Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Severe COVID-19 Infection and Pediatric Comorbidities: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: There is limited information on the severity of COVID-19 infection in children with comorbidities. We investigated the effects of pediatric comorbidities on COVID-19 severity by means of a systematic review and meta-analysis of published literature.

Methods: PubMed, Embase, and Medline databases were searched for publications on pediatric COVID-19 infections published January 1st to October 5th, 2020. Articles describing at least one child with and without comorbidities, COVID-19 infection, and reported outcomes were included.

Results: 42 studies containing 275,661 children without comorbidities and 9,353 children with comorbidities were included. Severe COVID-19 was present in 5.1% of children with comorbidities, and in 0.2% without comorbidities. Random-effects analysis revealed a higher risk of severe COVID-19 among children with comorbidities than for healthy children; relative risk ratio 1.79 (95% CI 1.27 – 2.51; I^2 = 94%). Children with underlying conditions also had a higher risk of COVID-19-associated mortality; relative risk ratio 2.81 (95% CI 1.31 – 6.02; I^2 = 82%). Children with obesity had a relative risk ratio of 2.87 (95% CI 1.16 – 7.07; I^2 = 36%).

Conclusions: Children with comorbidities have a higher risk of severe COVID-19 and associated mortality than children without underlying disease. Additional studies are required to further evaluate this relationship.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the human coronavirus disease 2019 (COVID-19) pandemic that officially began on March 11, 2020 (Cucinotta and Vanelli, 2020). At the time of writing of this report —November 9th, 2020 — there had been 50,539,082 confirmed cases with an associated 1,258,321 deaths worldwide resulting from COVID-19 infection (COVID-19 Map, 2020). The virus primarily affects the lower respiratory tract, and infected individuals primarily present with fever, cough, and dyspnea, however gastrointestinal (GI) manifestations can also occur (Huang et al., 2020; Shi et al., 2020). Although the infection course is usually non-fatal, severe COVID-19 infection with life-threatening presentations of acute respiratory distress syndrome (ARDS) and multiple organ failure can occur (Huang et al., 2020; Zhou et al., 2020). Risk factors for severe manifestations of SARS-CoV-2 illness and associated mortality include age greater than 65 years (Du et al., 2020; Wu and McGoogan, 2020), and underlying comorbidities such as diabetes, hypertension, and obesity (Caussy et al., 2020; Du et al., 2020; Guan et al., 2020; Wu and McGoogan, 2020).

Multiple studies on COVID-19 infection in children have noted differences in infection rates, symptoms, and mortality as compared to adults (Dong et al., 2020; Wu and McGoogan,

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2020). One of the most comprehensive early studies of pediatric patients with SARS-CoV-2 infection reported that children develop a relatively mild disease course with 83% of confirmed cases presenting with mild to moderate infection, with an additional 13% being asymptomatic, and only 3% presenting with severe and critical illness (Dong et al., 2020). However, such early case series potentially suffer from decreased testing of mildly infected individuals thereby leading to a potentially low rate of documented asymptomatic infections. A recent outbreak in a children's overnight camp in the United States reported an asymptomatic infection rate of 26% among COVID-19 infected children (Szablewski, 2020). Nonetheless, the disease course in children can be heterogenous in nature, with the most common clinical signs and symptoms including fever, headaches, and sore throat (Szablewski, 2020). Critical illness in children and adults alike typically manifests with severe pneumonia characterized by specific oxygen concentrations less than 92%, autoinflammatory shock, and respiratory distress (Sankar et al., 2020). Such cases frequently require mechanical ventilation and treatment with antiviral and immunomodulating regimens (Sankar et al., 2020; Zimmermann and Curtis, 2020).

Even so, previous reports have indicated clusters of an inflammatory syndrome, called "Multisystem Inflammatory Syndrome associated with COVID-19 (MIS-C)" or "Paediatric inflammatory multisystem syndrome (PIMS)" Kawasaki-like disease, a potentially fatal vasculitis, occurring in children following COVID-19 infection (Riollano-Cruz et al., 2020; Verdoni et al., 2020). Such reports indicate the potential (albeit uncommon) for severe and potentially fatal COVID-19 in pediatric patients. Although previous studies have established pre-existing comorbidities as significant risk factors for severe SARS-CoV-2 infection in adults (Du et al., 2020; Guan et al., 2020), questions remain regarding childhood comorbidities and associated COVID-19 outcomes. While systematic reviews and meta-analyses examining COVID-19 in pediatric patients have been published (Ding et al., 2020; Hoang et al. 2020), these reports did not evaluate the risk of severe SARS-CoV-2 infection specifically in children with pre-existing conditions. Consequently, the objective of this systematic review and meta-analysis is to examine the relative risk of severe COVID-19 infection and associated mortality in children with comorbidities.

Methods

Search Strategy and Selection Criteria

For this systematic review and meta-analysis PubMed, Medline, and Embase databases were queried for articles published from January 1st, 2020 until October 5th, 2020. The Medline and Embase searches were conducted via the Ovid interface. The search terms "COVID-19", "SARS-nCoV-2", "SARS-CoV-2", "2019-nCoV", "novel coronavirus", and "coronavirus" were used to obtain articles relating to the novel coronavirus pandemic occurring in 2020. To obtain literature pertaining specifically to SARS-CoV-2 infection in pediatric patients, the terms "child*", "pediatr*", "paediatr*", "teenage", "adolescent", "infant", and "newborn" were queried in conjunction with the coronavirus search. For the full search queries, see Supplement S1. To capture articles potentially missed by our systematic search, *Google Scholar* was queried for articles pertaining to COVID-19 infection in pediatric patients. Further articles were obtained by examining the references of highly relevant systematically retrieved articles. Only articles in English were considered for inclusion. References were managed with Endnote (version X9.0) software which was also used for duplicate removal. The systematic literature search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) recommendations (Moher et al., 2009).

