

Review Paper

COVID-19 in Children With Inflammatory Bowel Disease: A Systematic Review



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ABSTRACT

Background: Considering the chronic immunosuppression in inflammatory bowel disease (IBD) patients, it is necessary to evaluate the course of COVID-19 in these patients. Studies have shown various results in adult IBD patients. This study aimed to find out the course of this infection in pediatric IBD patients.

Methods: This was a systematic review study according to the PRISMA 2020 guideline. International databases including Scopus, PubMed, and the Web of Science were searched with a combination of "COVID-19" AND "IBD" or synonyms until October 16, 2021. Studies that have reported the outcomes of COVID-19 infection in patients less than 19 years of age were selected. Name of author, country, study duration and type, IBD type and drugs, and COVID-19 outcomes were extracted.

Results: From the initially retrieved 2215 articles, finally 16 articles were eligible. Data from 1040 pediatric IBD patients were reported. Twenty-four patients were hospitalized, 5 developed patients multisystem inflammatory syndrome in children, and others had a mild disease course and were outpatient. Steroid use, severe IBD activity, and comorbidities were shown to increase risk of hospitalization and disease severity.

Conclusion: COVID-19 is a benign and self-limited disease in pediatric IBD patients. Comorbidities, steroid use, and severe IBD activity affect the outcomes.

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Introduction

The first case of pneumonia with the novel beta-corona virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found in Wuhan, China in the late 2019 and turned rapidly into a pandemic worldwide in March 2020 [1]. The course of the disease caused by SARS-CoV-2, named coronavirus disease 2019 (COVID-19) can range from asymptomatic or mild infection to severe and fatal illness with a variety of signs and symptoms related to different body organs [1].

Research has shown that patients with co-morbidities and the elderly are at greater risk for the development of severe complications following infection with SARS-CoV-2 [2], possibly due to cytokine storm formation, which is an excessive and inappropriate immune response to the virus [3].

Patients with inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD), and ulcerative colitis (UC) are believed to be at increased risk of opportunistic bacterial or viral infections due to chronic immunosuppressive medications [2, 4]. In the meantime, it is essential to assess whether these individuals are at risk for the development of more intense cases of the disease caused by the novel coronavirus [1, 5, 6].

According to the literature, taking immunosuppressive drugs is not correlated with increased intensity of COVID-19 [7]. However, the augmented risk of COVID-19 severity may be due to the increased cytokine production or angiotensin-converting enzyme (ACE-2) overexpression, the receptor for SARS-CoV-2 on the host cells, in IBD patients [8].

Since the beginning of this pandemic, many efforts have been made by various research teams to answer this question. For example, the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease database (SECURE-IBD) is an international registry recruiting IBD patients with SARS-CoV-2. European society for pediatric gastroenterology, hepatology, and nutrition (ESPGHAN) also created a database for IBD patients with SARS-CoV-2. The data acquired from this registry so far have shown that the risk of being infected with this virus or developing severe complications following the infection in IBD patients is not different from the healthy population can increase the risk of complications from the virus [9]. However, there is still not enough informa-

tion in the literature [6]. In addition, most studies in this field have been performed on adult patients and few studies have been performed on children. Accordingly, in the present study, we intended to collect data on COVID-19 in children with IBD through conducting a systematic literature review.

Methods

Search strategy and databases

This systematic review study is based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2020. The research question were as follows:

P: Children with IBD and COVID-19

I: IBD treatments

C: Children with COVID-19 and without IBD

O: COVID-19 outcome

The search was based on the keywords listed in Table 1 through Scopus, PubMed, and the Web of Science databases until October 16, 2021. The search strategy in each database is listed in Table 1.

Inclusion and exclusion criteria

All English language original articles and meeting abstracts of any type including case reports, case series, cross-sectional, cohort, and case-control were included in the present systematic review study. The study population included patients with COVID-19 and IBD who were less than 19 years old. In this study, all studies that examined the course of COVID-19 in patients with IBD less than 19 years old were included. Unrelated studies, reviews, duplicates, and low-quality studies were excluded from the review process.

