Review Article

Incidence of Multisystem Inflammatory Syndrome in Children (MIS-C) with Covid-19 (SARS-CoV-2): Systematic Review and Meta-Analysis

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Abstract

Background: MIS-C associated with Covid-19 is characterized by way of persistent fever and is often associated with a stomach ache, vomiting, diarrhea, rash, and conjunctivitis, and other mucocutaneous manifestations. **Aim:** This work aims to determine the clinical course, safety profile, and inflammatory markers of Multisystem Inflammatory Syndrome in Children (MIS-C) which is associated with Covid-19 children. **Methodology:** A systematic search was performed over different medical databases to identify Pediatrics studies, which studied the outcome of the MIS-C of Covid-19 children. We conducted a meta-analysis process on the incidence of MIS-C as a primary outcome, and on the estimated level of serum C-Reactive Protein (CRP), ferritin, and D-dimer as secondary outcomes. Six studies were identified involving 1747 children with Covid-19. Our meta-analysis process showed a pooled incidence of MIS-C in Covid-19 children of 39.8%. Concerning the secondary outcome measures, the Fixed-effects model of the meta-analysis process revealed an average estimate CRP level of 223.1 mg/dl, an average estimate ferritin level of 566.5 mg/dl, and an average estimate D-dimer level of 595.6 mg/dl, respectively. **Conclusion:** To conclude, Covid-19 infection is typically very mild and often asymptomatic in children. Multisystem Inflammatory Syndrome in Children (MIS-C), which is a rare complication associated with Covid-19, presenting after infection as high fever, organ dysfunction, and strongly elevated markers of inflammation.

Keywords: MIS-C; Covid-19; Inflammatory marker; Children

Introduction

Covid-19, an extreme viral respiratory infection caused by SARS-CoV-2, impacts all age groups, but it is more severe in the elderly and individuals with co-morbidities. These days, a severe multisystem inflammatory syndrome has been mentioned in individuals <21 years of age. The work presented here details our multidisciplinary method to this syndrome and discusses current expertise on the case definition and clinical manifestations and proposes recommendations on diagnosis and treatment. As the symptoms of many of those children may deteriorate quickly and may require attendance to non-tertiary care facilities, a preferred guide for an approach to such children is warranted. [1] Medical manifestations of Covid-19 as a result of the novel coronavirus SARS-CoV-2 are related to age. At the same time as children are largely spared from severe respiratory symptoms, they can present with a SARS-CoV-2-related Multisystem Inflammatory Syndrome (MIS-C) similar to Kawasaki's disease. Here, we show distinct Antibody (Ab) responses in kids with MIS-C in comparison to adults with excessive Covid-19 causing Acute Respiratory Distress Syndrome (ARDS), and those who recovered from the mild disease. There has been a reduced breadth and specificity of anti-SARS-CoV-2 precise antibodies in MIS-C patients compared to the Covid affected person companies; MIS-C predominantly generated IgG Abs specific for the spike S-protein but now not for the nucleocapsid N-protein, while the Covid-19 cohorts had anti-S antibodies, as well as anti-N IgG. [2] MIS-C associated with Covid-19 is characterized by way of persistent fever and is often associated with a stomach ache, vomiting, diarrhea, rash, and conjunctivitis, and other mucocutaneous manifestations.

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In affected youngsters, MIS-C related to Covid-19 might also develop hypotension and shock with cardiac and different end-organ injuries. Because most kids with MIS-C have serologic evidence of prior SARS-CoV-2 infection, MIS-C may additionally represent an immune-mediated delayed host response to the virus. [3] This work aims to determine the clinical course, safety profile, and inflammatory markers of Multisystem Inflammatory Syndrome in Children (MIS-C) in Covid-19 children.

Methodology

Our review came following the (PRISMA) statement guidelines. [4]

Study eligibility

The included studies should be in English, a journal published article, and a human study describing Covid-19 in children. The excluded studies were either animal or non-English studies or articles describing adult Covid-19 patients.

Study identification

Basic searching was done over the pubmed, cochrane library, and google scholar using the following keywords: MIS-C, Covid-19, inflammatory marker, children.