Following deduplication, the reference titles were reviewed by BKT. Titles that did not imply a subject matter relevant to COVID-19 in pediatric patients were excluded. Following title review, the full-text content of the remaining literature was thoroughly analyzed by the author BKT. The following exclusion criteria were applied to the full-text articles: articles not mentioning pediatric comorbidities; adult only studies; articles where the pediatric comorbidity data was indistinguishable from adult comorbidity data; pre-existing reviews, systematic-reviews, and meta-analyses; articles with patients without confirmed COVID-19 infections; basic science studies; clinical discussions, recommendations, and guidelines; articles without reported patient outcomes; and studies of other coronaviruses. Articles containing at least one paediatric patient with comorbidities, and one paediatric patient without comorbidities were included. Furthermore, we included articles for which the severity and outcomes of SARS-CoV-2 infection in the paediatric patients was clearly defined. Following full-text review, BKT and KJ graded the remaining studies using the National Institutes of Health (NIH) Quality Assessment Tool for Case Series and Studies (Study Quality Assessment Tools, 2020). Any disagreements in rating were handled via discussion by the two reviewers until a consensus was reached. For the literature grading see Supplement S2.

Data Extraction and Case Definitions

The study authors; design; country of origin; aims; pediatric sample size; COVID-19 infection counts; disease severity; comorbidity counts; pediatric intensive care unit (PICU) admittance counts; and mortality counts were extracted from the included literature. The extracted comorbidities were either defined by the studies or classified into representative broader categories by BKT and KJ. Comorbidities such as trisomy 21, prematurity, and undefined genetic abnormalities were deemed as "other" pre-existing conditions. Obesity was defined by the studies where available, or by the authors as a body mass index (BMI) at or greater than the 95th percentile for children of the same age and sex according to CDC definitions (Defining Childhood Obesity, 2019). To operationalize severe COVID-19 infection across the different studies, severe infection was deemed as any SARS-CoV-2 infection requiring supplemental help to normal breathing and/or admission to a PICU unless otherwise explicitly stated in the literature. Finally, paediatric patients were defined as participants suffering from COVID-19 who were below 21 years of age.

Statistical Analyses

PICU admission and mortality outcomes were assessed using a random effects meta-analysis (Schwarzer et al., 2015). A random effects model was chosen due to the potential variation in sampled study populations leading to differences in outcomes by comorbidities. Estimation of random-effects variance was conducted using the Sidik-Jonkman estimator with Hartung-Knapp adjustment (IntHout et al., 2014). For individual trials with no events in one or both groups, a continuity correction of the opposite treatment arm size was added to each cell for each effect measure (Sweeting et al., 2004). Binary estimators including risk ratios, and risk difference were estimated using the Mantel-Haenszel method (Mantel and Haenszel 1959; Robins et al., 1986). All analyses and data visualization were conducted in R version 4.0.2 using the meta and tidyverse libraries (Balduzzi et al., 2019; Team, R Core, and others, 2020; Wickham et al., 2019).

Role of the Funding Source

This study did not receive any funding. The study design, data analysis, and writing of the manuscript was conceptualized only by the authors.

Results

There were 13310 studies identified from our systematic search across the three databases (Fig. 1). Following de-duplication, 8206 records were reviewed based on a title screen, of which 7398 were deemed irrelevant to the subject matter of this study. The full-texts of the remaining 808 articles were reviewed for the presence of pediatric study participants who had: 1) pre-existing comorbidities; and 2) COVID-19 infection, for which clear outcomes were reported. 98 articles then underwent literature grading, with 86 studies deemed fair for further analysis. Among these 86 articles, only 42 had pediatric case-control participants without comorbidities with either severe COVID-19 and/or COVID-19-associated mortality. Five studies (Bellino et al., 2020; Bixler et al., 2020; Blumfield and Levin, 2020; Moraleda et al., 2020; Otto et al., 2020) only examined children who died from COVID-19 and were therefore only included in the mortality analysis. These 42 studies were therefore the basis for our analysis examining the effects of comorbidities on severe and potentially fatal manifestations of pediatric SARS-CoV-2 infection. Among the 42 articles, 18 studies were from the USA (43%), and 4 studies were from China (10%), Italy (10%), and Spain (10%) respectively. Of the remaining studies, 3 were from France (7%), 2 were from the United Kingdom (5%), and Iran (5%), and 1 was from Austria (2%), Brazil (2%), India (2%), Turkey (2%), and Uruguay (2%) (Table 1).