Study selection process

After removing duplicates, the title and the abstracts of the articles were evaluated for eligibility and then, the full text of the remaining articles was reviewed independently by two reviewers. Unrelated ones and studies that did not report COVID-19 outcomes in patients under 19 years of age were removed from the review process. Final articles entered the quality assessment.

Table 1. Search strategy

Scopus	TITLE-ABS-KEY [(ibd) OR (inflammatory bowel disease*) OR (ulcerative colitis) OR (Crohn’s disease)] AND TITLE-ABS-KEY [(COVID-19) OR (sars-cov-2) OR (2019 novel coronavirus disease) OR (2019 novel coronavirus infection) OR (2019-ncov disease) OR (2019-ncov infection) OR (COVID-19 pandemic) OR (COVID-19 pandemics) OR (COVID-19 virus disease) OR (COVID-19 virus infection) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (sars coronavirus 2)]
PubMed	(((IBD [Title/Abstract]) OR (inflammatory bowel disease* [Title/Abstract]) OR (ulcerative colitis [Title/Abstract]) OR (Crohn’s disease [Title/Abstract]) OR (Inflammatory Bowel Diseases [MeSH Terms])) AND ((2019 Novel Coronavirus Disease [Title/Abstract]) AND (2019 Novel Coronavirus Infection [Title/Abstract]) AND (2019-nCoV Disease [Title/Abstract]) AND (2019-nCoV Infection [Title/Abstract]) AND (COVID-19 Pandemic [Title/Abstract]) AND (COVID-19 Pandemics [Title/Abstract]) AND (COVID-19 Virus Disease [Title/Abstract]) AND (COVID-19 Virus Infection [Title/Abstract]) AND (COVID19 [Title/Abstract]) AND (Coronavirus Disease 2019 [Title/Abstract]) AND (Coronavirus Disease-19 [Title/Abstract]) AND (SARS Coronavirus 2 [Title/Abstract]) AND (SARS-CoV-2 [Title/Abstract]) OR (COVID-19 [MeSH Terms])))
Web of Science	TI OR AB=(ulcerative colitis OR Crohn’s disease OR inflammatory bowel disease OR IBD) AND TI=(COVID-19 OR sars-cov-2 OR 2019 novel coronavirus disease OR 2019 novel coronavirus infection OR 2019-ncov disease OR 2019-ncov infection OR COVID-19 pandemic OR COVID-19 pandemics OR COVID-19 virus disease OR COVID-19 virus infection OR coronavirus disease 2019 OR coronavirus disease-19 OR sars coronavirus 2)
Science Direct	(Inflammatory bowel disease OR Crohn’s disease OR ulcerative colitis) AND (COVID-19 OR sars-cov-2 OR 2019 novel coronavirus OR 2019-ncov OR coronavirus disease 2019 OR sars coronavirus 2)

