. Despite following a structured framework to undertake this review, we acknowledge certain limitations. The data was collected from individual case series, because of non-availability of any randomized control trial in our population that could have shed light on the efficacy of various therapeutic regimes. The heterogeneity among the included studies could have led to an over- or under-estimation of some parameters reported in the current review. Data reporting was quite variable among studies. In addition, the effect of various comorbidities and any underlying risks could not be assessed because of insufficiency of data in this regard. We recommend further studies monitoring the long term effects of MIS-C through follow-up evaluations. Many such studies are ongoing and results awaited. Nevertheless, this systematic review provides adequate evidence from Indian population that will help pediatricians in a better management of this disease.

Note: Additional material related to this study is available with the online version at *www.indian pediatrics.net*

Contributors: MS: wrote the protocol, did screening of articles, data extraction and synthesis, compilation and interpretation of results and wrote the manuscript. AA: confirmed the data extraction. HS did the screening; MR, SS: did quality assessment and was confirmed by MS. PP did literature search in databases; MaS: reviewed the manuscript; MeS: conceived the idea, obtained the funding, finally supervised, reviewed and approved the manuscript. All authors reviewed the manuscript.

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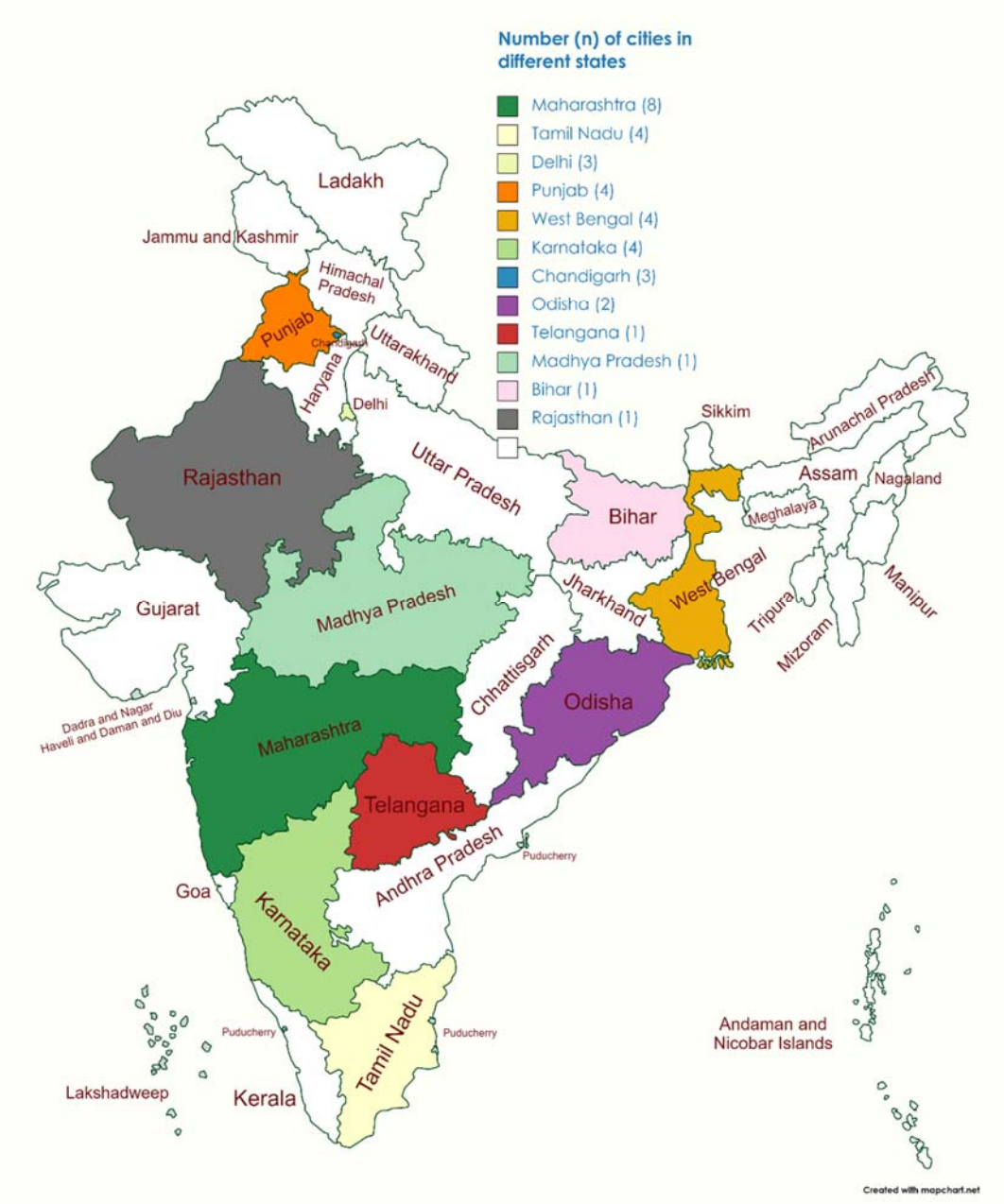
Web Table I: Critical appraisal of included case-series by NIH tool.

