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Ocular Manifestations in Children with COVID-19: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: COVID-19 ocular manifestations commonly occur in adults; however, there is limited data on this manifestation in children. This systematic review and meta-analysis investigated the prevalence of ocular manifestations in children. **Methods:** We searched PubMed, Scopus, EMBASE, Web of Science, and MedRxiv from December 1, 2019, to February 3, 2021. Two independent reviewers screened the articles, extracted the data, and assessed the quality of the articles. **Results:** After screening 1,510 articles, 19 were approved and included in the systematic review and meta-analysis. The literature review showed that 89 out of 749 children with COVID-19 had at least one ocular manifestation. The estimated pooled prevalence of ocular manifestations was 8.0% (95% confidence intervals 4.0 – 12.0). The most common symptoms were conjunctival discharge (n = 31, 23.1%), conjunctival congestion (n = 21, 16.0%), eye rubbing (n = 19, 14.2%). **Conclusion:** Ocular manifestations are common in children with COVID-19; one out of 14 infected children shows at least one ocular manifestation. Physicians should pay attention to the ocular manifestations associated with COVID-19 in children.

INTRODUCTION

COVID-19 pandemic began in Wuhan, China and more than 145 million people became infected with SARS-C0V2 by April 23, 2021 [1]. Although children may be less prone to SARS-COV-2 infection [2], COVID-19 also affects children and adolescents [3], and some may become severely affected and even die [3]. There is some evidence that children play a role in transmitting SARS-COV-2 infection [4]. While respiratory droplets are the primary source of SARS-COV-2 virus transmission, transmission through conjunctivitis is controversial [5, 6].

SARS-COV-2 infection involves various organs, e. g., respiratory symptoms (cough or dyspnea with or without fever) and gastrointestinal symptoms (vomiting, diarrhea with or without fever) [7]. Some patients with SARS-COV-2 infection have viral conjunctivitis [7] and ocular manifestations [8]. Although ocular manifestations of COVID-19 rarely occur in children, angiotensin-converting enzyme 2 (ACE2), the cell receptor for the virus, is expressed on the ocular surface. Hence, we needed to know about ocular manifestations in children with SARS-CoV-2 infection [9, 10].

Several studies reported ocular manifestations of COVID-19 in adults. A systematic review and meta-analysis study estimated ocular manifestations in COVID-19 patients at around 11%, not to mention this clinical manifestation in children [11]. Knowledge of the prevalence and type of ocular manifestations could help physicians better diagnose the infection and protect themselves when encountering children with similar ocular manifestations.

There is no information about ocular manifestations, and there is a lack of evidence of ocular manifestations in children [12]. Hence, we performed this systematic review

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and meta-analysis to estimate the prevalence of ocular manifestations in children with COVID-19.

MATERIAL AND METHODS

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (supplementary 1).

Study Eligibility Criteria. We included reports of ocular manifestations of COVID-19 in children with positive PCR, including case reports, case series, and cross-sectional studies. Ocular manifestations reports in individuals over 18 years of age were excluded from the study. Also, we excluded studies that did not separate ocular manifestations in children and adults or did not define COVID-19 in children.

Search Strategy. We searched PubMed, Scopus, EMBASE, Web of Science, and MedRxiv databases for published and pre-published studies from December 1, 2019, to April 23, 2021, and only studies in English were included. In Google Scholar, a systematic reference list of studies was also searched for potentially eligible citations. A combination of medical headings terms and keywords related to ocular manifestations and COVID-19 were identified. Moreover, we consulted with a librarian to complete the search strategy. After removing duplicate articles, two individuals independently screened the titles and abstracts (NN, TR). Two individuals independently reviewed full-text studies (GHSH, TR) to determine the final articles. Discrepancies were resolved by the corresponding author (ASH) (Please see supplementary 2 for search strategy).

Quality Appraisals. The quality of the studies was independently assessed by two authors (NN, HSH) using the Joanna Briggs Institute Critical Appraisal tool. The Joanna Briggs Institute (JBI) is a critical appraisal tool for evaluating quantitative studies included in the systematic review. This tool suggests eight items for case reports studies, nine for prevalence studies, and ten for case series. Disagreement about the quality of studies was resolved through a discussion with the corresponding author (ASH) (Please see supplementary 3).