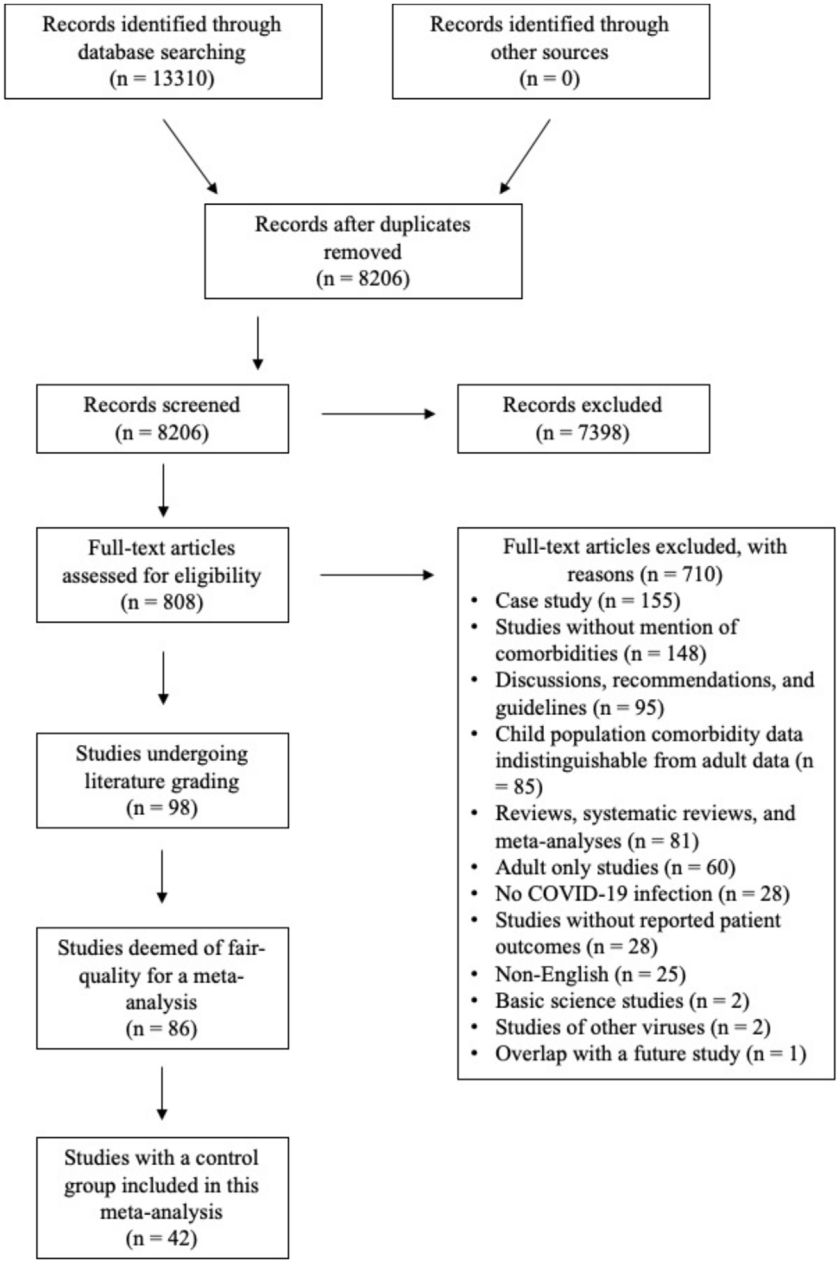

Fig. 1. PRISMA flow diagram for the identification of studies pertaining to COVID-19 and children with comorbidities published between January 1 st, 2020 and October 5th, 2020.

Table 1
Summary and characteristics of the 42 studies included in this systematic review and meta-analysis.

STUDY	Study type	Country	Study Aim	COVID-19 Infection (N = 285,004)	With comorbidities and COVID-19 (n = 9353)	COmorbidities and Severe COVID-19[A] (n = 481)	Comorbidities and mortality (N = 135)
(Abdel-Mannan et al., 2020)	Retrospective	U.K	Report neurological manifestations of children with COVID-19	4	1	1	0
(Anand et al., 2020)	Retrospective	India	Describe the clinical profile of neonates born to mothers with COVID-19	7	3	0	0
(Bellino et al., 2020)	Retrospective	Italy	Describe characteristics of COVID-19 in pediatric patients	3836	206		4
(Belhadjer et al., 2020)	Retrospective	France	Report cases of acute heart failure associated with COVID-19 in children	31	4	4	0
(Bhumbra et al., 2020)	Retrospective	USA	Describe the infection course of children hospitalized with COVID-19	24	8	3	
(Biko et al., 2020)	Retrospective	USA	Describe imaging features, comorbidities, and outcomes of children with COVID-19	313	41	17	0
(Bixler et al., 2020)	Retrospective	USA	Report the SARS-CoV-2-associated deaths in children residing in the USA	121	91		91
(Blumfield and Levin, 2020)	Retrospective	USA	Report the outcomes of critically-ill children with COVID-19	18	12		2
(Cai et al., 2020)	Case-series	China	Report the outcomes and clinical characteristics of pediatric patients with COVID-19 that did not have respiratory symptoms as the first manifestation of infection	5	3	2	0
(Chao et al., 2020)	Retrospective	USA	Report the risk factors associated with severe COVID-19 in pediatric patients	46	31	12	1
(de Farias et al., 2020)	Prospective	Brazil	Describe the characteristics of COVID-19-associated PIMS in 11 children	11	5	5	2
(DeBiasi et al., 2020)	Retrospective	USA	Examine the epidemiology of pediatric COVID-19 infection in Washington, DC	165	69	5	0
(Derespina et al., 2020)	Retrospective	USA	Describe outcomes of COVID-19 in children in New York City	70	52	52	2
(Diorio et al., 2020)	Prospective	USA	Report the hematological differences between MIS-C and COVID-19 in children	14	13	9	2
(Du et al., 2020)	Retrospective	China	Report the outcomes of and laboratory characteristics of COVID-19 among hospitalized pediatric patients with a focus on allergic patients	182	59	2	0
(Eghbali et al., 2020)	Case-series	Iran	Describe 4 cases of pediatric COVID-19 in Iran	4	2	2	1
(Garazzino et al., 2020)	Retrospective	Italy	Report outcomes and disease characteristics of COVID-19 among multiple pediatric care centres in Italy	168	33	2	0
(García-Salido et al., 2020)	Prospective	Spain	Describe series of children admitted to a Spanish PICU due to COVID-19	7	1	1	0
(Giacomet et al., 2020)	Retrospective	Italy	Describe the characteristics of severe vs non-severe COVID-19 in children	127	20	6	0
(González-Dambrauskas et al., 2020)	Retrospective	Uruguay	Examine the characteristics and outcomes of pediatric patients in PICUs due to COVID-19 infection	17	12	12	1
(Götzinger et al., 2020)	Cross-sectional	Austria	Examine the characteristics and outcomes of children with COVID-19 across Europe	582	145	25	2
(Kainth et al., 2020)	Retrospective	USA	Describe the presentation, course, and severity of pediatric COVID-19	65	30	10	1
(Kaushik et al., 2020)	Retrospective	USA	Assess the outcomes of COVID-19-associated MIS-C	33	16	16	
(Leeb, 2020)	Retrospective	USA	Examine the epidemiology of COVID-19 among US children	277,285	7738	109	14
(Lovinsky-Desir et al., 2020)	Retrospective	USA	Examine the impact of asthma on COVID-19 severity	55	24	24	
(Mannheim et al., 2020)	Case-series	USA	Report the clinical characteristics of pediatric COVID-19 in Chicago	64	13	4	
(Meslin et al., 2020)	Case-series	France	Present outcomes of 6 children with COVID-19 in France	6	2	0	0
(Moraleda et al., 2020)	Case-series	Spain	Describe clinical features of MIS-C in Spain	31	10		2
(Moreno-Galarraga et al., 2020)	Retrospective	Spain	Describe the presentations of COVID-19 in Spain	11	4	0	0
(Otto et al., 2020)	Retrospective	USA	Describe the outcomes and features of COVID-19 in children	424	242		2
(Oualha et al., 2020)	Retrospective	France	Describe severe presentations of COVID-19 in children	27	19	19	2
(Parri et al., 2020)	Retrospective	Italy	Examine the diagnostic, clinical presentation, interventions and outcomes of pediatric patients with confirmed COVID-19 in Italy.	170	38	6	0
(Riollano-Cruz et al., 2020)	Retrospective	USA	Describe the first COVID-19 MIS-C associated cases in New York City	15	5	4	0