Data extraction

Comparative studies, clinical trials, and Randomized Controlled Trials (RCTs), which studied the outcome of MIS-C of Covid-19 in children, will be reviewed. Outcome measures included the incidence of MIS-C as a primary outcome, and on the estimated level of serum C-Reactive Protein (CRP), ferritin, and D-dimer as secondary outcomes.

Study selection

We found 250 records, 190 excluded because of the title; 60 articles are searched for eligibility by full-text review; 24 articles cannot be accessed; 13 studies were reviews and case reports; 17 were not describing the functional outcome. The studies which met all inclusion criteria were 6 studies.

Statistical analysis

Pooled Standard Mean Differences (SMDs), Proportions (%), with 95% Confidence Intervals (CI) assessed, using a statistical package (MedCalc, Belgium). The meta-analysis process was established via I^2-statistics (either the fixed-effects model or the random-effects model), according to the Q test for heterogeneity.

The included studies were published between 2020 and 2021. Regarding children's characteristics, the total number of children in all the included studies was 1747 children, with 764 children met MIS-C criteria. The mean age of all children was (10.2 years) [Table 1]. Our meta-analysis included 6 studies describing Covid-19 children: with a total number of children (N=1747) [Table 2].

Each outcome was measured by

Proportions (%)

- For the incidence of MI0053-C in Covid-19 children.

Average estimate level (mg/dl)

- For average CRP level.
- For average ferritin level.
- For average D-dimer level.

Concerning the primary outcome measure, we found 5 studies that reported the incidence of MIS-C. I2 (inconsistency) was 98.1%, Q test for heterogeneity ($p<0.0001$), so random-effects model was carried out; with overall incidence=39.8% (95% CI=21.035 to 60.436). The random-effects model of the meta-analysis process revealed a pooled incidence of MIS-C in Covid-19 in children of 39.8% [Figure 1].

Concerning the secondary outcome measures, we found 4 studies reported average CRP level. I^2 (inconsistency) was 0%, Q test for heterogeneity ($p>0.05$), so fixed-effects model was

Table 1: Children and study characteristics.

S.no	Author	Number of Children		Age
		Total	MIS-C children	(average years)
1	Abdel-Mannan et al. [5]	50	27	12
2	Davies et al. [6]	78	33	11
3	Dufort et al. [7]	191	99	---
4	Feldstein et al. [8]	1116	539	9.7
5	Hameed et al. [9]	--- #	35	11
6	Moraleda et al. [10]	312	31	7.6

Table 2: Summary of outcome measures in all studies.

S.no	Author	Primary outcome	Secondary outcomes								
		Incidence of MIS-C	CRP level			Ferritin level			D-dimer level		
		MIS-C children (%)	Estimate	Upper limit	Lower limit	Estimate	Upper limit	Lower limit	Estimate	Upper limit	Lower limit
1	Abdel-Mannan et al.	54%	---	---	---	---	---	---	---	---	---
2	Davies et al.	42.30%	264	192	316	4030	2349	7422	1042	538	1746
3	Dufort et al.	51.80%	---	---	---	---	---	---	---	---	---
4	Feldstein et al.	48.20%	152	69.4	231	---	---	---	---	---	---
5	Hameed et al.	---	267	180	309	631	293	1023	490	330	1030
6	Moraleda et al.	9.90%	166	83.7	233	627	365	1278	2896	2059	5355

