Arch Pediatr Infect Dis. 2022 October; 10(4):e119701. https://doi.org/10.5812/pedinfect-119701.

Published online 2022 October 9. **Systematic Review**

A Comprehensive Comparison of COVID-19 Characteristics (Wuhan Strain) Between Children and Adults During Initial Pandemic Phase: A Meta-Analysis Study

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Received 2021 October 09; **Revised** 2022 July 27; **Accepted** 2022 August 11.

Abstract

Objectives: This systematic review and meta-analysis aimed to compare coronavirus disease 2019 (COVID-19) (Wuhan strain) features in children and adults during the initial pandemic phase.

Methods: Until June 4, 2020, a systematic search was conducted on the EMBASE, PubMed, Web of Science, Google Scholar, and Scopus to find and collect studies based on available data among adults and children. The heterogeneity of the studies was assessed using I^2 statistics and chi-square testing. The random-effect model was used to pool the effect sizes due to inter-study heterogeneity (chi-square P-value 0.1 and I^2 >50%).

Results: Fever (65.73%), cough (53.78%), expectoration (37.9%), gastrointestinal symptoms (37.01%), headache (23.41%), shortness of breath (21.65%), and myalgia (20.79%) were the most common symptoms reported in children, according to the pooled estimation analysis. Arthralgia (Effect estimate (ES): adults = 2.15, children = 17.94) and headache (ES: adults = 9.22, children = 23.41) were significantly observed higher in children (P-value = 0.019). Adult patients had a higher rate of abnormal computed tomography (CT)-scan findings, while most children had a normal imaging studies. Adults had significantly higher rates of comorbidities, whereas children had significantly higher rates of asthma (ES: 17.94% vs 8.85%; P-value = 0.026) and malignancy (ES: 10.36% vs 5.47%; P-value = 0.045). During initial pandemic phase, hydroxychloroquine (ES: 66.21% vs 29.01%; P-value = 0.001) and antibiotics (ES: 77.86% vs 38.01%; P-value = 0.001) were used much more frequently in adult patients. Adults used much more antibiotics than children. Nonetheless, antibiotics were given to around 40% of the children studied.

Conclusions: Although children were afflicted less than adults in the early stages of the pandemic and had lower mortality, clinical and radiological findings, as well as prognostic factors, did not differ significantly between adults and children. However, with the advent of novel variants, clinical signs and symptoms, complications, and outcomes changed in children significantly.

Keywords: COVID-19, SARS-CoV-2, Adults, Children

1. Context

Coronavirus 2019 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which appeared in Wuhan, Hubei, the People's Republic of China, at the end of September 2019. Novel coronavirus disease 2019 (COVID-19) poses a serious medical challenge, as well as significant societal and economic consequences (1, 2). The disease is a global epidemic that affects 632,161,336 cases and causes 6,580,216 deaths in 237 countries, regions, or territories until October 21, 2022 (3). Although COVID-19 can affect all age groups, children or adolescents appear less susceptible to the infection (4). In addition, reports of severe forms of COVID-19 are rare in the pediatric population (5). Although the pandemic is not over and a new variant of concern (Omicron) and its sublineages BA.1, BA.2, BA.2.12.1, BA.4, and BA.5 cause considerable concern at the end of 2021, COVID-19 cases and hospitalizations are on the downslope, and deaths also continue to decrease, which promises the final days of the coronavirus pandemic (6).

2. Objectives

Our systematic review and meta-analysis aimed to determine the most common comorbidities, clinical signs and symptoms, imaging features, treatments, outcomes, and complications in the early phase of the COVID-19 pan-

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demic. Our systematic review and meta-analysis compared adult and pediatric patients to identify the differences better.

3. Methods

3.1. Search Strategy

The study is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (7). Until June 4, 2020, systematic searches were conducted on the EMBASE, PubMed, Web of Science, Google Scholar, and Scopus databases to identify and retrieve studies on clinical symptoms, computed tomography (CT)-scans findings, and clinical outcomes in adults and children. The search strategy is shown in Supplementary File. In addition, we performed a manual search to find additional related studies.

3.2. Study Selection

The PICO format is considered and accordingly all children and adult cases with COVID-19 infection were included and compared for clinical symptoms, CT-scans findings, and clinical outcomes. Clinical signs and symptoms, CT-scan findings, supportive care, and patient outcomes were all investigated in observational and interventional studies on adults and children. The prevalence percentages and 95% confidence intervals were calculated by comparing different variables. Animal studies, as well as reviews and meta-analyses, were omitted. The meta-analysis rejected studies that did not provide sample sizes. Non-English articles have been removed as well.

3.3. Data Extraction and Quality Assessment

The full relevant data was investigated by M. V. and H. F. separately. A third researcher (A. A.) also investigated their accuracy. The following information is gathered using standardized forms: The first author's name, publication year, nation, population characteristics, study design, sample size, comorbidity percentage, children and adult support, and therapies, as well as signs and symptoms. The Newcastle-Ottawa rating form was used to assess the studies' quality. Selection (four items), comparability (one item), and outcome (three items) are all included in this assessment form. Three types of final scores were provided: Good (three or four stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome/exposure domain), fair (two stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome/exposure domain), and poor (no or one star in the outcome/exposure domain) (8). Table 1 represents the quality assessment results.

3.4. Statistical Analysis

MedCalc v.19.0.4 and STATA v.16.0 (Stata Corporation, College Station, TX) were employed to perform the statistical analyses. Comorbidities, signs and symptoms, supportive care, and treatments were measured using the prevalence percentage. I^2 statistics and chi-square tests were performed to evaluate the heterogeneity of the studies. The random effect model was used to pool the effect sizes due to inter-study heterogeneity (P-value chi-squared test < 0.1 and $I^2 > 50\%$). The following potential moderator variables were employed to conduct subgroup analysis: continent and type of article. No article has been removed from the study by quality assessment. The publication bias was not evaluated because the prevalence as a proportion is always a positive number, and if we saw asymmetry in the funnel design, it is not due to publication bias.

4. Results

4.1. Study Selection

Clinical, diagnostics, treatments, and outcomes in children and adult COVID-19 patients were compared during the first pandemic phase. After searching identified databases, 2022 studies were found, 1,655 were reviewed, and 367 duplicate studies were rejected. After the title and abstract were reviewed, one thousand two hundred thirty-five articles were discarded. By applying the inclusion and exclusion criteria, finally 215 articles left for review (Figure 1). It is worth mentioning that the cited publications were also examined for any relevant research. During the screening process, additional studies were excluded for some other reasons, including lack of numerical values for data analysis (n = 90), unreported confidence intervals (n = 63), and lack of sample size (n = 52). Figure 1 depicts the study selection procedure.