Data Collection. We designed an Excel form to extract the data, including the first author, design study, location, sample size, and ocular manifestations, and extracted the data independently.

Statistical Analysis. We used descriptive statistics (mean, median, and SD for continuous variables and frequency and percent for categorical variables). We also applied the Metaprop command to estimate the pooled prevalence in cross-sectional studies using random effects for calculated pooled prevalence and 95% confidence intervals (95% CI). Only four studies were appropriate for calculating the pooled prevalence; therefore, we cannot use I^2 and meta-regression. All statistical analyses were performed by Stata software version 14.2.

RESULTS

After removing duplicates, we found 1,510 studies in the database; among which 19 were approved for systematic review, including six case reports [13-18], seven case series [7, 19-24], and six cross-sectional [8, 25-29] (Fig. 1).

Table 1. Ocular manifestations in COVID-19 children (n =139)

Variable	No. (%)
Conjunctival discharge	33 (23.6)
Conjunctival congestion	24 (17.3)
Eye rubbing	19 (13.6)
Hemorrhagic conjunctivitis	11 (8.0)
Chemosis	11 (8.0)
Periorbital edema	11 (8.0)
Corneal edema	6 (4.3)
Ocular pain	4 (3.0)
Eyelid swelling	4 (3.0)
Tearing	3 (2.1)
Cotton wool spots	2 (1.4)
Unilateral episcleritis	2 (1.4)
Rubeosis	1 (0.7)
Posterior synechiae	1 (0.7)
Stinging	1 (0.7)
Vitreous hemorrhage	1 (0.7)
Unilateral optic neuritis	1 (0.7)
Unilateral retinal vasculitis	1 (0.7)
Perivascular infiltrate	1 (0.7)
Retinal exudates	1 (0.7)
Yellowish discoloration	1 (0.7)

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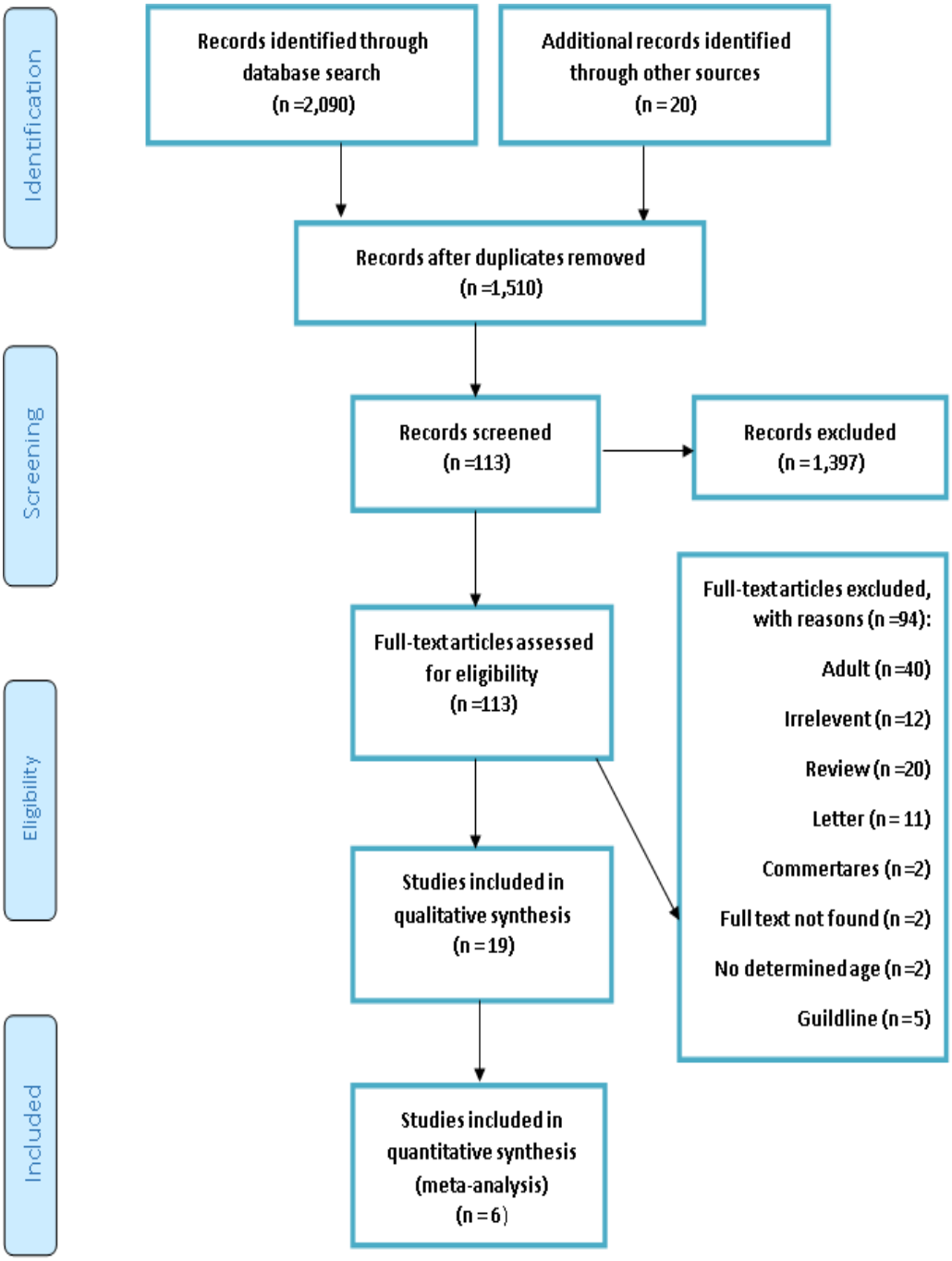