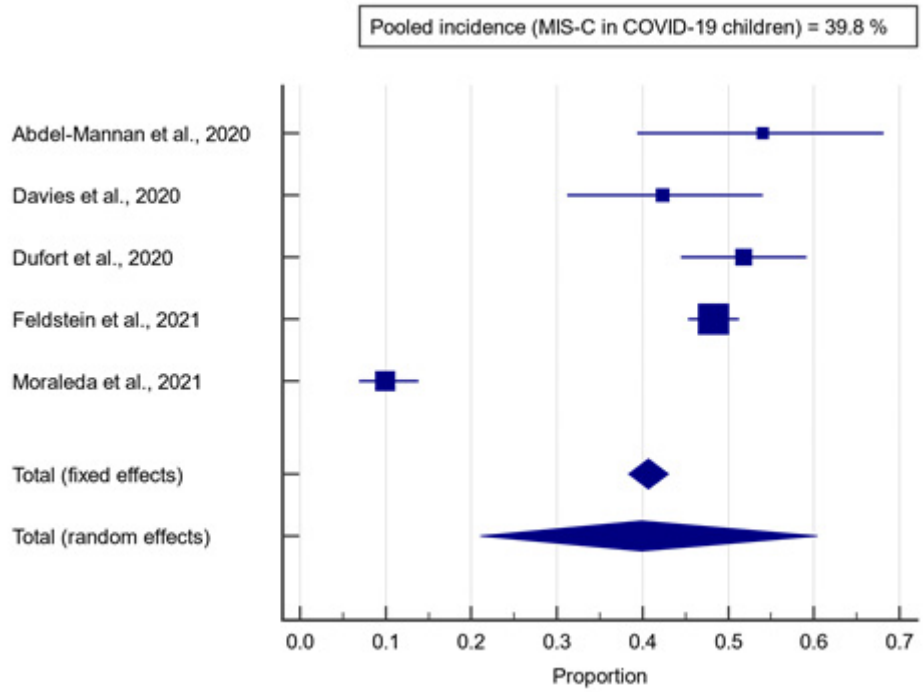

Figure 1: Forest plot (incidence of MIS-C).

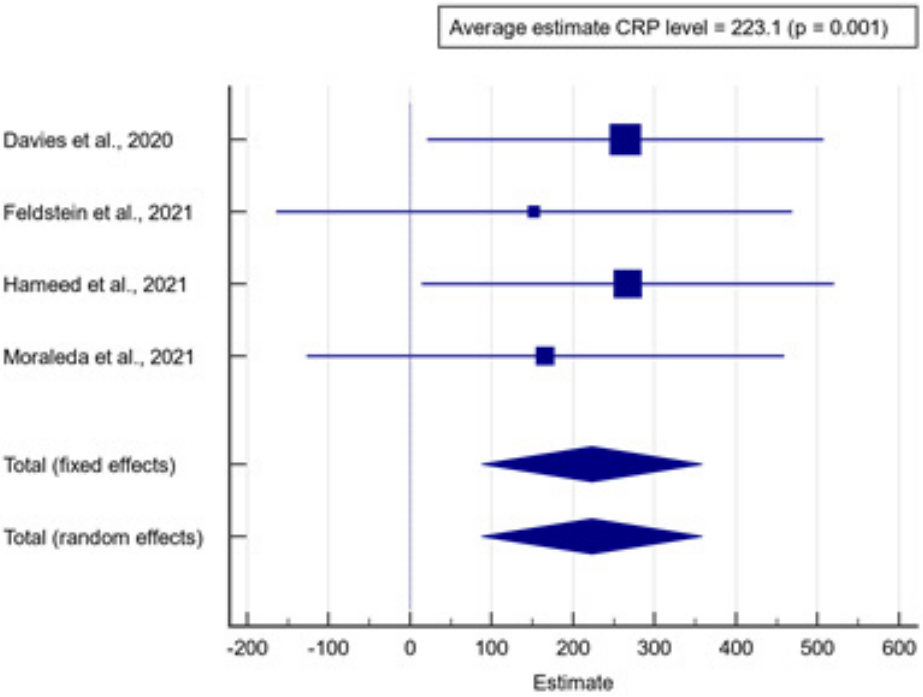

Figure 2: Forest plot (average CRP level).

carried out; with overall average CRP estimate=223.1 (95% CI=87.3 to 358.9). The fixed-effects model of the meta-analysis process revealed an average estimate CRP level of 223.1 mg/dl, in MIS-C in children (p=0.001) [Figure 2].

We found 3 studies reported average ferritin level. I^2 (inconsistency) was 0%, Q test for heterogeneity (p>0.05), so fixed-effects model was carried out; with overall average ferritin estimate=566.5 (95% CI=438.6 to 1782.3). The fixed-effects model of the meta-analysis process revealed an average estimate ferritin level of 566.5 mg/dl, in MIS-C in children [Figure 3].

We found 3 studies that reported average D-dimer level. I^2 (inconsistency) was 0%, Q test for heterogeneity (p>0.05), so fixed-effects model was carried out; with overall average D-dimer estimate=595.6 (95% CI=464.7 to 1870.3). The fixed-effects model of the meta-analysis process revealed an average estimate D-dimer level of 595.6 mg/dl, in MIS-C in children [Figure 4].