4.2. Results of Quality Assessment

Our findings revealed that 200 studies were of good quality, whereas 15 were of fair quality. No studies were excluded from our study after quality assessment. The results of the quality assessment are presented in Supplementary File.

4.3. Heterogeneity and Synthesis of Results

The I^2 index and the chi-square test results showed significant between-study heterogeneity, so results were analyzed by percentages based on the random effect model. The patient's information was divided into four categories, including signs and symptoms, CT-scan findings, comorbidities, and treatment/outcome. Table 2 summarizes detailed P-values, I^2, and confidence intervals. The forest plots

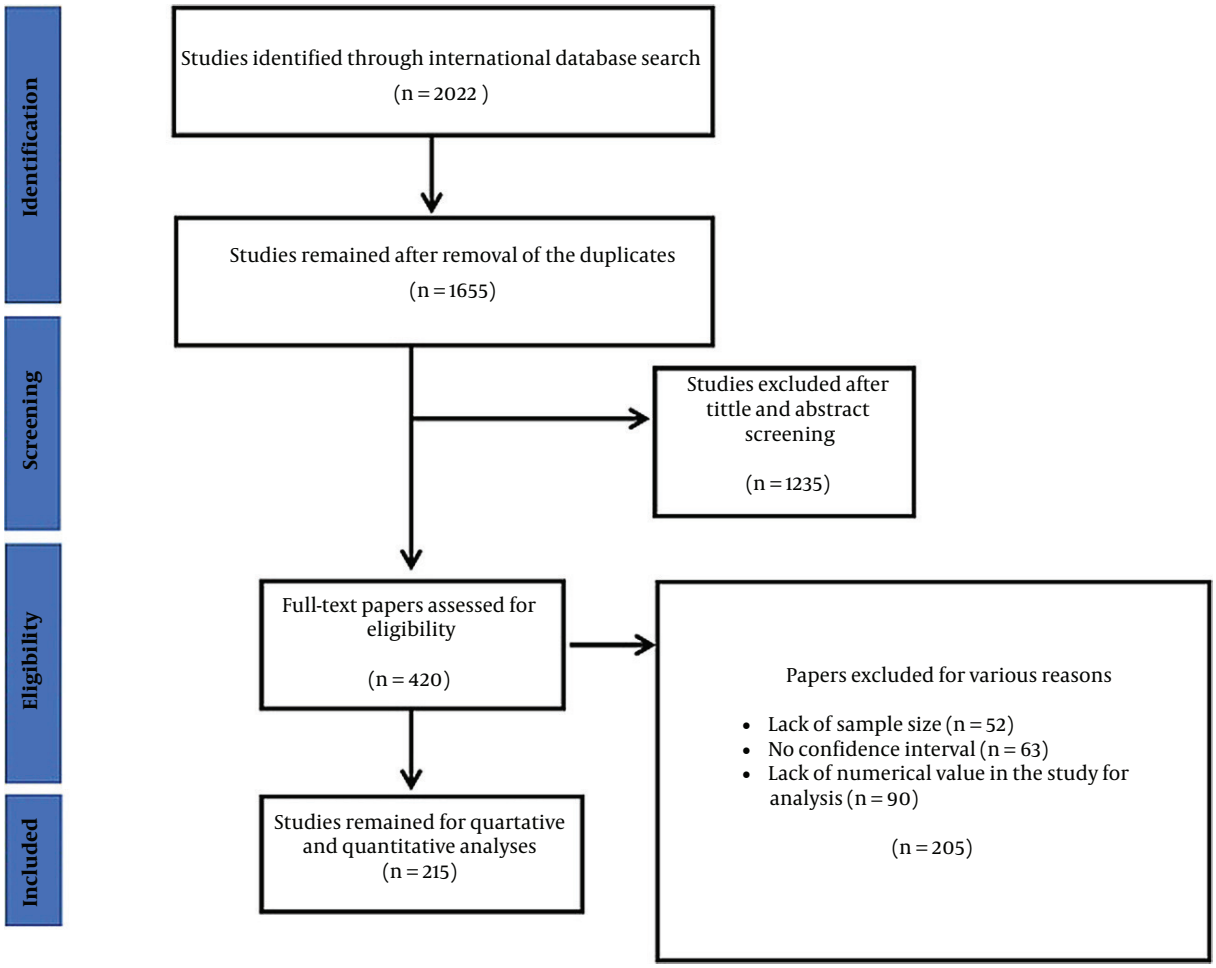

Figure 1. The study flowchart outlining article selection process

of the variables are provided in Supplementary File. Result of meta-analysis and heterogeneity of signs and symptoms, comorbidities, treatments, supportive cares, and CT-scan findings in adults and children with COVID-19 are summarized in Table 2. We also performed subgroup analysis for indicators that had high I^2. Its results can be seen in Table 3.

4.4. Signs and Symptoms

Fever (65.73 %), cough (53.78 %), expectoration (37.9%), gastrointestinal symptoms (37.01 %), headache (23.41 %), shortness of breath (21.65 %), and myalgia (20.79 %) were the most common symptoms reported in children, according to the pooled estimation analysis (Table 1). Fever (81.8 %) and cough (63.54 %) were the most commonly reported symptoms in adults, similar to children, whereas dyspnea (47.64 %), malaise (46.14 %), fatigue (34.39 %), and anorexia (30.97 %) were more frequently reported in adults.

Fever, anorexia, dizziness, dyspnea, fatigue, malaise, and sputum were markedly higher in adults (P-values = 0.001, 0.001, 0.001, 0.001, and 0.001, respectively), while the arthralgia, headache, and nasal congestion or rhinorrhea were significantly more common among children (P-values = 0.020, 0.019, and 0.029, respectively) (Figure 2). During the beginning phases of the pandemic, the most unusual symptoms were delirium, arthralgia, hemoptysis, and chest pain in adults, and anorexia, malaise, and fatigue in children.

4.5. Computed Tomography (CT)-Scan

Adult patients had a higher rate of abnormal CT-scan findings (including unilateral/bilateral pneumonia and multiple ground-glass opacities) (Figure 3). Children had a greater rate of normal imaging studies.

