Review Article

Alteration of inflammatory markers in children and adolescents of multisystem inflammatory syndrome group during novel corona virus infectious disease-2019: A systematic review and meta-analysis

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Abstract

Background: To determine the impact of multisystem inflammatory syndrome (MIS) caused by novel coronavirus infectious disease-2019 (nCOVID-19) more investigations are needed related to children and adolescents. Among several inflammatory markers, C-reactive protein (CRP), procalcitonin (PC), ferritin (F) and erythrocyte sedimentation rate (ESR) can be easily done among infected cases to assess the inflammatory status even in asymptomatic cases.

Objective: A systematic review and meta-analysis to compare MIS and non-MIS cases in relation to elevation of inflammatory marker in children and adolescents due to nCOVID-19.

Method: Studies providing data on the prevalence of n-COVID-19 in children and adolescents (<21 years) were compared between MIS and non-MIS groups. All studies were selected from PubMed and other electronic database and PRISMA guidelines were followed for data abstracting. During screening and quality assessment, each article has been evaluated by two reviewers independently. For each parameter, the rate ratio and 95% confidence intervals (CIs) were compared between increased and non-increased group through Forest plot model.

Results: The present study indicated elevated range of all studied markers in the children during nCOVID-19 outbreak. The Forest plot indicated low heterogeneity for three studied markers, which can be the important parameter for identifying clinical feature of MIS during nCOVID-19.

Conclusions: All studied markers (CRP, PC, F and ESR) were elevated in children and adolescents during nCOVID-19 outbreak

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(Key words: nCOVID-19, inflammatory markers, clinical features, children, adolescents)

Introduction

The outbreak of novel corona virus infectious disease (nCOVID-19) commenced in Wuhan, Hubei Province, China in December 2019 and later, the World Health Organization declared it a pandemic[1]. It was named as severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) after taxonomical identification by the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses[2]. This virus spread rapidly in China followed by different parts of the globe and all states in India. It is reported that n-COVID-19 has a higher risk of disease severity and deaths among older people and in persons with underlying co-morbidities like hypertension, cardiac disease, chronic lung disease and cancer[3-6]. Many studies indicated that most children did not show manifestations and accounted for 1-2% of infected cases with minimal casualties[7-15].

It is well-known that interferon (IFN) is produced by host cells through an antiviral response during viral infection within the body because IFN is the first-line innate immune defence of the body, categorized into IFN-α, IFN-β, etc.[16-17]. A study was conducted on the treatment of upper respiratory tract infections in children using recombinant human IFN-α2b spray in the mouth and nose as topical therapy, which inhibited viral infection[17]. It is well-established that children have relatively mild clinical manifestations of nCOVID-19 in comparison with adults and a few studies on immunologic features, which may distinguish children with and without "multisystem inflammatory syndrome in children (MIS-C)" are still unclear[19-20]. Moreover, a few studies were elaborated about inflammatory markers in which C-reactive protein (CRP) is a common marker and increased due to SARS-CoV-2[21-26].

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Objectives

To assess the alteration of inflammatory markers, especially CRP, in children and adolescents after mild or severe infection by nCOVID-19 through a systemic review and meta-analysis from the diagnostic evidence among hospitalized multisystem inflammatory syndrome (MIS) or non-MIS and asymptomatic patients.

Method

Search summary: According to the recent article by Viner RM, *et al*[27] and Institute of Medicine (IOM) standards & guidelines[28], the present study was performed by a comprehensive literature search from PubMed, Embase, Cochrane Library and Scopus database, and the last search was done on December 23, 2020. The search keywords for present study were 'nCOVID-19' OR 'Coronavirus' OR 'CoV-2' OR 'nCOVID-19 pandemic' AND 'Children' OR 'Inflammatory markers in children' OR 'Inflammatory markers in paediatrics' OR 'Inflammatory markers in infants' used in varying permutations and combinations, along with extensive cross-referencing. Firstly, we screened all titles and abstracts for relevance to the study and reviewed the full content of the relevant studies. All the relevant studies in the English language were checked and included. The search protocol was followed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as per earlier articles of Viner RM, *et al*[27] and Wu Z and Yang D[29]. Moreover, the researchers selected standards for the development and reporting of clinical practice guidelines from the 'IOM recommendations in *Clinical Practice Guidelines We Can Trust'*[28]. Each clinical practice guideline summary was independently evaluated for compliance by 2 of the reviewers.