Fig. 1. Flowchart of studies included in the systematic review of COVID-19 ocular manifestations

The PCR confirmed COVID-19 infection in 1071 children (96.0%). Most children were boys (58.4%), with a mean age of 8.4 years, ranging from 4 days to 17 years. One hundred twenty-five (11.2%) out of 1117 children with COVID-19 had ocular manifestations. The pooled prevalence for ocular manifestations in children with COVID-19 was 8.0% (95% CI: 1.0- 21.0) (Fig. 2).

The most ocular findings were conjunctival discharge (33, 23.6%), conjunctival congestion (24, 17.3%), eye rubbing (19, 13.6%), periorbital edema (11, 8.0%) and chemosis (11, 8.0%), respectively (Table 1); these symptoms could be related to conjunctivitis. Some studies reported conjunctivitis as an ocular manifestation in children with COVID-19.

The most common complications in children with COVID-19 were respiratory system diseases (n=25, 26.0%), rhinitis (n=25, 26.0%), cardiovascular diseases (n=11, 11.5%), and sickle cell disease (n=7, 7.3%), respectively (Table 2).

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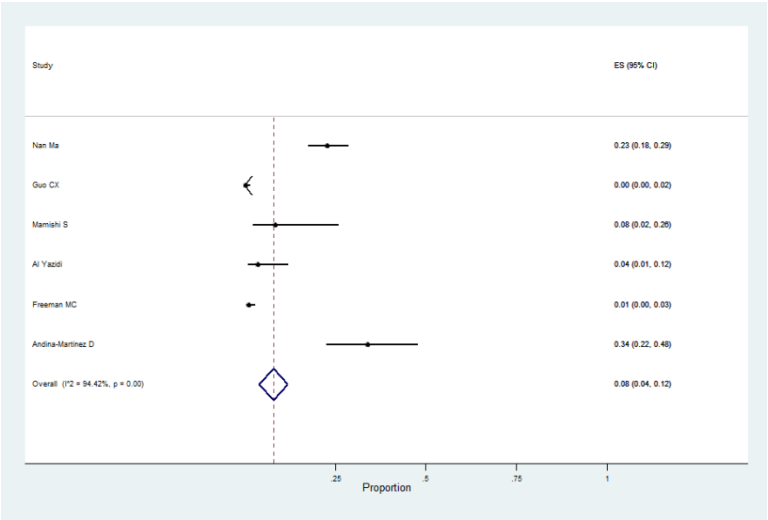