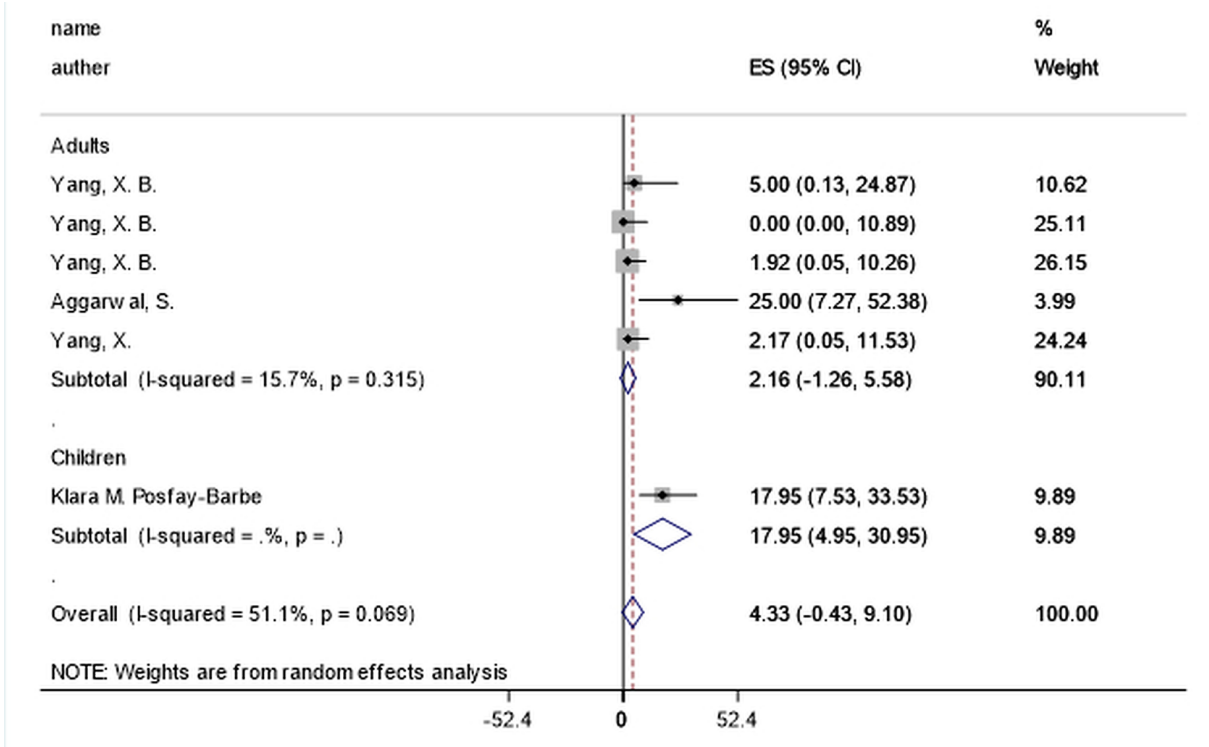

Figure 2. The frequency of arthralgia in children and adults with novel coronavirus disease 2019

4.6. Comorbidity

Adults had significantly higher rates of comorbidities such as cardiovascular disease (14.34% vs 2.25%; P-value < 0.001), chronic liver disease (5.61% vs 0.93%; P-value = 0.003), obesity (37.54% vs 8.54%; P-value < 0.001), and diabetes (4.48% vs 2.95%; P-value < 0.001), whereas children had significantly higher rates of asthma (17.94% vs 8.85%; P-value = 0.026) and malignancy (10.36% vs 5.47%; P-value = 0.045) (Figure 4). The most unusual underlying diseases in children were liver disease, cardiovascular disease, diabetes, and kidney disease, respectively. Autoimmune disease is not reported in children.

4.7. Treatment

During initial pandemic phase, hydroxychloroquine (66.21% vs 29.01%; P-value = 0.001) and antibiotics (77.86% vs 38.01%; P-value = 0.001) were used much more frequently in adult patients. Adults are also more likely to require mechanical ventilation (32.37% vs 7.54%; P-value = 0.002) (Figure 4). Extracorporeal membrane oxygenation (ECMO), mechanical ventilation, and remdesivir therapy were infrequently utilized to treat children with COVID-19.

5. Discussion

Despite the appearance of Omicron subvariants, we are nearing the ending of the pandemic, and the current phase appears to be a transition from previous sharp peaks to a less severe surge. So, to better understand SARS-CoV-2 features, it is time to classify pandemic phases based on the different virus strains. In this regard, the current study, which relooked at the COVID-19 pandemic in its initial stages, can be considered pioneering. Early in the pandemic, the clinical characteristics of pediatric patients with SARS-CoV-2 infection were not well recognized (9). The original SARS-CoV-2 infection primarily affects adults, whereas newer variations of concern (VOC) variably affect children. In critically ill adult patients, the beta variant did not vary from the alpha variant in terms of patient characteristics, management, or outcomes (10). In the United States, the first occurrence of multisystem inflammatory syndrome in children (MIS-C) started shortly after the beta variant peak (11). Furthermore, the alpha variant has been associated with an increase in COVID-19 cases and hospitalizations among young people (12). In children under the age of five, the incidence rate of SARS-CoV-2 infection with the Omicron variant was six to eight times that of the delta variant, but overall severe clinical consequences were less