Data extraction: One reviewer (JS) performed the searches and screened for duplicates. Other three reviewers RB, GD and KB independently screened all unique search results for potential above-mentioned inclusions used in the systemic review and meta-analysis. In case there were conflicts, discrepancies in the evaluations were resolved through open discussion by two reviewers (JS and RB). Articles passing reviewers' approval were finally considered for inclusion. Finally, data extraction was done (KB) by using a standardized data extraction sheet for extracted data from each study. The data extraction form included (1) author name, (2) year of publication, (3) study area, (4) age-groups for nCOVID-19 diagnosed, (5) inflammatory markers disorders during diagnostic procedure, and (6) number of children/adolescents affected. For Quality Assessment (QA) of selected six studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for studies reporting prevalence data was used. The final set of articles for inclusion in the review were identified based on the quality of those selected studies. Only the studies of appropriate and good quality were included.

Statistical analysis: The forest plot was used to determine the combined rate ratio (RR) and weight ratio (%) on specific studies along with corresponding 95% confidence intervals (CI) to assess the relationship between inflammatory marker and impact of nCOVID-19 among children. This study was carried out by using the meta-analysis software (MetaXL, Version 5.3) developed by Barendregt for obtaining forest plot[29-30], which determined the elevation of inflammatory markers, especially CRP level, compared between increased and non-increased groups of MIS and non-MIS, or other's groups of asymptomatic children and adolescents by nCOVID-19.

In the present study, the contribution made by each reviewer is as follows: JS performed the searches and screened for duplicates; RB, GD, and KB independently screened all unique search results; conflicts were openly discussed and resolved by JS and RB for discrepancies in the evaluations; data extraction was done by KB and JS.

Results

Selection of studies and characteristics of included studies

Figure 1 depicts the process of study inclusion. In total, 28 citations were screened, and 24 full articles were retrieved, of which 6 were identified as full text research articles. Of these full text articles, 6 were included in the systemic review and meta-analysis study. The present study carried out the quality appraisal process for these six articles and each article was evaluated by two reviewers (JS and RB) independently and conflicts were resolved after open discussion. After the QA process, only the articles that met quality criteria for inclusion in the review were considered.

Study processing

The systematic review is based on nCOVID-19 or SARS-CoV-2 infection among children with an alteration of CRP during infection. Six appropriate studies from different countries are compiled only on the patients presenting hyper-inflammatory disorders by increasing CRP, procalcitonin (PC), ferritin (F) and erythrocyte sedimentation rate (ESR) level in MIS or non-MIS groups in nCOVID-19. Table 1 describes the diagnostic features among children after nCOVID-19 symptoms