Study ID	Type of Study	1. Was the study question or objective clearly stated?	2. Was the study population clearly and fully described, including a case definition?	3. Were the cases consecutive?	4. Were the subjects comparable?	5. Was the intervention clearly described?	6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	7. Was the length of follow-up adequate?	8. Were the statistical methods well-described?	9. Were the results well-described?	Quality Rating
		Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Yes/No/Cannot Determine/Not Applicable/Not Reported	Good/Fair/Poor
Aishwarya Venkataraman et al 2021	Case Series	yes	yes	yes	yes	yes	yes	No	yes	yes	Fair
Anu Maheshwari et al 2021	Case Series	yes	yes	yes	yes	no	yes	not reported	yes	yes	Fair
Haripal Kashyap et al 2021	Case Series	yes	no	yes	yes	yes	yes	not reported	no	Yes	Poor
K Dhanalakshmi et al 2020	Case Series	yes	yes	yes	yes	yes	yes	yes	no	Yes	Good
Lakshmi Shobhavat et al 2020	Case Series	yes	yes	yes	yes	yes	yes	yes	yes	yes	Good
Muruganantham Balagurunathan et al 2021	Case Series	yes	yes	yes	yes	yes	yes	yes	yes	yes	Good
Nathella Pavan Kumar et al 2021	Case Series	yes	yes	yes	yes	yes	yes	no	yes	yes	Good
Sheeja Sugunan et al 2021	Case Series	yes	yes	cannot Determine	yes	yes	yes	yes	yes	yes	Good
Shobhna Gupta et al 2021	Case Series	yes	yes	yes	yes	yes	yes	not reported	yes	yes	Good
Shreepal Jain et al 2020	Case Series	yes	yes	yes	yes	yes	yes	yes	no	yes	Fair
Suresh Kumar Angurana et al 2021	Case Series	yes	yes	yes	yes	yes	yes	yes	yes	yes	Good



Web Fig. 1 Distribution of studies among different states in India**.** The number of cities belonging to different states in which studies on MISC were taken is given in the legend.

Web Box I Key Terms Applied to Search for Relevant Studies

((((((((((misc) OR ("pediatric multisystem inflammatory disease, COVID-19 related" [Supplementary Concept])) OR (Multisystem Inflammatory Syndrome)) OR (Multisystem Inflammatory Syndrome in Children)) OR (pediatric multisystem inflammatory syndrome, SARS-CoV-2 related OR pediatric multisystem inflammatory syndrome, COVID-19 related OR pediatric multi-system inflammatory syndrome, COVID-19 related OR pediatric multi-system inflammatory syndrome, SARS-CoV-2 related OR MISC associated with COVID-19 OR multisystem inflammatory syndrome, pediatric, COVID-19 related OR multi-system inflammatory disease, pediatric, COVID-19 related OR multi-system inflammatory syndrome, pediatric, COVID-19 related OR PIMS-TS OR multisystem inflammatory syndrome in children MIS-C associated with COVID-19 OR MIS-C associated with COVID-19 OR pediatric multi-system inflammatory disease, COVID-19 related OR multisystem inflammatory disease, pediatric, COVID-19 related OR pediatric inflammatory multisystem syndrome OR MIS-C multisystem inflammatory syndrome in children OR multisystem inflammatory syndrome in children)) OR (COVID-19 related multi-inflammatory syndrome)) OR (COVID-19 Systemic inflammatory syndrome)) OR (pediatric inflammatory multisystem syndrome)) OR ((((((multisystem inflammatory) OR (pims-ts)) OR (children multisystem inflammatory syndrome)) OR (covid children multisystem inflammatory)) OR (multisystem inflammatory syndrome children)) OR (covid multisystemic inflammatory syndrome))) OR ((((((Kawasaki disease) OR (covid-19 kawasaki)) OR (kawasaki disease children)) OR (Kawasaki Syndrome)) OR (kawasaki like disease)) OR (kawasaki like covid children))) AND (India)) AND (("2020/01/01"[Date - Publication]:"2021/06/15"[Date - Publication]))) AND (("2021/06/15"[Date - Publication] : "2021/12/31"[Date - Publication]))