Fig. 2. The pooled prevalence of ocular manifestations in COVID-19 children

Table 2. Comorbidities in children with COVID-19

Variable	N (%)
Respiratory system diseases	25 (26.0)
Rhinitis	25 (26.0)
Cardiovascular diseases	11 (11.5)
Sickle cell disease	7 (7.3)
Urticaria	6 (6.3)
Neonatal jaundice	6 (6.3)
Neurological disease	4 (4.3)
Cystic fibrosis	4 (4.3)
Endocrine diseases	2 (2.0)
Hyper inflammatory syndrome*	2 (2.0)
Juvenile idiopathic arthritis	1 (1.0)
Bone marrow aplasia	1 (1.0)
Hemolytic anemia	1 (1.0)
Cow's milk protein allergy	1 (1.0)
Total	**96**

*Hyper inflammatory syndrome with multi-organ involvement similar to Kawasaki disease shock syndrome

Please see supplementary 4 for the details of studies enrolled in this systematic review.

DISCUSSION

This systematic review and meta-analysis showed that among children with COVID-19, 8.0% had at least one ocular symptom. The most common symptoms were conjunctival discharge and congestion, and eye rubbing.

In this study, the pooled prevalence of ocular manifestations was 8.0%. In China (2020), of 136 children with COVID-19, 0.7% exhibited ocular manifestations [25]. A case study in 2020 reported that four out of 27 Italian children with COVID-19 had viral conjunctivitis [7]. In 2020 among 216 Chinese children with COVID-19, 49 (22.7%) presented ocular manifestations [8]. A study in Iran (2021) reported ocular manifestation in a three-year-old boy about 11 days after the onset of the systemic disease [16]. In 2020, the prevalence of ocular manifestations was 8.3% among 24 Iranian children with COVID-19 [26]. Two systematic reviews and meta-analyses in 2020 and 2021 estimated the prevalence of ocular manifestations in the total population at around 11% [11, 30]. This difference between the total population and children may be because children are less likely to become symptomatic [12]. For those involved in the diagnosis of COVID-19, it is necessary to consider ocular manifestations as a sign of COVID-19. Moreover, ophthalmologists should consider these manifestations when examining the suspected patients.

This study showed that conjunctival discharge, congestion, and eye rubbing were the main ocular manifestations. In China (2020), among 49 COVID-19 children with ocular manifestations, 27 exhibited conjunctival discharge (55.1%), 19 (38.8%) eye rubbing, and five (10.2%) conjunctival congestion [8]. In India (2020), eight out of 11 COVID-19 children with ocular manifestations had conjunctival congestion [31]. In a systematic review comprising the total population, dry eyes or foreign body sensation and redness were the most common symptoms in patients with SARS-CoV-2 infection [11]. We showed different signs and symptoms in children compared to the total population;

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ophthalmologists and other healthcare providers should consider different ocular symptoms due to SARS-CoV-2 infection in the total population. Ocular manifestations and conjunctivitis may be less prevalent in children with COVID-19 [32] but are common in severe COVID-19 conditions [10, 30]. The ocular manifestations may be the only symptom of SARS-CoV-2 infection in the early phase of the disease [10, 33]. Therefore, physicians should consider these manifestations when visiting children suspected of COVID-19.

This review had some limitations. First, some reports did not separate ocular manifestations in adults and children, and some did not denote ocular manifestations in children with COVID-19 and children without COVID-19. Second, since only six cross-sectional studies were eligible for inclusion in the meta-analysis, the pooled prevalence exhibited a wide range of estimates. Finally, we could not estimate the pooled prevalence without considering the heterogeneity among the studies.

Children with SARS-CoV-2 infection may show ocular manifestations, although children had different ocular symptoms than the total population. Any health personnel should consider these differences when working with suspected patients. Paying attention to ocular manifestations could help better diagnose patients with COVID-19 and protect physicians, especially ophthalmologists who are in close contact with the patients.

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All authors contributed to the study design and data analysis. Naser Nasiri and Tahereh Rahimi performed the screening, and Ali Sharifi supervised the screening process. Ghodsieh Sharif and Tahereh Rahimi did data extraction. Hamid Sharifi and Naser Nasiri performed the analysis. Naser Nasiri, Hamid Sharifi, and Ali Sharifi wrote the first draft of the manuscript. This review received no external funding or other support.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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