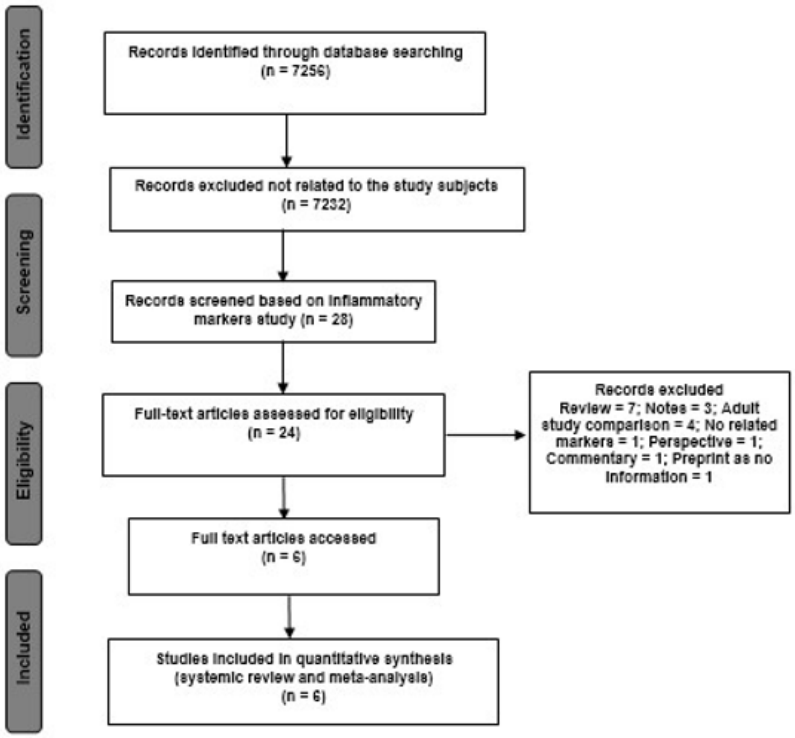

Figure 1: ***PRISMA flow diagram for included study on inflammatory marker elevation in children during nCOVID-19 outbreak***

Table 1: ***Diagnostic features among children and adolescents due to nCOVID-19***

Sl. No.	Study area	Study groups	Study type	Total cases (n)	Diagnostic features
					PCR+ & antibody testing (n)
1.	USA	Lee PY, *et al*[21]	R	28	17
2.	China	Bai K, *et al*[22]	R	25	25
3.	USA	Fernandes DM, *et al*[23]	R and P	281	281
4.	Brazil	Prata-Barbosa A, *et al*[24]	P and O	79	79
5.	USA	Feldstein LR, *et al*[25]	P	186	131
6.	USA	Dufort EM, *et al*[26]	P	99	99

R: Retrospective, P: Prospective, O: Observational, PCR: polymerase chain reaction

Lee PY, *et al*[21] evaluated a retrospective study in USA among 28 confirmed cases of SARS-CoV-2 infection in children aged 1 month to 17 years. The study was conducted on MIS in children. Of the 28 children, 17 were found positive through polymerase chain reaction (PCR) test of nasopharyngeal swabs.

Bai K, *et al*[22], in a retrospective study in China found 25 confirmed cases of 2019-nCoV infection after real-time reverse transcription-PCR (RNA-PCR) test in children aged 0.6 to 17 years.

A retrospective and prospective study by Fernandes DM, *et al*[23] revealed confirmed hospitalized SARS-CoV-2 infection in children and youth aged ≤22 years with MIS in USA.

Prata-Barbosa A, *et al*[24] conducted a prospective observational study among 79 children aged 1 month to 19 years infected with nCOVID-19 in Brazil in which 10 had MIS confirmed through real-time reverse transcription-PCR (RT-PCR) test.

Feldstein LR, *et al*[25] conducted a prospective study among 186 children and adolescents of USA aged <21 years in which 73 confirmed cases of SARS-CoV-2 were based on RT-PCR test and 55 were confirmed after linking with infected COVID persons, but 172 cases were found as MIS children and 14 as non-MIS cases.

Dufort EM, *et al*[26] carried out a prospective study in USA among 191 children and adolescents aged <21 years in which 99 were confirmed SARS-CoV-2 by RT-PCR test and these cases were with MIS.

Table 2 describes the demographic profiles viz. age and gender, as well as clinical symptoms, among children and adolescent who underwent hospitalization due to nCOVID-19.

Table 3 describes the alteration of different biomarkers of CRP, PC, F and ESR among children and adolescents after nCOVID-19 outbreak.