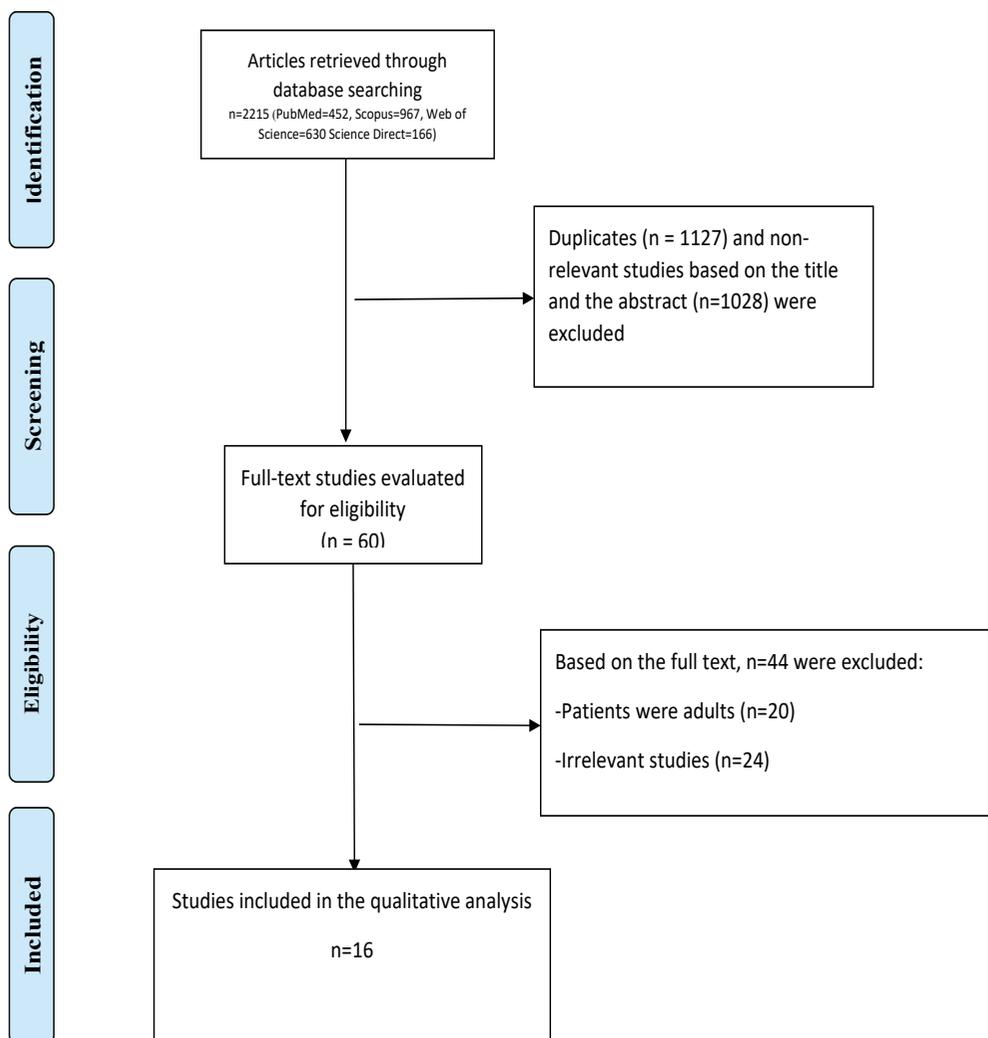


Figure 1. Study selection process

Table 2. Studies reporting outcomes of SARS-CoV-2 infection in pediatric ibd patients

Authors	Country, Duration	Study Design	Sample Size	Age of Participants (y)	IBD Type	IBD Drugs	COVID-19 Outcomes
Ludvigsson et al. [21]	Sweden, February 1 to July 31, 2020	Cohort, multi-center	608 pediatric IBD patients were followed. (total number of COVID-19 cases?)	<18	NR in the age group	NR in the age group	No patients had severe disease. Only one patient was hospitalized with COVID-19.
Brenner E. et al. [27]	USA, data from the SECURE-IBD registry	Cohort, multi-center	29	0-19	NR in the age group	NR in the age group	Three 0-9 years old IBD patients with COVID-19, all outpatient and without any complications. 26 10-19 years old IBD patients with COVID-19, 23 outpatients, and 3 of them were hospitalized, without any complications.
Queiroz et al. [28]	USA, data from the SECURE-IBD registry	Cohort, multi-center	18	0-19	NR in the age group	NR in the age group	Four 0-9 years old and 14 10-19 years old pediatric IBD patients with SARS-CoV-2 were reported. One patient was hospitalized but there were no deaths, ICU admissions, or other adverse outcomes.
Turner et al. [29]	UK, until March 26, 2020	Cohort, multi-center	8 (From 102 sites affiliated with the pediatric Porto group of ESPGHAN, no cases were reported in Korea and China.)	14-18	5 CD, 2 UC, 1 IBD-U	3 on biologics, 2 on biologics, thiopurines, and 5-ASA, 1 on steroids alone, 2 on 5-ASA and thiopurines	All patients experienced a mild disease, recovered completely, and were outpatients. Symptoms were as follows: Fever (n=3), cough (n=4), fatigue (n=4), rhinitis (n=1), myalgia (n=2), Anosmia and Ageusia (n=1), mild chest pain (n=1)
D'Arcangelo et al. [30]	Italy, patients who have received biological therapy from April 2012 to September 2020 for at least two months	Cohort, multi-center	4	<18	2 UC, 2 CD	IFX	Two patients were asymptomatic and two had mild disease.
Spencer et al. [23]	USA, May 6, 2020, to November 5, 2020	Retrospective observational cross-sectional, single center	26 patients had positive antibodies against SARS-CoV-2	Median (IQR): 14 (11-16)	21 CD, 5 UC	17 on biologics, 3 on 5-ASA, 1 on ciprofloxacin/metronidazole, and 5 on no medications	19 patients had records of their disease course, of which 68% reported mild symptoms. 32% of them were asymptomatic. One CD patient (male) mentioned MIS-C. *There was no relation between symptomatic COVID-19 and biological use