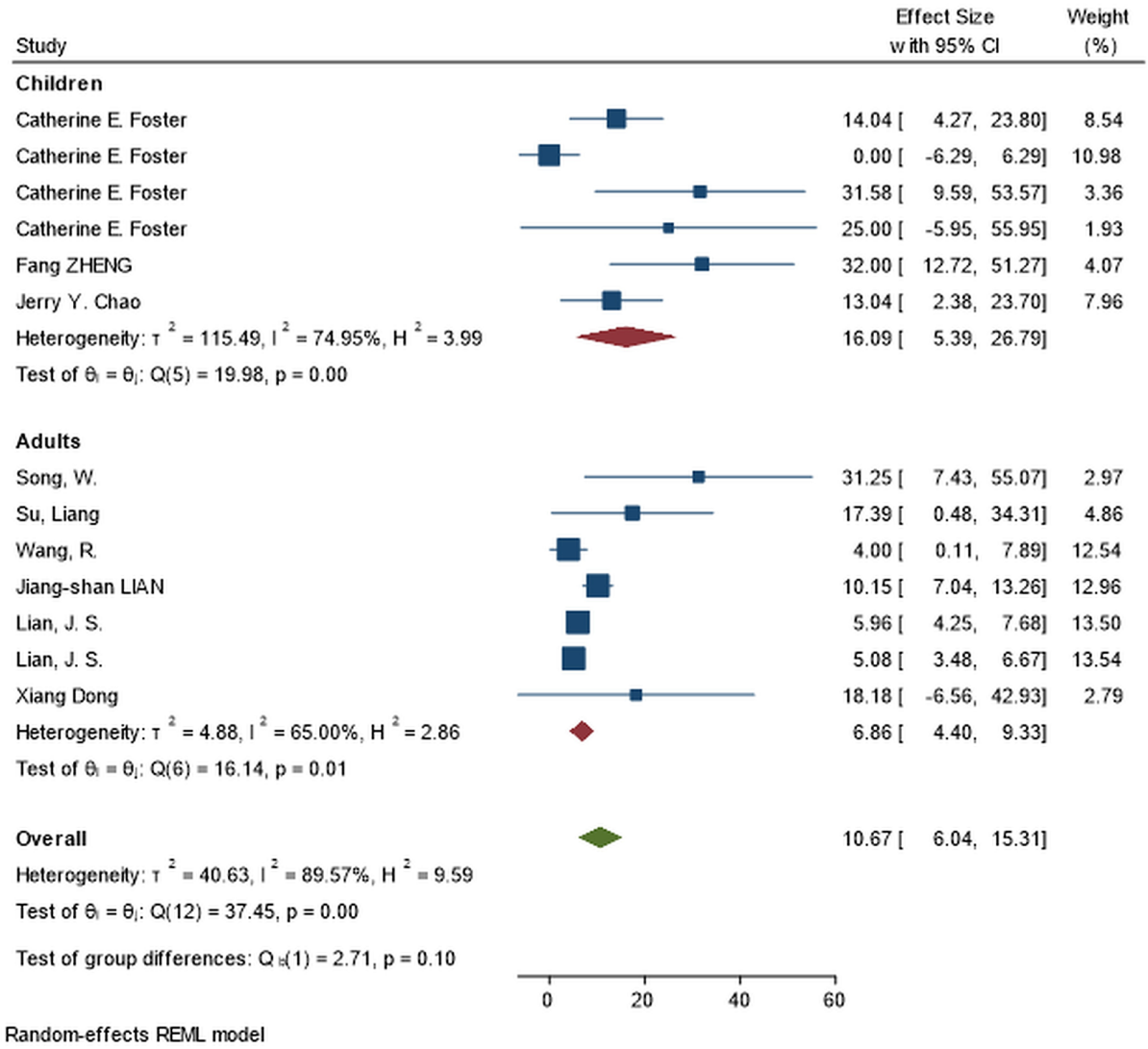

Figure 3. Abnormal computed tomography (CT)-scan findings in children and adults with novel coronavirus disease 2019

common than with the delta variant (13). However, there has been some concern about the risk of cardiac arrest associated with the Omicron variant's rapid-onset upper airway obstruction (14).

As earlier noted, new VOC-related clinical manifestations changed quickly, particularly in children infected with COVID-19; however, based on our findings in the early pandemic phase, fever and cough were the most common symptoms in both adults and children. Therefore, the patient's age is one of the main determinants of different disease phenotypes (15-17). The preponderance of arthralgia and headache in children was one of the key findings in our study, whereas other studies observed a higher proportion of headaches in adults (18, 19). Furthermore, nausea and vomiting, chest pain, gastrointestinal symptoms, and gastric pain are all insignificantly higher in children, according to our findings. Adult patients had considerably higher rates of fever, fatigue, and dyspnea. Moreover, no cases of chest tightness, confusion, or myalgia were found in children. Although there was no statistical difference in CT-scan findings, children had more normal imaging studies. Our findings are similar to that of another systematic review on children, which found that more than a third of COVID-19 patients had a normal chest CT scan (20). Small subpleural nodular ground-glass opacity is the most common CT-scan abnormality in children infected with