Table 2: ***Demographic profiles and clinical symptoms of children and adolescents during nCOVID-19***

Studies	Lee et al[21]	Bai et al[22]	Fernandes et al[23]	Prata-Barbosa et al[24]	Feldstein et al[25]	Dufort et al[26]
Total cases (n)	28	25	281	79	186	99
Age (years)	0.1 – 17.0	0.6-17.0	1.0 – 17.0	IQR (1.0 −10.3)	<1.0-20.0	<20
Gender (%)	M = 57; F = 43	M = 56; F = 44	M = 61; F = 39	M = 54; F = 46	M = 62; F = 38	M = 54; F = 46
Symptoms (%)	Fever 100 Gastrointestinal 54 Conjunctivitis 57 Skin rash 36	Asymptomatic 32 Fever 24 Cough 52 Sore throat 12 Running nose 12 Nasal obstruction 12 Diarrhoea 4 Weakness 4	Respiratory 60.8 MIS 60.9 Others 59.4	Pneumonia or bronchiolitis 70 MIS + Kawasaki-like disease 60 Acute cardiac dysfunction 20 Toxic shock syndrome 10 MAS 10	Fever 78 Gastrointestinal 92 Cardiovascular 80 Haematologic 76 Mucocutaneous 74 Respiratory 70	Fever or chills 99 Chest pain 11 Gastrointestinal 80 Dermatologic 62 Mucocutaneous 61 Neurological 30 Musculoskeletal 20

MIS: Multisystem inflammatory syndrome; MAS: Macrophage activation syndrome

Table 3: ***Alteration of inflammatory markers among children and adolescents due to nCOVID-19***

IM effect	Lee et al[21]	Bai et al[22]	Fernandes et al[23]	Prata-Barbosa et al[24]	Feldstein et al[25]	Dufort et al[26]
Parameter	CRP >0.5 mg/dl	CRP (mg/l)	CRP (mg/l)	CRP ≥3 mg/dl	CRP ≥3 mg/dl	CRP ≥3 mg/dl
Increased (n)	26	17	212	10	172	98
No or little change (n)	02	08	69	63	14	01
Parameter	PC ≥ 0.1 ng/mL	-	-	PC ng/mL	-	-
Increased (n)	24	-	-	02	-	-
No or little change (n)	01	-	-	01	-	-
Parameter	F > 200 ng/mL	-	-	F ng/mL	F>500 ng/mL	F>300 ng/mL
Increased (n)	24	-	-	07	163	62
No or little change (n)	04	-	-	17	23	37
Parameter	ESR > 30 mm/h	-	-	ESR mm/1st h	ESR ≥ 40 mm/ h	ESR≥ 40mm/h
Increased (n)	15	-	-	09	117	40
No or little change (n)	09	-	-	05	69	59

IM = Inflammatory markers; CRP = C-reactive protein; PC = Procalcitonin; F = Ferritin; ESR = Erythrocyte sedimentation rate; h = Hour

Lee PY, *et al*[21] found 26 of 28 children had elevated CRP levels, 24 of 25 cases had increased PC, 24 of 28 cases had increased F and 15 of 24 cases had elevated ESR (Table 1).

Bai K, *et al*[22] found elevated CRP levels in 17 of 25 cases. According to them, CoV-2 infection increased CRP in mild cases by 1.76mg/l (0.42-2.27mg/l) and common cases by 2.10mg/l (0.33-13.18mg/l) compared to asymptomatic cases by 0.09mg/l (0.03-1.09mg/l).

Fernandes DM, *et al*[23] studied all MIS cases that SARS-CoV-2 infection increased overall CRP value (212 cases) of 7.8 mg/l (1.73-27.2mg/l) when combined respiratory data of 4.5 mg/l (1.0-14.5mg/l), MIS-C data of 25.7mg/l (10-38.1mg/l) and others of 3.5mg/l (0.5-7.9) in comparison with not elevated as normal cases (69 cases).

Prata-Barbosa A, *et al*[24] compared the level of CRP, PC, F and ESR between MIS and Non-MIS children after a SARS-CoV-2 infection. Of 79 children, 10 cases of MIS had increasing CRP level of 10mg/dl (9-30mg/dl) when compared to non-MIS group of 3mg/dl (0.6-18mg/dl). Interestingly, 63 of 79 children of non-MIS group increased by ≥3mg/l while all 10 children of MIS group increased by ≥10mg/l of CRP level. The marker PC (ng/L) was increased in only 2 cases of MIS and did not increase in 1 case among non-MIS. Another marker F (ng/L) was also elevated in 7 cases of MIS and was not elevated in 17 cases of Non-MIS. In the case of ESR (mm/1st h), 9 cases of MIS group found an increasing trend while 5 cases of non-MIS group did not observe any elevation.