Discussion

This study aims to determine the clinical course, safety profile,

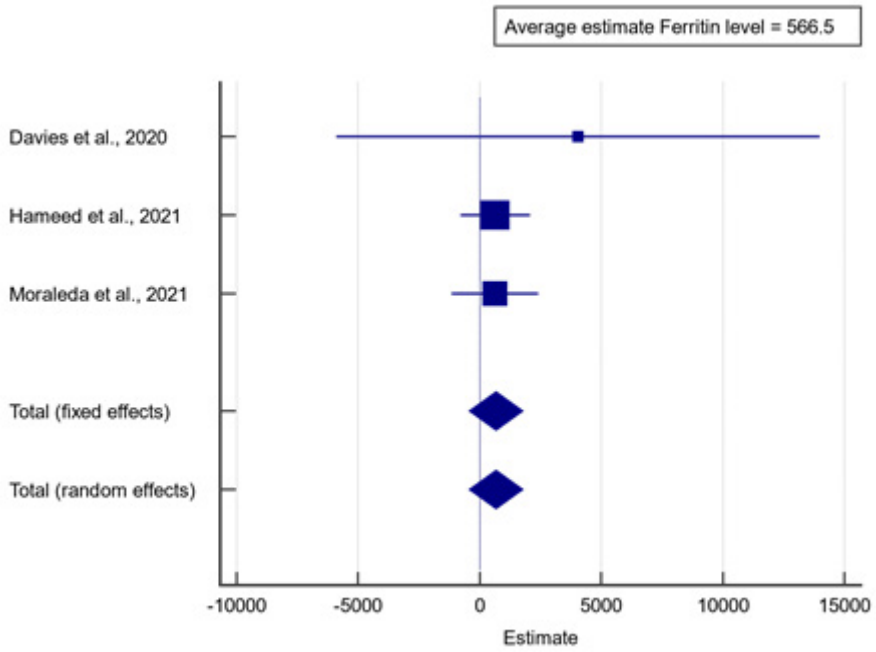

Figure 3: Forest plot (average ferritin level).

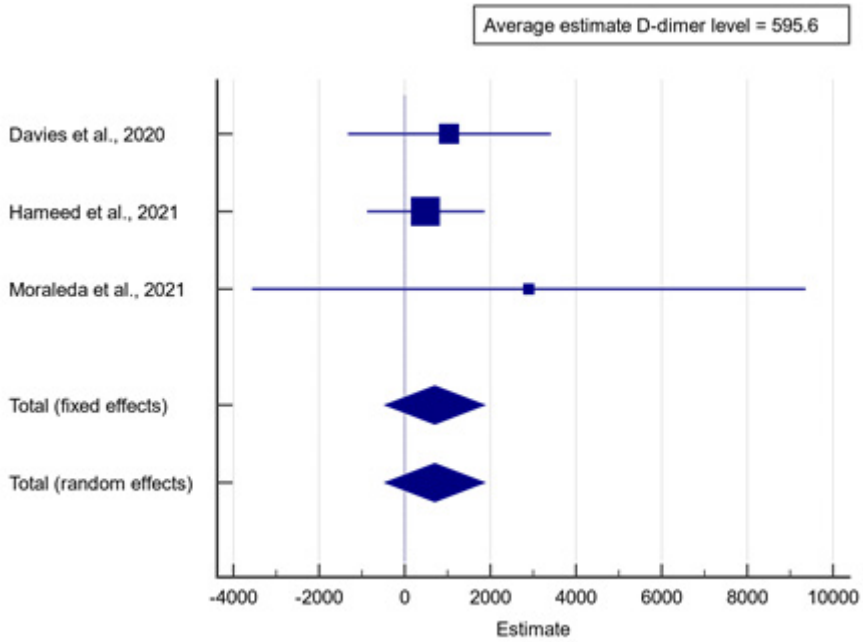

Figure 4: Forest plot (average D-dimer level).

and inflammatory markers of Multisystem Inflammatory Syndrome in Children (MIS-C) in Covid-19 in children. The included studies were published between 2020 and 2021. Regarding children's characteristics, the total number of children in all the included studies was 1747 children, with 764 children met MIS-C criteria. The mean age of all children was (10.2 years).