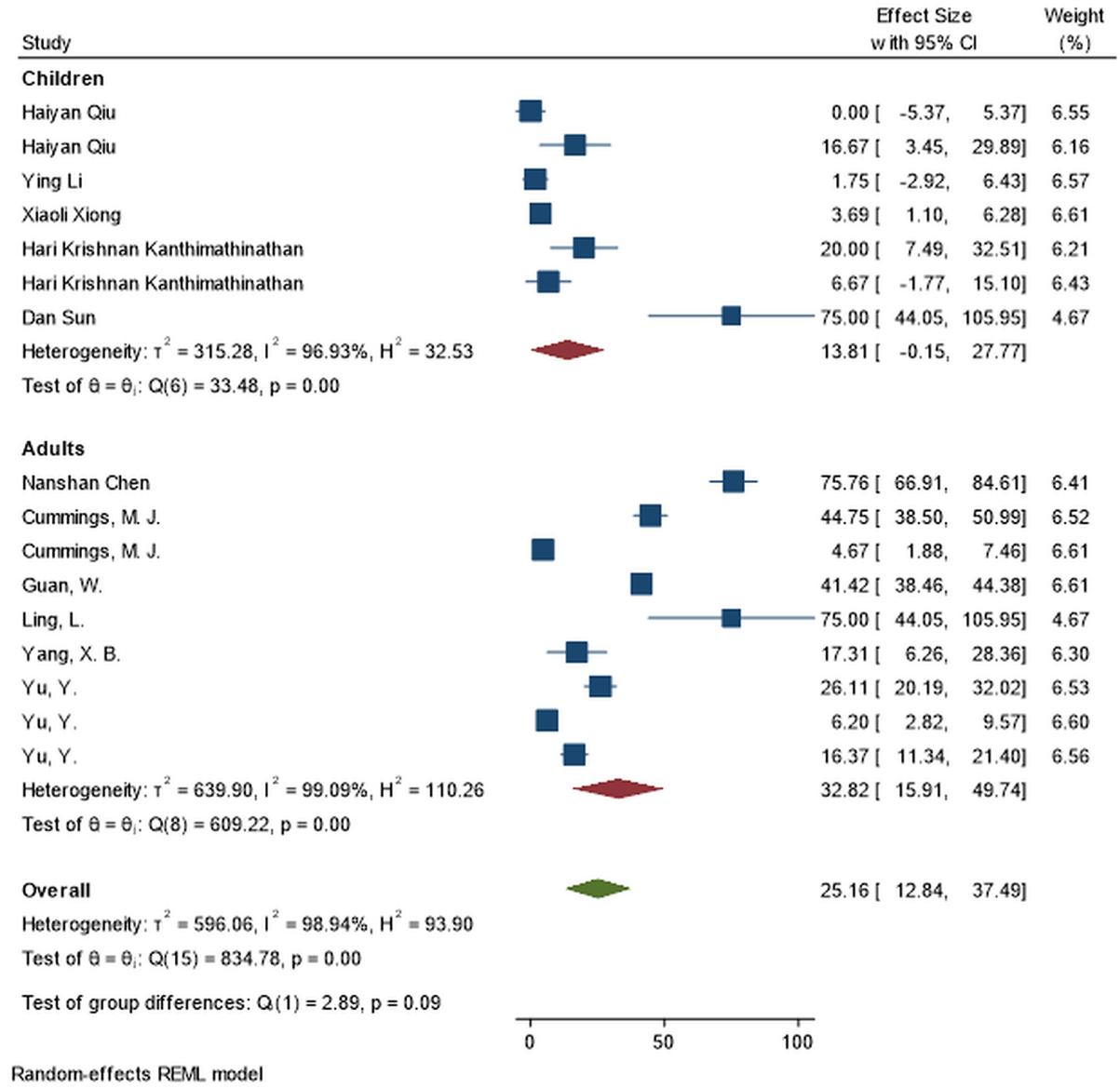

Figure 4. The frequency of oxygen therapy in children and adults with novel coronavirus disease 2019

the original strain (21). Patchy shadows, ground-glass opacities, consolidation, partial air bronchogram signs, nodules, and halo signs were the most commonly reported pulmonary manifestations in a systematic review conducted before the resurgence of the alpha, delta, gamma, and Omicron strains, while pleural effusion and paving pattern were rare (22). Besides, the delta variant showed fewer abnormalities than the original strain, mainly found in the lower lungs on both sides confined in a single lobe (unlike the initial strain, which was distributed over multiple lobes) (21). Unilateral/bilateral pneumonia, multiple mottling, and ground-glass opacities were detected in children and adults infected with the original SARS-CoV-2 strain without statistically significant differences, according to our data acquired during the initial pandemic phase.

Adult COVID-19 cases had significantly more comorbidities, such as cardiovascular disease, obesity, and diabetes; however, our findings show that the risk of malignancy is significantly higher in infected children. Following the emergence of the Omicron variant, the incidence

of pediatric cases has considerably increased. Even though children's symptoms are milder than adults', severe disease can still occur, especially in children with comorbidities (23).

Poor outcomes were connected to heart failure, acute respiratory distress syndrome (ARDS), and renal failure. Compared to non-severe cases, individuals with severe COVID-19 more often need mechanical ventilation and renal replacement therapy. Prehospital comorbidities are an important factor in children as well (24). according to evidence from Middle East respiratory syndrome (MERS) or the flu, patients who have been given corticosteroids have longer viral replication, need mechanical ventilation, and have a higher death rate (25-28). However, systemic corticosteroids may improve all-cause mortality in critically ill patients with COVID-19, according to the results of a meta-analysis of clinical studies (29). Antibiotics are prescribed to most COVID-19 patients, even though the estimated prevalence of bacterial co-infection is much lower (30). In patients with COVID-19, the usage of unnecessary antibiotics is likely to be considerable. In addition, we found that adults used much more antibiotics than children. Nonetheless, antibiotics were given to around 40% of the children studied.

This meta-analysis has some advantages. The most remarkable advantage of our study may be the investigation of COVID-19 characteristics in adult and pediatric patients during the early phases of the pandemic, which is carried entirely during the wild-type SARS-CoV-2 (Wuhan's strain) circulation in the first six months of the pandemic. Given that the beta, alpha, delta, and gamma strains were discovered in May, September, October, and November of 2020, respectively, the current study mainly analyzes clinical, and radiological findings and clinical outcomes of the disease during the COVID-19 initial phase induced by Wuhan strain. Second, we collected our data from more than 25,000 articles based on five different databases, increasing the comprehensiveness of this review. Third, we used almost all data about pediatric patients in our systematic review; however, articles about pediatric patients were published later. Fourth, our results were analyzed by two different software, and three experts checked quantitatively and qualitatively. Finally, the authors recommend that future studies focus on the various phases of the pandemic when performing similar studies. There are some limitations to our study. For example, the results could have been influenced by different research locations, methodology, and outcome measures. Another drawback was the inclusion of different types of research, which may inadvertently influence the conclusions based on the strengths and limitations of each study.

6. Conclusions

Although children were afflicted less than adults in the early stages of the pandemic and had lower mortality, clinical and radiological findings, as well as prognostic factors, did not differ significantly between adults and children. However, with the introduction of novel variants, clinical signs and symptoms, complications, and outcomes have all changed significantly in children.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Acknowledgments

The authors thank student research committee members for their general assistance.

Footnotes

Authors' Contribution: Conceived and designed the experiments: A. A.; performing the experiments: H. F., K. S., H. F., M. R. R., M. J. E. M.; data analysis: M. V. and Z. M.; interpretation of the study results: A. A. and M. V.; supervision: A. A.; writing the first draft of the manuscript: M. V. All authors read and approved the final manuscript.

Conflict of Interests: The authors declare that they have no competing interests.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

Funding/Support: The study was supported by a grant from Shiraz University of Medical Sciences (grant number: 20637). The funders had no role in the design, methods, participant recruitment, data collection, analysis, or manuscript preparation.