Authors	Country, Duration	Study Design	Sample Size	Age of Participants (y)	IBD Type	IBD Drugs	COVID-19 Outcomes
Sansotta et al. [31]	Italy, from February 21 to May 4, 2020	Cross-sectional, multicenter	24 children with IBD and COVID-19 symptoms (one patient was positive for SARS-CoV-2 PCR)	Median (range): 15.2 (2-18)	11 UC 1 IBD-U 12 CD	10 on AZA, 7 on 5-ASA, 1 on ADA, 3 on IFX, 1 on CD exclusion diet, 2 on no medications	The most common symptoms were: fever (80%, n=20), cough (28%), fatigue (8%), and vomiting (4%). All patients had a mild course of the disease with no complications.
Ruan et al. [32]	USA	Cohort, single center	13	Pediatric IBD patients	7 CD 3 UC 3 very early onset IBD	5 on biologics, 2 on biologics and immune modulators, 2 on 5-ASA and immune modulator, 1 on biologics and steroids, 1 on the immune modulator, 1 on 5-ASA, 1 on steroids and antibiotics	Six patients were asymptomatic. Seven patients had mild symptoms including fever, fatigue, loss of smell or taste, diarrhea, abdominal pain, and dizziness.
Koletzko et al. [33]	Germany, first survey from March 2020 till the end of summer 2020 to April 2021	Cohort, multi-center	90 Pediatric IBD patients were followed	Median (IQR) 15 (12-17)	44 CD 34 UC 10 IBD-u	10 on only 5-ASA, 42 on any 5-ASA, 37 on any Immune modulator, 60 on any biologics, 8 on any steroids, 74 on immune modulators, steroids, and 5-ASA, 25 on combination therapy, 3 on no medications	Of the total 504 patients in the entire cohort, 90 were 6-20 years. While 41.7% of the entire cohort reported COVID-19-related symptoms, 56.7% of them were 6-20 years. Symptoms included: fever (5.9%), chills (4.9%), infectious rhinitis (16.5%), sore throat (14.8%), a dry persistent cough (5.7%), loss of smell or taste (1.6%), muscle pain (12%), headache (26.6%), fatigue (25.3%), dyspnea (3.3%), and diarrhea. During the second survey, 4 children and 11 adults (8-63 years) were positive for SARS-CoV-2. None of them were hospitalized due to COVID-19 and the disease course was mild and self-limited.
Arrigo et al. [34]	Italy, from March 9 to May 5, 2020	Cohort, multi-center	6 COVID-19 cases in 2291 pediatric IBD patients	9-18	2 CD 4UC	3 on AZA, 1 on ADA, 1 on IFX, 1 on 5-ASA +steroids	Except for one 18-year-old patient with UC who was hospitalized but without any complications, other patients were outpatients and had a mild disease course. IBD course remained stable during the infection and no drugs were stopped. The hospitalized patient was on AZA and the underlying disease was in the remission phase.