Our meta-analysis included 6 studies describing Covid-19 children; with a total number of children (N=1747). Concerning the primary outcome measure, we found 5 studies that reported incidence of MIS-C. I^2 (inconsistency) was 98.1%, Q test for heterogeneity ($p<0.0001$), so random-effects model was carried out; with overall incidence=39.8% (95% CI=21.035 to 60.436). Which came in agreement with Cato et al.; Feldstein et al.; Consiglio et al. [11-13]

Cato et al. reported that a total of 203 (35.6%) of the patients had a clinical course consistent with previously published MIS-C reviews, characterized predominantly via shock, cardiac disorder, abdominal ache, and markedly extended inflammatory markers, and nearly all had positive SARS-CoV-2 take a look at results. The ultimate 367 (64.4%) of MIS-C patients had manifestations that seemed to overlap with acute Covid-19, had a much less severe medical route, or had features of Kawasaki disease. [11] Feldstein et al. reported that, of 1116 patients, 48% were diagnosed with MIS-C and 52% with Covid-19. Compared with patients with Covid-19, patients with MIS-C were more

likely to be 6 to 12 years old. [12] Consiglio et al. reported that, enrolled 41 children with acute SARS-CoV-2 infection in Rome, Italy, all with a moderate disorder, and denote those as CoV-2 children at some point. They additionally enrolled three youngsters providing MIS-C in Rome and 10 children offering MIS-C in Stockholm, Sweden. They examined these children with 28 children presenting with Kawasaki disease before the Covid-19 pandemic (March 2017 to May). [13]

Concerning the secondary outcome measures, we found 4 studies that reported average CRP levels. The fixed-effects model of the meta-analysis process revealed an average estimate CRP level of 223.1 mg/dl, in MIS-C children (p=0.001). Which came in agreement with Consiglio et al.; Toubiana et al.; Blumfield et al.; Weisberg et al.; Feldstein et al. [2,3,12-14] Consiglio et al. reported that lymphopenia is a hallmark of Covid-19 and changed into more mentioned in MIS-C than in kids with moderate SARS-CoV-2 infection or Kawasaki disease. MIS-C patients additionally had markedly higher stages of C-Reactive Protein (CRP) and ferritin and decrease platelet counts in comparison to each Kawasaki disorder patient and CoV-2+ children. [13] Toubiana et al. reported that all patients had high levels of inflammatory markers, including leukocytosis with a predominance of neutrophils, and high levels of C reactive protein, procalcitonin, and serum Interleukin 6 (IL-6). CRP was 253 (89-363) (mg/L). [14] Blumfield et al. reported that liver function results were atypical in almost all of the patients; alanine aminotransferase become elevated in 15 patients (94%), and aspartate aminotransferase was extended in 14 (88%) patients. Acute kidney damage developed in 5 patients (31%). CRP and d-dimer values were expanded in all 16 patients (100%), and leukocytosis was found in 13 of sixteen patients (81%). All 16 patients (100%) exhibited hypoalbuminemia. [3]

Weisberg et al. reported that each MIS-C and Covid-ARDS subject exhibited markers of systemic inflammation which include exceptionally extended degrees of IL-6 and C-Reactive Protein (CRP), while ferritin and Lactate Dehydrogenase (LDH), were substantially elevated in Covid-ARDS compared to MIS-C subjects. [2] Feldstein et al. reported that, selected commonly tested laboratory values with values on at least 70 patients (absolute lymphocyte matter, absolute neutrophil count number Neutrophil to Lymphocyte Ratio [NLR], platelet remember, hemoglobin degree, alanine aminotransferase degree, C-Reactive Protein [CRP] degree, and albumin level) or of relevance to MIS-C (B-type Natriuretic Peptide [BNP] or N-terminal-pro-BNP). On laboratory trying out inside 48 hours of admission, patients with MIS-C had a higher median LR (6.4 *vs.* 2.7, P<0.001) and CRP level (152 mg/L *vs.* 33 mg/L, P<0.001) and greater thrombocytopenia (platelets<150 × 103 cells/μL) than patients with Covid-19 (41% *vs.* 17%, P<0.001). [12]