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Table 1. Newcastle-Ottawa Quality Assessment Form for 215 Cohort Studies (Some of These References Were Used Repeatedly for Different PICO Components; Full References Are Available in Supplementary File)

Author	Selection	Comparability	Outcome	Total	Quality
Abrishami, A.	3	1	2	6	Good
Aggarwal, S.	2	1	2	5	Fair
Jianghong A.	3	1	3	7	Good
Ashraf, M. A.	3	1	2	6	Good
Benelli, G.	3	1	2	6	Good
Bhatraju, P. K.	3	1	3	7	Good
Bo, X.	3	1	2	6	Good
Cao, D.	2	1	2	5	Fair
Chen, J.	3	1	2	6	Good
Chen, N.	3	1	2	6	Good
Chen, S.	2	1	2	5	Fair
Colombi, D.	3	1	3	7	Good
Du, Y.	3	1	2	6	Good
Eghbali, A.	2	1	2	5	Fair
Haseli, S.	3	1	2	6	Good
He, W.	3	1	2	6	Good
Hu, L.	3	1	2	6	Good
Huang, K. S.	3	1	2	6	Good
Huang, C.	2	1	2	5	Fair
Jiang, X.	2	1	2	5	Fair
Luo, X.	3	1	2	6	Good
Ng, M. Y.	3	1	2	6	Good
Su, L.	3	1	2	6	Good
Tian, S.	3	1	2	6	Good
Wang, R.	3	1	2	6	Good
Xu, H.	3	1	2	6	Good
Yang, N.	2	1	2	5	Fair
Jiang-shan, L.	3	1	2	6	Good
Zhang, J.	3	1	2	6	Good
Chen, Y.	3	1	2	6	Good
Wang, L.	3	1	3	7	Good
Palaiodimos, L.	3	1	3	7	Good
Zhou, Y.	3	1	3	7	Good
Sun, H.	3	1	3	7	Good
Belhadjer, Z.	3	1	2	6	Good
Cummings, M. J.	3	1	2	6	Good
Fadel, R.	3	1	2	6	Good
Guan, W.	3	1	3	7	Good
Li, L.	3	1	2	6	Good

Ling, L.	2	1	2	5	Fair
Liu, T.	2	1	2	5	Fair
Pan, C.	2	1	2	5	Fair
Yan, Y.	3	1	2	6	Good
Yang, X. B.	3	1	2	6	Good
Zhang, G.	3	1	2	6	Good
Zhu, L.	2	1	2	5	Fair
Spinello, A.	2	1	2	5	Fair
Mayla Gabriela Silva, B.	3	1	2	6	Good
Cao, B.	3	1	2	6	Good
Chao, J. Y.	3	1	2	6	Good
Mahévas, M.	3	1	2	6	Good
Buckner, F. S.	3	1	3	7	Good
Chen, T.	3	1	3	7	Good
Docherty, A. B.	3	1	2	6	Good
Du, R. H.	3	1	2	6	Good
Hur, K.	4	1	1	6	Good
Inciardi, R. M.	3	1	2	6	Good
Israelsen, S. B.	2	1	2	5	Fair
Itelman, E.	3	1	2	6	Good
Jeong, E. K.	3	1	2	6	Good
Nikpouraghdam, M.	3	2	2	7	Good
Pedersen, H. P.	3	1	2	6	Good
Petrilli, C. M.	3	1	2	6	Good
Petrilli, C. M.	3	1	2	6	Good
Ren, H.	3	1	2	6	Good
Ren, H.	3	1	2	6	Good
Wang, D.	3	1	2	6	Good
Wang, J.	4	1	1	6	Good
Wang, Z.	3	1	2	6	Good
Yang, X.	4	1	1	6	Good
Yang, Y.	3	1	2	6	Good
Yu, Y.	3	1	2	6	Good
Zhang, B.	3	1	2	6	Good
Zhao, X. Y.	3	1	3	7	Good
Yingxia, L.	3	1	3	7	Good
McMichael, T. M.	3	1	2	6	Good
Heshui, Sh.	3	1	2	6	Good
Shi, Q.	3	1	2	6	Good
The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team	3	1	2	6	Good
Tang, N.	4	1	1	6	Good
Wu, Ch.	3	1	2	6	Good
Zhou, F.	3	1	2	6	Good
Zhou, Sh.	3	1	3	7	Good

Wei, X.	3	1	2	6	Good
Wu, J.	3	1	2	6	Good
Wu, J.	3	1	2	6	Good
Pan, L.	3	1	2	6	Good
An, P.	2	1	2	5	Fair
Cai, J.	3	1	2	6	Good
Cao, W.	3	1	2	6	Good
Chen, J. Y.	3	1	2	6	Good
Chen, J.	3	1	3	7	Good
Chen, L.	3	1	2	6	Good
Chen, N.	3	1	2	6	Good
Chen, Zh.	3	1	2	6	Good
Cheng, J. L.	3	1	2	6	Good
Cheng, Z.	3	1	2	6	Good
Cui, P.	3	1	2	6	Good
Fu, B.	3	1	2	6	Good
Fu, H.	3	1	2	6	Good
Guan, W.	3	1	2	6	Good
Henry, B. M.	3	1	2	6	Good
Huang, C.	3	1	2	6	Good
Liu, J.	3	1	2	6	Good
Li, J.	3	1	2	6	Good
Li, J.	3	1	2	6	Good
Liu, X.	3	1	2	6	Good
Li, Y. Y.	3	1	2	6	Good
Liang, Y.	3	1	3	7	Good
Liu, K.	3	1	3	7	Good
Ru, Liu.	3	1	3	7	Good
Chen, S.	2	1	2	5	Fair
Colaneri, M.	3	1	3	7	Good
Xu, Y.	3	1	2	6	Good
Kang, K.	3	1	2	6	Good
Liang, T.	3	1	2	6	Good
Liao, J.	3	1	2	6	Good
Liu, J.	3	1	2	6	Good
Liu, K.	3	1	2	6	Good
Lo, I. L.	3	1	2	6	Good
Nie, R.	3	1	2	6	Good
Qiu, Ch.	3	1	3	7	Good
Qiu, H.	3	1	2	6	Good
Song, W.	3	1	2	6	Good
Song, C. Y.	3	1	2	6	Good
Sun, D.	3	1	2	6	Good
Wang, K.	3	1	2	6	Good

Yuan, M.	3	1	2	6	Good
Zhang, X.	3	1	2	6	Good
Zhou, F.	3	1	2	6	Good

Table 2. Result of Meta-Analysis and Heterogeneity of Signs and Symptoms, Comorbidities, Treatments, Supportive Cares, and Computed Tomography (CT)-Scan Findings in Adults and Children with Novel Coronavirus Disease 2019