Feldstein LR, *et al*[25] analysed the CRP, F and ESR level in MIS children and adolescents in which they categorized MIS age groups as <5 years (50 cases), 5-12 years (67 cases), and 13-20 years (39 cases). Their research indicated maximum increase in CRP level (overall 17.8 mg/dl) in age groups of <5 years (13.6 mg/dl; IQR [interquartile range] 6.8-19.7 mg/dl), 5-12 years (19.3 mg/dl; IQR 15.6-29.2 mg/dl) and 13-20 years (23.9 mg/dl IQR 16.3-29.9 mg/dl), respectively. For overall F (>500 ng/mL) marker, an elevated level was observed in 163 cases of MIS group compared to 23 in non-MIS group while the researchers categorized the highest F level in age groups of <5 years (403.0 ng/mL; IQR 259.8-732.5 ng/mL), 5-12 years (679.8 ng/mL; IQR 377.9-1126.9 ng/mL) and 13-20 years (938 ng/mL IQR 449.0-1609.2 ng/mL), respectively. In case of ESR (≥ 40 mm/h), an elevated level was observed in 117 cases of MIS group when compared to 69 in non-MIS group and age group-based categorization indicated as <5 years (62 mm/h; IQR 36.8-88.5 mm/h), 5-12 years (68 mm/h; IQR 46-100 mm/h) and 13-20 years (66.5 mm/h IQR 44.2-84.0 mm/h), respectively. The comparison was done with non-MIS group due to CoV-2 infection.

Dufort EM, *et al*[26] studied children and adolescents of about 99 cases were confirmed by infection of SARS-CoV-2 in which MIS of 99 cases were found.

The present study was concerned with the CRP level of ≥3mg/dl in which 98 cases were observed elevated level (median 21.9 mg/dl, IQR 15.0-30.0 mg/dl) and 1 case was reported without increasing value. For F marker (>300 ng/mL), it was observed an increasing trend of about 62 cases (median 522 ng/mL, IQR 305-820 ng/mL) among MIS group and did not show any change of about 37 cases among non-MIS group. In the case of ESR (≥ 40 mm/h), an elevated level was found of about 40 cases of MIS (median 61.5 mm/h, IQR 43.0–77.5 mm/h) while did not show elevation of about 59 cases of non-MIS. Figure 2 (A-C) represents the Forest plot in which the rate ratio, 95% confidence interval (CI) and weight (%) values in each study was exhibited.