Authors	Country, Duration	Study Design	Sample Size	Age of Participants (y)	IBD Type	IBD Drugs	COVID-19 Outcomes
Brenner et al. [11]	USA, from March to October 2020 data from the SECURE-IBD registry and the COVID-19 database of the pediatric IBD Porto group of the ESPGHAN	Cohort, multi-center	209 (from 23 countries)	≤18 years Median (IQR) 16 (14-18)	CD 138 UC 61 IBD-U 10	2 on biologics only, 4 on 5-ASA only, 3 on steroids and biologics, 3 on 5-ASA and biologics, 2 on steroid, biologics, and 5-ASA	Hospitalization due to COVID-19: n=14 (females=9) Deaths due to COVID-19: n=0 Mechanical ventilation is needed due to MIS-C and severe disease (on 5-ASA, UC): n=2 Symptoms length: 4-21 days; Between patients hospitalized and outpatients, there were significant differences regarding disease activity, medications (including steroids and 5-ASA), presence of gastrointestinal symptoms, and other comorbidities. TNF antagonist monotherapy (without 6MP/AZA/MTX) was associated with a lower hospitalization likelihood ratio.
Bardasi et al. [35]	Italy	Case report	A 17-year-old CD patient	17	CD	Anti-TNF-α + ADA	The patient was in the remission phase. ADA was discontinued due to COVID-19. The patient recovered completely without any complications. (disease duration: 2 weeks, fever and malaise).
Abdullah et al. [36]	Germany	Case report	An 18-year-old patient with UC	18	UC	5-ASA + IFX	The patient had a dry cough, mild dyspnea, and abdominal and back pain and was positive for SARS-CoV-2. The patient recovered completely. (disease duration: 2 weeks)
Meredith et al. [24]	UK	Case report	A 10-year-old UC patient	10	UC	IFX (anti-TNF-α) + 5-ASA	The patient developed pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Finally, the patient was discharged without any complications, and the condition resolved completely within 8 weeks.
Dolinger et al. [25]	USA	Case report	A 14-year-old CD patient	14	CD	NR	MIS-C with complete remission within 4 weeks.
Sweeny et al. [26]	USA	Case report	A 16-year-old patient with CD	16	New-onset CD	-	MIS-C and new-onset CD The patient recovered completely without any complications [27].

Quality assessment

Newcastle Ottawa scale was used for quality assessment. A score of less than 14 was considered low quality. No studies were excluded at this stage. The methodological quality of the "final" studies.

Data extraction

A checklist with the following items was used for data extraction by two independent reviewers: Author name, country, sample size, IBD type, medications, and COVID-19 outcomes.

Results

From the initially retrieved 2215 papers, 1127 were duplicates. Based on the titles and the abstracts, 1028 articles were irrelevant or review papers. Finally, 60 articles were assessed for eligibility. Twenty-four articles were irrelevant. Twenty articles did not include pediatric patients or did not report COVID-19 outcomes in this group. Finally, 16 studies (14 articles, 2 meeting abstracts) were eligible (Figure 1).

Characteristics of the studies

Nine articles had cohort design, five were case reports, and two were cross-sectional. Data from 1040 pediatric patients with IBD were reviewed. Regarding IBD type, 124 patients had UC, 234 had CD, 25 had IBD-unknown (IBD-U), and other patients not reported. Twenty-four patients were hospitalized due to COVID-19, but there were no related deaths or severe complications, and all patients recovered completely. Five patients (3 CD, 2 UC; 3 males and two females) developed multisystem inflammatory syndrome in children (MIS-C). One other patient also needed intensive care unit (ICU) due to secondary infection and disease severity. These patients were on biologics or 5-aminosalicylic acids (5-ASA). Except for these five patients, others mainly reported mild signs and symptoms, including fatigue, fever, and dry cough, or were asymptomatic. One study showed that IBD activity status, steroid or 5-ASA use, presence of gastrointestinal symptoms, and other comorbidities increase the risk of hospitalization in children with COVID-19 and IBD.

In contrast, tumor necrosis factor (TNF) antagonist monotherapy lowered hospitalization likelihood ratio. Another study also revealed no significant relation between biological agent use and the development of symptomatic COVID-19. Disease symptoms lasted from 4 days to 8 weeks to complete remission in an MIS-C patient (Table 2).

Discussion

According to the data from the SECURE-IBD registry and the COVID-19 database of the pediatric IBD Porto group of the European society for pediatric gastroenterology hepatology and nutrition, COVID-19 is a benign illness in the pediatric patients with IBD, please replace this part with the above phrase and disease, and other reviewed studies, severity and complications will not be increased in these children compared to normal children. Symptoms of COVID-19 in pediatric IBD patients are not significantly different from the general population and mainly include fever, fatigue, dry cough, and gastrointestinal symptoms. However, limited data show that chronic steroid use may rise the COVID-19 severity [10-12]. Moreover, studies indicate that disease activity status is related to the patient's outcomes when infected with SARS-CoV-2 [11, 13], particularly in younger individuals [14].