Table 1 (*Continued*)

STUDY	Study type	Country	Study Aim	COVID-19 Infection (N = 285,004)	With comorbidities and COVID-19 (n = 9353)	COmorbidities and Severe COVID-19[A] (n = 481)	Comorbidities and mortality (N = 135)
(Schwartz et al., 2020)	Case-series	Iran	Describe the characteristics and outcomes of COVID-19 in neonates in Iran	19	15	10	0
(Shekerdemian et al., 2020)	Cross-sectional	USA	Characterize COVID-19 infection in North American PICUs	48	40	40	
(Sun et al., 2020)	Retrospective	China	Examine the clinical characteristics of pediatric COVID-19	8	1	1	0
(Swann et al., 2020)	Prospective	UK	Explore the clinical characteristics of pediatric COVID-19 and MIS-C in the UK	651	276	63	6
(Tagarro et al., 2020)	Retrospective	Spain	Describe the epidemiology and treatment of COVID-19 in Madrid	41	11	1	0
(Waltuch et al., 2020)	Case series	USA	Describe the characteristics and outcomes of 4 pediatric cases of COVID-19	4	2	2	0
(Yayla, 2020)	Retrospective	Turkey	Examine characteristics of COVID-19 in children in Turkey	220	21	2	0
(Zachariah et al., 2020)	Retrospective	USA	Compare the features of pediatric COVID-19 disease between severe and mild infection	50	33	8	
(Zheng et al., 2020)	Retrospective	China	Describe the clinical characteristics of pediatric COVID-19	25	2	2	0

Abbreviations: COVID-19 - coronavirus disease 2019; PICU - pediatric intensive care unit.
[A] Defined by the studies, or PICU admission, or need for supplemental breathing aid during the course of infection.

Study Patient Characteristics

From the 42 articles, a total of 285,004 pediatric patients with laboratory-confirmed SARS-CoV-2 infection were identified. Among this cohort, 9,353 (3.3%) had at least one underlying comorbidity (Table 1). Gender demographic data was available for 280,999 COVID-19 infected children, of which 142,411 (50.7%) were female and 138,588 (49.3%) were male. We were able to

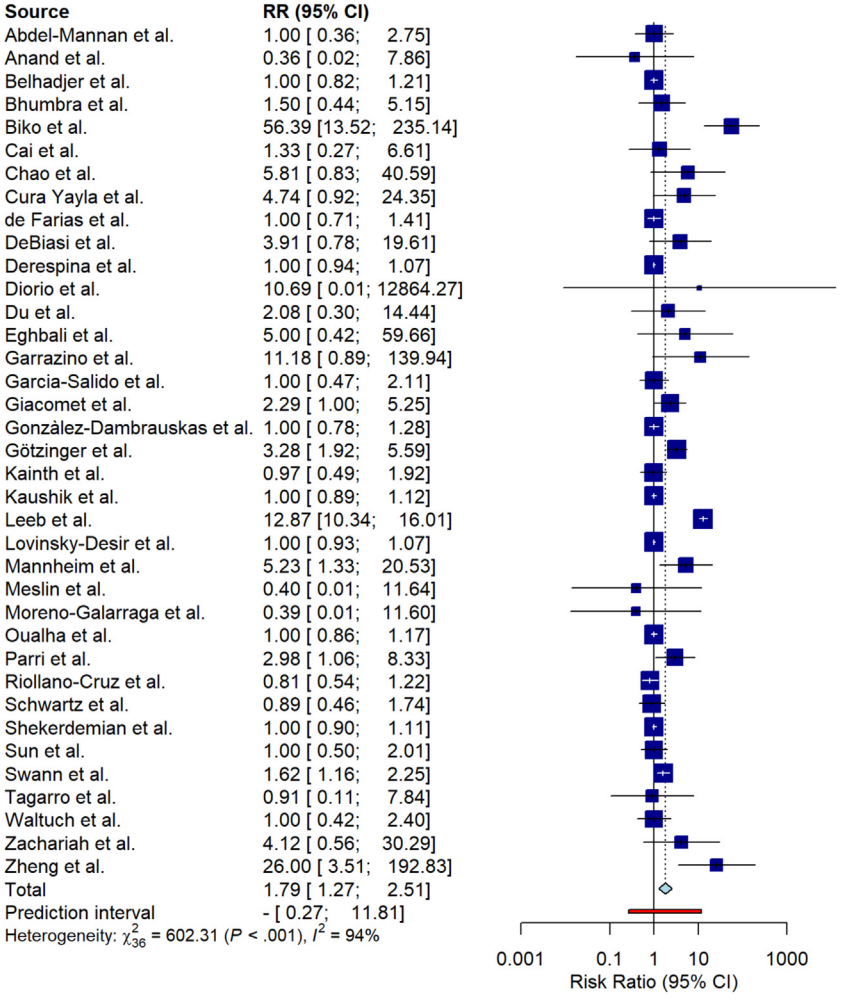

Fig. 2. Pooled estimate of the relative risk of severe COVID-19 among pediatric patients with comorbidities.

extrapolate age-category data in 362 children. Of these, 138 (38%) were under 1 year of age, 82 (21%) 1 to 5 years of age, 31 (8%) 6 to 10, 22 (6%) 10 – 14, and 89 (23%) were older than 14 years of age. To the best of our ability, we have excluded any study participants that were over 21 years, such as those present in the study by DeBiasi and colleagues.