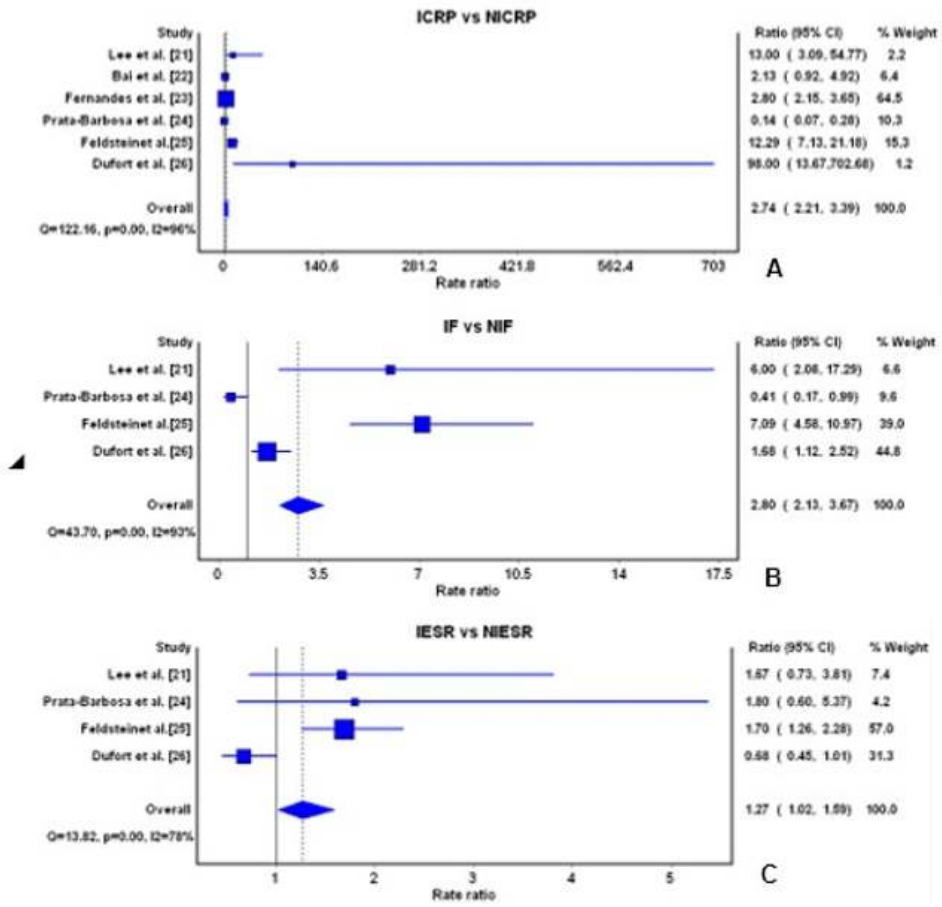

Figure 2: Forest plot representing comparison between increased versus non-increased inflammatory markers (CRP, F, and ESR) during nCOVID-19 outbreak (I = increased; NI = non-increased; A = ICRP vs NICRP; B = IF vs NIF and C = IESR vs NIESR)

Among the six studies for CRP marker, maximum value of weight (64.5%) was obtained for Fernandes DM, *et al*[23] due to higher sample size. Moreover, the overall I^2 value of about 96% with a Chi square P = 0.000 and pooled rate ratio with 95% CI (2.74%, 2.21-3.39) were obtained. In the case of F marker four studies were evaluated, maximum value of weight (39.0%) was obtained for Fernandes DM, *et al*[23] due to higher sample size. Moreover, the overall I^2 value of about 93% with a Chi square P = 0.000 and pooled rate ratio with 95% CI (2.80%, 2.13-3.67) were obtained. For ESR four studies were evaluated, maximum value of weight (39.0%) was obtained for Fernandes DM, *et al*[23] due to higher sample size. Moreover, the overall I^2 value of about 78% with a Chi square P = 0.000 and pooled rate ratio with 95% CI (1.27%, 1.02-1.59) were obtained. In the present study low heterogeneity was observed, which indicated CRP, F and ESR are important diagnostic markers for identifying clinical feature of nCOVID-19.

Discussion

The present systematic review and meta-analysis observed that CRP is elevated in children and adolescents due to nCOVID-19 among increased (MIS or non-MIS) groups compared to non-increased groups. However, a positive PCR without

clinical symptoms was found in children and adolescents of asymptomatic cases as they were MIS or non-MIS group or mild symptoms of nCOVID-19[21-26]. The relationship between nCOVID-19 and MIS in children needs more research. The forest plot indicated low heterogeneity, but overall studies showed significant level of CRP, F and ESR elevated groups compared to non-altered groups. Few studies have evaluated the inflammatory biomarkers in which CRP, F and ESR are common[21-26]. This review was done to assess whether CRP is increasing or not as well as other biomarkers like PC, F and ESR[22] but CRP, PC, F and ESR are common in all six studies except the parameter PC and the present study considered CRP, F and ESR to know heterogenicity by using Forest plot. The present study found elevated levels of CRP, F and ESR in the children during nCOVID-19. In all studies clinical symptoms were more or less same as viral infection. In this study, the samples were small and further research with large numbers of samples is suggested where higher heterogenicity can be achieved. This biomarker can be useful to assess the prevalence of nCOVID-19 in adults followed by comparative study of children versus adult in future studies on systemic review and meta-analysis with higher samples.

Conclusions

All studied markers (CRP, PC, F and ESR) were elevated in children and adolescents during nCOVID-19 outbreak

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