IBD patients show higher levels of ACE-2 expression. However, whether ACE-2 overexpression increases COVID-19 severity or has protective functions is not clear [15, 16]. Studies also have shown a benign course of COVID-19 in immunosuppressed adults with IBD [17-19] and even the protective roles of immunosuppressive agents [20]. However, one study showed a moderately increased risk of hospitalization in adult patients but a not severe disease or mortality [21]. Currently, it is recommended for these patients to stop their medications except for 5-ASA when infected with this virus [16]. In children, immunosuppressive drugs does not increase the risk of complications SARS-CoV-2 infection [22]. One study that evaluated the association between biological use in children with IBD and symptomatic COVID-19, found no association [23].

Preliminary reports have shown that steroid use, increasing age, and other comorbidities increase the risk of COVID-19 complications in adults with IBD. Although biological therapy is safe, thiopurine use is accompanied by increasing adverse events [9].

Brenner et al. studied a group of pediatric IBD patients hospitalized due to SARS-CoV-2 and compared them with outpatients. They concluded that the presence of other having comorbidities, gastrointestinal symptoms, more severe IBD activity, and steroid or 5-ASA use is accompanied by a higher risk for hospitalization. Anti-TNF monotherapy was shown to reduce the due to COVID-19 risk of hospitalization. They had two patients who required ICU admission, one due to MIS-C and the other one due to disease severity and

secondary infections. Both patients were on 5-ASA and also suffered from asthma [11].

Several studies have reported MIS-C development following SARS-CoV-2 contracting in children with IBD [24, 25]. In these cases, the patient has recovered without any long-term complications and has been on biologic or 5-ASA before contracting COVID-19. Meredith et al. reported a 10-year-old female patient with UC who developed MIS-C. The patient was on 5-ASA and infliximab treatment [24]. Dolinger et al. also reported a 14-year-old boy with CD and MIS-C development following COVID-19. The patient was treated with two doses of infliximab and recovered [25]. Sweeny et al. reported a 16 years old boy with no known past medical history presenting with fever and gastrointestinal symptoms consistent with both new-onset IBD and MIS-C and with a hyperinflammatory state. The patient had a history of flu-like disease six weeks before to these symptoms. However, the nasopharyngeal swab test for SARS-CoV-2 was negative at admission. The patient had signs of IBD in endoscopy, but submucosal vasculitis was consistent with MIS-C. After receiving Intravenous immune globulin, the patient first showed clinical improvement. However, the clinical condition again worsened thereafter. Finally, he was successfully treated with infliximab [26]. Brenner et al. reported the other case of MIS-C; a six years old girl with UC and on 5-ASA who presented with respiratory failure and coagulopathy and needed ICU care and mechanical ventilation. The symptoms lasted for 19 days and the patient recovered after corticosteroid admission [11]. Other studies have reported a mild and benign course of COVID-19 in these patients. Literature reports no deaths related to infection with SARS-CoV-2 in pediatric IBD patients.

Compared to the hospital admission rate of 33 to 66% reported in adult IBD patients with SARS-CoV-2, Brenner et al. reported a rate of 7% in children. In total, COVID-19 in the pediatric population is usually asymptomatic [11].

Limitations

This study has several limitations. First, IBD type and medications are not reported in several included studies. Second, there is a lack of case-control studies that compare the outcomes of COVID-19 in healthy children and children with IBD. Third, we have only included English language articles. In general, current data suggest that that COVID-19 outcome is not significantly affected by IBD, disease activity status, steroid use, and other comorbidities affect the patients' outcome following infection with SARS-CoV-2. However, further case-control studies with larger sample sizes are needed to confirm these results.

Conclusion

COVID-19 is a benign and self-limited disease in children with IBD even on immunosuppressive therapy. Corticosteroids, severe IBD activity, and other comorbidities increase the risk of disease severity. Case-control studies with larger sample sizes are needed to confirm these results.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the [Isfahan University of Medical Sciences](#) (Code: IR.MUI.MED.REC.1400.558). This article is a systematic review study with no human or animal sample.

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Authors' contributions

All authors contributed the same in this study.

Conflicts of interest

The authors declared no conflicts of interest.

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