Group and Subgroup	Population								P-Value
	Adults				Children				
	N	Effect Estimate (Confidence Interval)	I^2	P for Heterogeneity	N	Effect Estimate (Confidence Interval)	I^2	P for Heterogeneity	
Signs and Symptoms									
Fever	95	81.80 (79.06, 84.53)	95.6%	≤ 0.001	33	65.73 (57.30, 74.157)	98.1%	≤ 0.001	≤ 0.001 [a]
Abdominal pain	17	3.09 (1.39, 4.79)	94.01%	≤ 0.001	6	15.32 (-1.00, 31.64)	98.37%	≤ 0.001	0.144
Anorexia	16	30.97 (25.55, 36.39)	90.30%	≤ 0.001	1	4.05 (-1.22, 9.32)	NR	NR	≤ 0.001 [a]
Arthralgia	5	2.15 (-1.26, 5.57)	15.7%	0.315	1	17.94 (4.94, 30.94)	NR	NR	0.020 [a]
Bloating	8	1.13 (0.66, 1.60)	0.00%	0.913	0	NR	NR	NR	NR
Chest pain	15	1.17 (0.39, 1.96)	10.69%	0.199	4	5.27 (-0.44, 10.99)	83.33%	0.004	0.164
Chest tightness	19	24.57 (18.10, 31.04)	95.79%	≤ 0.001	0	NR	NR	NR	NR
Chills	7	13.69 (0.24, 27.14)	99.46%	≤ 0.001	1	1.03 (-0.74, 2.82)	NR	NR	0.067
Cough	67	63.54 (58.48, 68.59)	96.93%	≤ 0.001	24	53.78 (45.14, 62.42)	94.64%	≤ 0.001	0.056
Delirium	2	2.23 (-3.33, 7.81)	0.00%	0.360	0	NR	NR	NR	NR
Diarrhea	59	15.80 (12.57, 19.03)	96.43%	≤ 0.001	17	11.43 (5.25, 17.61)	94.26%	≤ 0.001	0.220
Dizziness	19	3.87 (2.77, 4.97)	57.33%	0.003	2	0.93 (-0.50, 2.37)	0.00%	0.473	0.001 [a]
Dry cough	22	62.84 (55.58, 70.10)	95.31%	≤ 0.001	3	42.60 (13.04, 72.16)	71.61%	0.018	0.193
Dyspnea	47	47.64 (41.20, 54.08)	96.32%	≤ 0.001	8	8.81 (0.39, 17.22)	94.24%	≤ 0.001	≤ 0.001 [a]
Expectoration	20	23.17 (-22.75, 69.10)	96.63%	≤ 0.001	2	37.90 (30.50, 45.30)	86.07%	0.007	0.535
Fatigue	58	34.39 (30.02, 38.76)	95.4%	≤ 0.001	5	2.63 (0.01, 5.26)	52.3%	0.078	≤ 0.001 [a]
Gastrointestinal symptoms	9	23.86 (12.34, 35.39)	98.18%	≤ 0.001	9	37.01 (13.69, 60.32)	98.68%	≤ 0.001	0.322
Headache	67	9.22 (7.52, 10.92)	91.42%	≤ 0.001	12	23.41 (11.68, 35.14)	96.27%	≤ 0.001	0.019 [a]
Hemoptysis	10	1.79 (0.75, 2.82)	30.21%	0.012	2	11.71 (-6.62, 30.04)	87.05%	0.005	0.290
Malaise	14	46.14 (37.65, 54.62)	83.36%	≤ 0.001	2	2.67 (0.28, 5.05)	25.11%	0.248	≤ 0.001 [a]
Muscle ache	17	10.18 (7.85, 12.51)	80.43%	≤ 0.001	0	NR	NR	NR	NR
Myalgia	48	14.68 (1.36, 28.01)	93.41%	≤ 0.001	5	20.79 (17.13, 24.45)	97.23%	≤ 0.001	0.386
Nasal congestion or rhinorrhea	32	8.05 (5.96, 10.14)	88.12%	≤ 0.001	9	19.67 (9.47, 29.88)	87.92%	≤ 0.001	0.029 [a]
Nausea and vomiting	63	6.20 (4.93, 7.46)	88.40%	≤ 0.001	12	12.28 (5.49, 19.07)	93.53%	≤ 0.001	0.084
Sore throat	34	10.18 (8.28, 12.09)	81.21%	≤ 0.001	14	18.66 (9.40, 27.91)	96.76%	≤ 0.001	0.079
Sputum	31	26.86 (20.12, 33.61)	96.65%	≤ 0.001	2	9.83 (6.44, 13.22)	0.00%	0.704	≤ 0.001 [a]
Shortness of breath	21	25.07 (13.47, 36.67)	99.49%	≤ 0.001	11	21.65 (14.81, 28.49)	86.23%	≤ 0.001	0.619
Computed Tomography (CT)-Scan									
Bilateral pneumonia	43	66.70 (58.62, 74.78)	99.35%	≤ 0.001	3	61.73 (45.62, 77.84)	30.84%	0.245	0.589
Multiple mottling and ground-glass opacity	6	40.28 (15.79, 64.76)	98.74%	≤ 0.001	1	52.77 (35.72, 69.83)	NR	NR	0.412
Unilateral pneumonia	14	17.85 (10.83, 24.87)	97.15%	≤ 0.001	4	15.67 (7.82, 23.52)	3.59%	0.566	0.685
Normal	7	6.86 (4.39, 9.33)	65.00%	0.013	6	16.09 (5.39, 26.78)	74.95%	0.001	0.100
Comorbidity									
Asthma	13	8.85 (5.58, 12.12)	97.57%	≤ 0.001	8	15.22 (10.66, 19.79)	17.94%	0.486	0.026 [a]
Autoimmune disease	7	1.31 (0.53, 2.10)	0.00%	0.285	0	NR	NR	NR	NR
Cancer	14	5.47 (2.34, 8.60)	99.70%	≤ 0.001	1	10.36 (6.74, 13.98)	NR	NR	0.045 [a]
Cardiovascular disease	54	14.34 (11.24, 17.44)	99.64%	≤ 0.001	20	2.25 (1.14, 3.37)	89.57%	≤ 0.001	≤ 0.001 [a]
COPD	71	5.59 (4.35, 6.82)	99.43%	≤ 0.001	2	4.92 (3.13, 6.72)	0.00%	0.822	0.551
Diabetes	74	4.48 (14.94, 19.84)	99.69%	≤ 0.001	7	2.95 (1.41, 4.48)	0.00 %	0.893	≤ 0.001 [a]
Chronic kidney disease	36	7.46 (4.86, 10.06)	99.18%	≤ 0.001	6	7.27 (-0.28, 14.82)	98.35%	≤ 0.001	0.962
Chronic liver disease	31	5.61 (2.75, 8.46)	99.25%	≤ 0.001	1	0.93 (-0.32, 2.19)	NR	NR	0.003 [a]
Obesity	2	37.54 (23.34, 51.74)	29.02%	0.235	11	8.54 (2.84, 14.23)	92.63%	≤ 0.001	≤ 0.001 [a]
Treatment									
Antibiotic	13	77.86 (66.72, 89.01)	98.55%	≤ 0.001	8	38.01 (23.51, 52.50)	87.27%	≤ 0.001	≤ 0.001 [a]
ECMO	11	2.74 (0.92, 4.57)	77.74%	≤ 0.001	2	4.46 (1.57, 7.35)	0.00%	0.817	0.325