Relative Risk of Pediatric Comorbidities on Severe COVID-19 Infection

Among the 9,353 pediatric patients with SARS-CoV-2 infection and underlying comorbidities, 481 (5.1%) had severe COVID-19 and/or were admitted to a PICU (Table 1). In contrast, only 579 of the 275,661 (0.21%) pooled pediatric patients without comorbidities had a severe manifestation of COVID-19. Employing a random-effects model to examine the relative risk of severe COVID-19 and/or PICU admission among children with comorbidities, we obtained a total relative risk ratio of 1.79 (95% CI 1.27 – 2.51; $\chi^2 = 602.31$ ($P < 0.001$); $I^2 = 94\%$) (Fig. 2). It is important to note that only 37 studies were included in this analysis as 5 studies only examined COVID-19-associated deaths (Bellino et al., 2020; Bixler et al., 2020; Blumfield and Levin, 2020; Moraleda et al., 2020; Otto et al., 2020). Nonetheless, 7 studies (Anand et al., 2020; Kainth et al., 2020; Meslin et al., 2020; Moreno-Galarraga et al., 2020; Riollano-Cruz et al., 2020; Schwartz et al., 2020; Tagarro et al., 2020) had a higher risk ratio of severe COVID-19 among pediatric patients without comorbidities than those with underlying conditions (Fig. 2). Furthermore, studies such as the CDC Mortality and Morbidity Weekly Report (Leeb, 2020) had noticeably larger participant cohort populations than other reports. To examine the potential preferential bias of these studies towards the overall relative risk ratio of our analysis, we individually excluded each of the 37 studies to determine the overall effect of each singular study on the net relative risk ratio. Notably, no article significantly influenced the risk ratio in either direction (Fig. 3).

Relative Risk of Pediatric Comorbidities on Mortality Associated with COVID-19 Infection

Nineteen of the 42 articles included in this meta-analysis reported children who died while being infected with SARS-CoV-2 (Fig. 4). Across the 19 articles, of the 274,647 pediatric patients with COVID-19 infection without comorbidities, only 77 (0.03%) died across 8 studies (Bixler et al., 2020; Cai et al., 2020; Du et al., 2020; Götzinger et al., 2020; Leeb, 2020; Oualha et al., 2020; Riollano-Cruz et al., 2020; Yayla, 2020). In contrast, 134 (1.5%) of the 8960 children with pre-existing conditions died during the course of their SARS-CoV-2 infection across 15 studies (Bellino et al., 2020; Bixler et al., 2020; Blumfield and Levin, 2020; Chao et al., 2020; Derespina et al., 2020; Diorio et al., 2020; Eghbali et al., 2020; de Farias et al., 2020; Götzinger et al., 2020; Kainth et al., 2020; Leeb, 2020; Moraleda et al., 2020; Otto et al., 2020; Oualha et al., 2020; Swann et al., 2020) (Table 1). The random effects model used to determine the risk of mortality among children with comorbidities and COVID-19 relative to pediatric patients without comorbidities revealed a total risk ratio of 2.81 (95% CI 1.31 – 6.02; $\chi^2 = 97.85$ ($P < 0.001$); $I^2 = 82\%$) (Fig. 4). In only five of the studies (Cai et al., 2020; Du et al., 2020; Oualha et al., 2020; Riollano-Cruz et al., 2020; Yayla, 2020) did children with comorbidities have a lower risk of mortality during the course of COVID-19 (Fig. 4). Notably, subsequent sensitivity analysis confirmed that no one article significantly affected the relative risk ratio of mortality among children with pre-existing conditions (Fig. 5).

Relative Risks of Various Pediatric Comorbidities on Severe COVID-19 Manifestations

Our previously presented analyses hinted at a higher risk of severe COVID-19 infection and associated mortality among pediatric patients with underlying comorbidities (Figs. 2 and 4). We next sought to examine the potential impact of specific comorbidities on

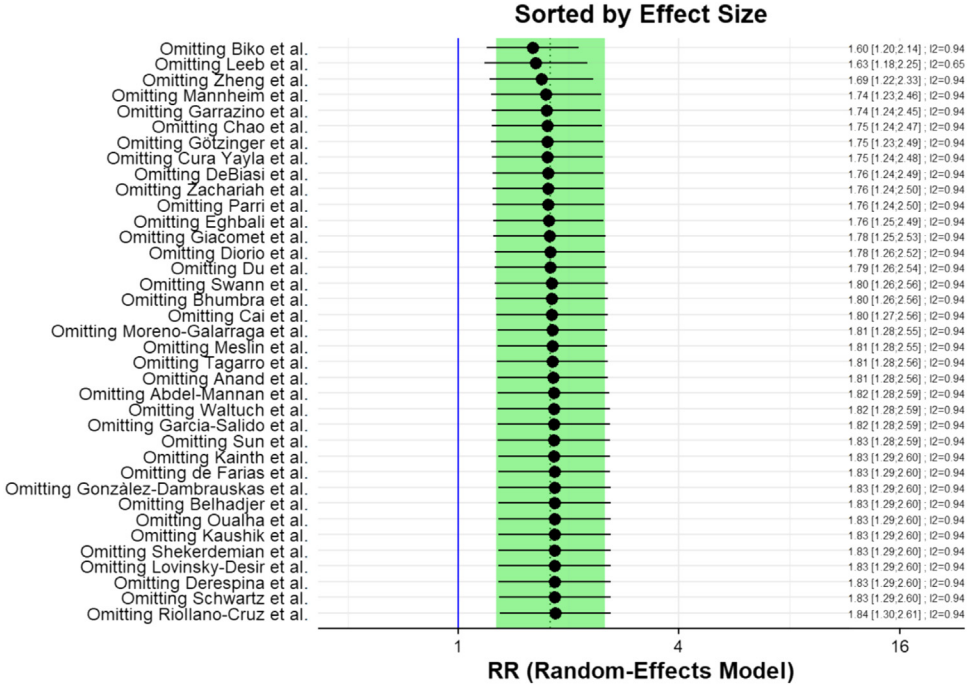

Fig. 3. Sensitivity analysis of the influence of each included study on the overall relative risk of severe COVID-19 among children with comorbidities.