Three of the reviewed studies reported average ferritin level. The fixed-effects model of the meta-analysis process revealed an average estimate ferritin level of 566.5 mg/dl, in MIS-C in children. Which came in agreement with Leon et al.; Yasuhara et al. [15,16]

Leon et al. reported that, Inflammatory cytokine markers were markedly elevated (CRP, 450 mg/L; lactate dehydrogenase, 794 units/L; and ferritin, 699.5 ng/mL) as had been troponins (114 ng/L), D-dimer (4.21 mg/L), and fibrinogen (834 mg/dL). Hyponatremia (118 mmol/L), hyperkalemia (5.8 mmol/L), and (blood urea nitrogen, 33 mg/dL; creatinine, 1.09 mg/dL) were noted as well as a white blood cell count of 13.3 103/ mm^3 (74% neutrophils, 15% lymphocytes, 2% monocytes, 9% bands); hemoglobin, 10.9 gm/dL; and platelet count, 225 103/mm^3. [15]

Yasuhara et al. reported that the search identified 372 articles that were reviewed based on the identity and summary, and of those, 307 articles had been excluded. Sixty-five complete texts have been assessed for eligibility and 38 articles have been excluded primarily based on the article kind (case reports, scientific tips, consensus documents, scientific trials, editorials, letters, reviews, systematic opinions, and meta-analyses), population (adult sufferers with Covid-19, cases without assembly the case definition for MIS-C) and topi (other viruses). Inflammatory markers, which include C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation. Ferritin was 711.0 (599.5-822.4). [16]

Three of the reviewed studies reported average D-dimer level. The fixed-effects model of the meta-analysis process revealed an average estimate D-dimer level of 595.6 mg/dl, in MIS-C children. Which came in agreement with Toubiana et al.; Consiglio et al.; Jiang et al.; Yasuhara et al. [13,14,16,17]

Toubiana et al. reported that all patients had excessive levels of inflammatory markers, consisting of leukocytosis with a predominance of neutrophils and high ranges of C reactive protein, procalcitonin, and serum interleukin 6 (IL-6). Seventeen (81%) patients had lymphopenia, and anemia changed into commonplace, with a mean hemoglobin stage of 86 (variety 53-122) g/L. Hyponatremia (<135 mmol/L) and hypoalbuminemia (<32 g/L) were observed in 20 (95%) patients. D-dimer levels were increased (>500 μg/L) in 19/20 (95%) patients. increased degrees of excessive sensitivity cardiac troponin I (>26 pg/mL) and B-type natriuretic peptide (>a hundred ng/L) have been observed in 17/21 (81%) and 14/18 (78%) patients, respectively. [14]

Consiglio et al. reported that a total of 41 children with CoV2+ (23 males, 18 female) and 13 children with MIS-C (8 males, 3 female) were analyzed in this study. In summary, this states that children and adolescents between 0 and 19 years old, with fever>3 days, and displaying two of the following signs: i) rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs, ii) hypotension or shock, iii) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP), iv) evidence of coagulopathy (by PT, PTT, elevated d-Dimers), v) acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain. [13]

Jiang et al. reported that MIS-C has elevated D-dimers which, in some institutions, are used as a manual for giving anticoagulants, especially for those with a high concentration of D-dimers. Normal, there may be substantial variability and a loss of consciousness on anticoagulants. Low-dose aspirin, used in Kawasaki disease, has additionally been used for MIS-C. In patients who're severely sick with Covid-19-associated inflammatory syndrome and with marked infection, raised D-dimers. [17]

Yasuhara et al. reported that cardiac markers were elevated especially troponin, B-type natriuretic peptide, and N-terminal pro-B-type natriuretic peptide. Also, D-dimer and neutrophils were increased while lymphocytes and albumin were reduced. [16]

Conclusion

To conclude, Covid-19 infection is typically very mild and often asymptomatic in children. Multisystem Inflammatory Syndrome in Children (MIS-C), which is a rare complication associated with Covid-19, presenting after infection as high fever, organ dysfunction, and strongly elevated markers of inflammation.

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All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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