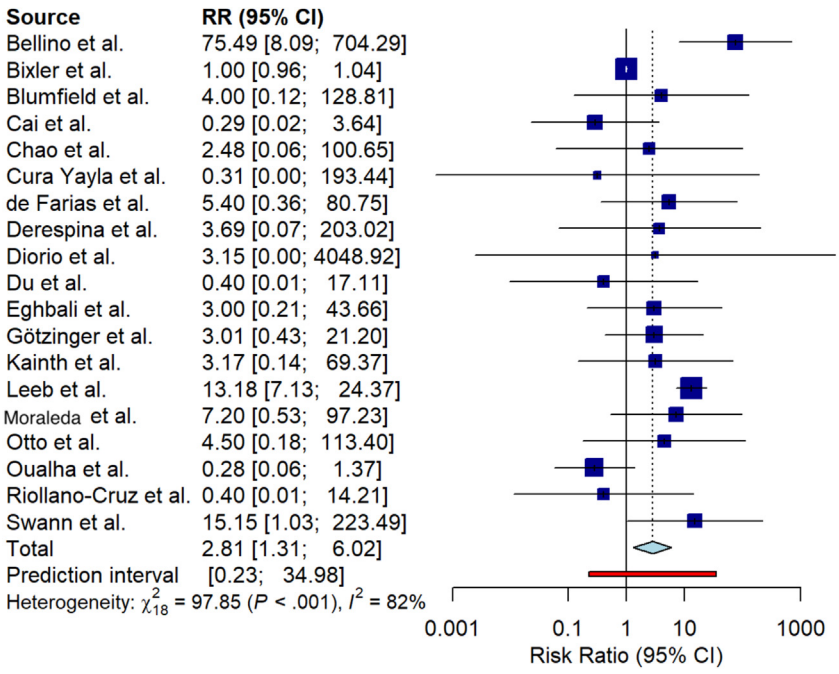

Fig. 4. Pooled estimate of the relative risk of COVID-19-associated mortality among pediatric patients with comorbidities.

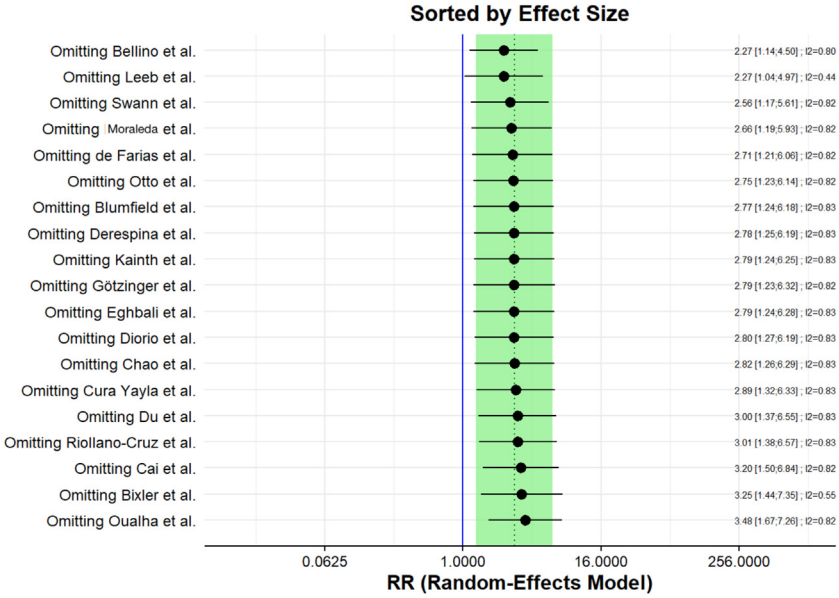

Fig. 5. Sensitivity analysis of the relative contributions of each study toward the relative risk of mortality during COVID-19 infection in pediatric patients with comorbidities.

the risks of severe SARS-CoV-2 manifestations. For details on the underlying conditions represented among all 9,353 children with comorbidities regardless of COVID-19 severity, see Supplement S3. In the 42 studies included in this meta-analysis, we found that among children with severe COVID-19, 64 children were obese (Abdel-Mannan et al., 2020; Chao et al., 2020; DeBiasi et al., 2020; Derespina et al., 2020; de Farias et al., 2020; Giacomet et al., 2020; González-Dambrauskas et al., 2020; Kaushik et al., 2020; Lovinsky-Desir et al., 2020; Shekerdemian et al., 2020; Swann et al., 2020; Waltuch et al., 2020; Zachariah et al., 2020), 58 had chronic respiratory disease (Belhadjer et al., 2020; Chao et al., 2020; DeBiasi et al., 2020; Diorio et al., 2020; González-Dambrauskas et al., 2020; Götzinger et al., 2020; Kaushik et al., 2020; Lovinsky-Desir et al., 2020; Mannheim et al., 2020; Riollano-Cruz et al., 2020; Shekerdemian et al., 2020; Swann et al., 2020; Waltuch et al., 2020; Yayla, 2020; Zachariah et al., 2020), 45 had cardiovascular disease (Chao et al., 2020; DeBiasi et al., 2020; Derespina et al., 2020; Diorio et al., 2020; Eghbali et al., 2020; Garazzino et al., 2020; Giacomet et al., 2020; González-Dambrauskas et al., 2020; Götzinger et al., 2020; Kainth et al., 2020; Kaushik et al., 2020; Mannheim et al., 2020; Schwartz et al., 2020; Shekerdemian et al., 2020; Swann et al., 2020; Zachariah et al., 2020; Zheng et al., 2020), 33 had neurologic disorders (Cai et al., 2020; Chao et al., 2020; DeBiasi et al., 2020; Diorio et al., 2020; Giacomet et al., 2020; González-Dambrauskas et al., 2020; Götzinger et al., 2020; Kainth et al., 2020; Oualha et al., 2020; Shekerdemian et al., 2020; Zachariah et al., 2020), 26 had immune disorders (Belhadjer et al., 2020; Chao et al., 2020; Kainth et al., 2020; Mannheim et al., 2020; Shekerdemian et al., 2020; Swann et al., 2020; Zachariah et al., 2020), and 19 had

metabolic disease (DeBiasi et al., 2020; Derespina et al., 2020; Riollano-Cruz et al., 2020; Shekerdemian et al., 2020; Waltuch et al., 2020; Zachariah et al., 2020; Zheng et al., 2020). Additionally, 12 had hematologic disorders (Eghbali et al., 2020; García-Salido et al., 2020; Kaushik et al., 2020; Oualha et al., 2020; Shekerdemian et al., 2020; Yayla, 2020; Zachariah et al., 2020), and 11 had cancer (Chao et al., 2020; Diorio et al., 2020; Du et al., 2020; González-Dambrauskas et al., 2020; Götzinger et al., 2020; Kainth et al., 2020; Sun et al., 2020). Five children had renal disease (Cai et al., 2020; Götzinger et al., 2020; Oualha et al., 2020), and 2 had GI comorbidities (Giacomet et al., 2020) respectively. Seventy-one children had other conditions (Diorio et al., 2020; Garazzino et al., 2020; González-Dambrauskas et al., 2020; Götzinger et al., 2020; Kainth et al., 2020; Kaushik et al., 2020; Mannheim et al., 2020; Schwartz et al., 2020; Shekerdemian et al., 2020; Swann et al., 2020; Zachariah et al., 2020) including prematurity, trisomy 21, or other genetic abnormalities. Finally, only 1 child presented with allergies (Du et al., 2020) and hepatobiliary disease (Riollano-Cruz et al., 2020) respectively.

We next analyzed the relative contribution of childhood obesity to pediatric COVID-19 severity. We chose to focus primarily on obesity as it has an easily definable metric (i.e. BMI) that can be compared across multiple studies. Although 64 pediatric patients with underlying obesity presented with severe COVID-19 across 13 studies (Abdel-Mannan et al., 2020; Chao et al., 2020; DeBiasi et al., 2020; Derespina et al., 2020; de Farias et al., 2020; Giacomet et al., 2020; González-Dambrauskas et al., 2020; Kaushik et al., 2020; Lovinsky-Desir et al., 2020; Shekerdemian et al., 2020; Swann et al., 2020; Waltuch et al., 2020; Zachariah et al., 2020), we chose to perform a meta-analysis only on the studies that included case-control participants (Abdel-Mannan et al., 2020; Chao et al., 2020; Giacomet et al., 2020; Moreno-Galarraga et al., 2020; Swann et al., 2020; Zachariah et al., 2020). Examining the risk of obesity on COVID-19 severity in relation to children without comorbidities, we obtained a relative risk ratio of 2.87 (95% CI 1.16 – 7.07; $\chi^2 = 7.81$ (P = 0.17); $I^2 = 36\%$) (Fig. 6). We also examined the relative risk of childhood cancer on severe COVID-19 (Supplement S4), from which we were not able to draw any conclusions due to the confidence interval of the relative risk ratio spanning a value of 1.0. Taken together, these results indicate that childhood obesity likely increases risk of severe COVID-19. However, more case-controlled, well-defined studies are needed to examine the effects that other childhood comorbidities such as cancer have on risk of severe manifestations of SARS-CoV-2.

Discussion

Current meta-analyses of publications involving children with COVID-19 infection primarily examine the overall characteristics, symptoms, and outcomes of SARS-CoV-2 infection regardless of comorbidity status (Ding et al., 2020; Hoang et al., 2020; Ludvigsson, 2020). Studies suggest that children typically have a milder infection course than adults, with an overall good prognosis. However, the effects of comorbidities on COVID-19 severity in children remain unclear. Although a previous correspondence suggested a worse SARS-CoV-2 infection course in children with comorbidities (Harman et al., 2020), the small sample size precludes definitive conclusions. In this systematic review and meta-analysis of 42 articles, we report that children with comorbidities are at higher risk for severe manifestations of COVID-19 and associated mortality relative to previously healthy children. Furthermore, we also note that childhood obesity probably leads to a worse COVID-19 prognosis. To our knowledge, we are the first to report these findings.

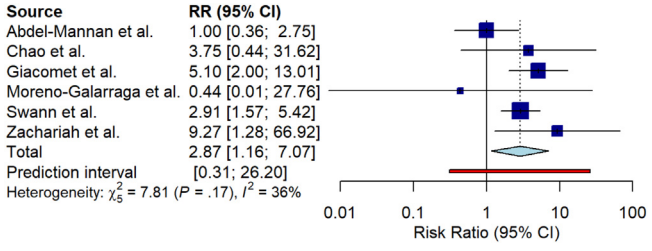

Fig. 6. Relative risk of childhood obesity on severe manifestations of COVID-19

Early analyses in adults with COVID-19 indicated that older age (Zhou et al., 2020) and comorbidities such as diabetes, hypertension, malignancies, chronic respiratory disease and obesity are significant risk factors for severe infection (Caussy et al., 2020; Guan et al., 2020; Yang et al., 2020). As such, the early lockdown measures implemented across the world in the spring of 2020 were aimed at protecting vulnerable populations (i.e., the elderly, and people with comorbid conditions) from COVID-19 infection, as well as preventing the overburdening of hospitals. In contrast, early epidemiological studies of pediatric populations (Dong et al., 2020) cited high rates of mild and asymptomatic COVID-19 infection, with certain publications advocating for their return to school (Munro and Faust, 2020; van Bruwaene et al., 2020). The results from our study suggest that children with specific comorbidities are a vulnerable population at risk for potentially life-threatening consequences of COVID-19 infection.

We report that childhood obesity is likely associated with a worsened prognosis of COVID-19 infection. This is in keeping with several adult studies noting that patients who had a BMI greater than or equal to 35 kg/m^2 required invasive mechanical ventilation due to SARS-CoV-2 infection more frequently than their leaner counterparts (Caussy et al., 2020; Simonnet et al., 2020). The effects of childhood obesity in potentiating severe COVID-19 are unsurprising. The high visceral adiposity present in obese individuals is known to induce higher levels of local and systemic inflammatory cytokines such as Interleukin-6 (IL-6), and C-reactive protein (CRP) (Fontana et al., 2007). The increased baseline of these cytokines in obesity are also likely the result of increased pro-inflammatory macrophage populations that have been observed in this population (Russo and Lumeng, 2018). These cytokines have been positively correlated with COVID-19 severity (Zeng et al., 2020) and their higher levels in obese individuals may contribute to their increased susceptibility to severe infection. However, childhood obesity likely contributes to severe COVID-19 infection in additional ways.

Unfortunately, we were unable to determine whether other comorbidities increase risk of severe COVID-19. This is in part due to the paucity of case-controlled literature examining the outcomes of children with COVID-19 who have well-defined comorbid conditions. Towards this aim, various international Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion (SECURE) databases and registries are set up to prospectively collect data, and will be particularly helpful in defining risk of COVID-19 infection and severity in patients with comorbidities. However, to date the available data remain quite limited. Apart from a recent article (Brenner et al., 2020a) and the SECURE-IBD database (Brenner et al., 2020b), a multi-national database examining the outcomes of patients with IBD and COVID-19, limited literature examining the effects of GI diseases on COVID-19 outcomes in children has been published. Furthermore, although recent approaches have begun examining the effects of COVID-19 infection on diseases such as sickle-cell disease (SSD) (McCloskey et al., 2020; Hussain et al., 2020), limited data exist for other systemic diseases. For example, for rheumatic diseases, apart from a retrospective report (Zhong et al., 2020), only a speculative review on the topic has been published (Licciardi et al., 2020). With

reports of MIS-C occurring in cohorts of children with COVID-19 infection (Riphagen et al., 2020; Verdoni et al., 2020) the dynamics and underlying characteristics of severe infection in the context of autoinflammatory comorbidities in children require further study.

Study Strengths

Our study has several important strengths. To our knowledge, this is the first systematic review and meta-analysis that examines the relative risk of severe COVID-19 and associated mortality among children with comorbidities. Furthermore, our study is the first to show that childhood obesity likely increases the risk of severe COVID-19 infection course. Lastly, our study has a relatively large sample size of 9,353 children with comorbidities among 42 articles. This relatively large sample size and study number allows for high statistical power, enabling accurate conclusions to be drawn from the study results.

Study Limitations

Our systematic review and meta-analysis have several potential limitations. Most importantly, there likely exists variations in PICU admission criteria across the studies, particularly regarding children with comorbidities and COVID-19 infection. We cannot ascertain whether admission to the PICU was primarily due to problems with underlying comorbidities in some children, with COVID-19 infection being subsequently discovered. Therefore, the increased risk of severe COVID-19 infection among children with comorbidities addressed in this meta-analysis could be the result of a selection bias of PICU admission in favor of children with underlying conditions. Furthermore, our study is subject to a high degree of study heterogeneity due to the small sample size in some of the included studies. In addition, based on the large body of rapidly-published literature surrounding COVID-19 infection, some studies may have used similar participants. Therefore, we cannot be certain that patients were not duplicated in our study. Our meta-analysis was also not able to capture the relative risk that comorbidities other than obesity contribute to severe SARS-CoV-2 viral infection. This is due to the sub-population heterogeneity of comorbidities that limits the ability to draw accurate comparisons between studies. Lastly, our meta-analysis amplifies the ascertainment bias of the primary literature. Asymptomatic COVID-19 infections among children with comorbidities do occur (Poli et al., 2020), however in most jurisdictions at this time, testing of asymptomatic or pauci-symptomatic children is very limited outside of outbreak settings. Consequently, such mild cases among children with comorbidities are likely less represented in the primary literature and therefore in our analysis. We therefore call for further availability of data on pediatric patients with comorbidities and COVID-19 outcomes, regardless of illness severity. Such broader representation within the literature would increase the accuracy of relative risk computation within this population by future meta-analyses.

Conclusions

To our knowledge, this is the first systematic review and meta-analysis examining the severity of COVID-19 infection among pediatric patients with comorbidities. We report that children with pre-existing conditions are at a greater risk of severe COVID-19 and associated mortality. In particular, childhood obesity is likely positively correlated with COVID-19 severity. However, further cross-sectional, case-controlled studies examining the effects of specific well-defined comorbidities are required to examine the effects that pediatric underlying conditions play in COVID-19 severity.

Author Contributions

BKT: study concept and design; literature review, acquisition of data; literature grading; analysis and interpretation of data; statistical analysis; drafting of the manuscript; approval of final manuscript.

JMA: study concept and design; critical revision of the manuscript for important intellectual content; approval of final manuscript.

MAI: statistical analysis, analysis and interpretation of data; critical revision of the manuscript for important intellectual content; approval of final manuscript.

AAL: literature review; critical revision of the manuscript for important intellectual content; approval of final manuscript.

LJS: critical revision of the manuscript for important intellectual content; approval of final manuscript.

BAV: study concept and design; critical revision of the manuscript for important intellectual content; approval of final manuscript.

KJ: study concept and design; literature grading; review and interpretation of data; drafting of the manuscript, critical revision of the manuscript for important intellectual content; approval of final manuscript.

Ethics Approval

No ethics approval was required for this publication.

Potential competing interest

None declared.

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The remaining authors disclose no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.11.163.

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