Mechanical ventilation	15	32.37 (18.39, 46.35)	99.31%	≤ 0.001	6	7.52 (-0.37, 15.41)	97.38%	≤ 0.001	0.002 [a]
Oxygen therapy	9	13.81 (-0.14, 27.76)	99.09%	≤ 0.001	7	32.82 (15.90, 49.74)	96.93%	≤ 0.001	0.089
Hydroxychloroquine	9	66.21 (57.37, 75.06)	92.25%	≤ 0.001	6	29.01 (13.30, 44.72)	79.82%	0.001	≤ 0.001 [a]
Remdesivir	7	5.41 (1.16, 9.67)	93.88%	≤ 0.001	4	16.86 (5.91, 27.81)	63.62%	0.042	0.056

Abbreviations: NR, not reported; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation
[a] P-value ≤ 0.05

Table 3. Result of Subgroup of Signs and Symptoms, Comorbidities, Treatments, Supportive Cares, and Computed Tomography (CT)-Scan Findings in Adults and Children with Novel Coronavirus Disease 2019

Type of Patients	Subgroup			Effect Estimate (Confidence Interval)	I^2 %
Adults	Asthma	Type of article	Case Series	8.30 (-10.83,27.43)	Not reported
			Cohort	9.24 (5.32, 13.15)	98.62
		Continent	Asia	0.63 (-0.33, 1.60)	32.62
			Europe	13.98 (11.71, 16.24)	31.86
			USA	11.63 (8.03, 15.22)	80.30
Adults	Cancer	Type of article	Prospective cohort	9.17 (5.01, 13.34)	51.55
			Retrospective cohort	4.98 (1.27, 8.69)	99.79
		Continent	Asia	0.60 (0.27, 0.94)	62.66
			Europe	11.27 (1.85, 20.69)	71.86
			USA	11.17 (9.73, 12.61)	12.65
Adults	Cardiovascular disease	Type of article	Prospective cohort	14.59 (9.29, 19.89)	99.26
			Retrospective cohort	14.36 (10.61, 18.117)	99.39
		Continent	America	20.30 (13.92, 26.68)	94.99
			Asia	9.06 (6.66, 11.47)	99.25
			Europe	26.91 (15.22, 38.60)	95.60
Children	Cardiovascular disease	Type of article	Retrospective	2.57 (0.88, 4.26)	95.83
			Prospective cohort	3.11 (1.27, 4.96)	37.46
		Continent	Asia	3.21 (0.51, 5.92)	77.38
			Europe	3.85 (0.31, 7.38)	99.12
			USA	2.62 (1.33, 3.91)	5.71
Adults	Chronic obstructive pulmonary disease	Type of article	Retrospective	4.95 (3.73, 6.18)	97.93
			Prospective cohort	8.30 (5.18, 11.41)	96.69
		Continent	Asia	3.56 (2.72, 4.40)	95.75
			Europe	11.71 (7.55, 15.87)	88.78
			USA	13.51 (8.22, 18.80)	86.50
Adults	Diabetes	Type of article	Retrospective	17.52 (14.70, 20.35)	95.42
			Prospective cohort	18.40 (12.93, 23.87)	99.78
		Continent	America	35.94 (32.58, 39.29)	54.53
			Asia	13.37 (11.33, 15.41)	95.88
			Europe	17.56 (12.99, 22.13)	98.62
Adults	Chronic kidney disease	Continent	America	17.17 (11.03, 23.32)	94.42
			Asia	2.89 (1.77, 4.02)	92.68
			Europe	11.59 (3.65, 19.54)	94.87
Children	Chronic kidney disease	Continent	Asia	1.32 (0.15, 2.50)	50.86
			Europe	17.41 (3.92, 30.90)	68.90
Adults	Chronic liver disease	Type of article	Retrospective	6.27 (2.86, 9.68)	72.17
			Prospective cohort	2.98 (1.33, 4.64)	98.76
		Continent	America	1.76 (0.91, 2.61)	0.00

			Asia	5.94 (2.48, 9.40)	98.72
			Europe	3.99 (3.70, 4.29)	NR
Children	Obesity	Continent	America	6.98 (1.07, 12.89)	93.72
			Europe	19.12 (7.50, 30.73)	0.00
Adults	Bilateral pneumonia	Continent	Asia	65.70 (57.83, 73.57)	99.19
			Europe	94.00 (90.86, 97.13)	0.0
Adults	Fever	Type of article	Retrospective	81.88 (78.80, 84.97)	94.65
			Prospective cohort	92.15 (84.87, 99.43)	93.29
			Observational study	68.15 (57.47, 78.84)	98.19
		Continent	America	79.76 (73.20, 86.32)	91.46
			Asia	82.12 (78.85, 85.38)	96.47
			Europe	39.39 (29.39, 49.39)	Not reported
Children	Fever	Continent	America	67.93 (48.19, 87.67)	96.37
			Asia	59.27 (49.30, 69.24)	96.44
			Europe	81.46 (70.46, 92.46)	88.85
Adults	Abdominal pain	Type of article	Retrospective	1.47 (0.88, 2.06)	41.38
			Cross-sectional	9.65 (-5.09, 24.41)	97.01
Children	Abdominal pain	Type of article	Retrospective	23.00 (0.72, 45.27)	93.54
			Cross-sectional	15.32 (-1.00, 31.64)	0.00
		Continent	Asia	1.77 (0.22, 3.32)	0.00
			Europe	41.05 (16.31, 65.78)	83.56
Adults	Cough	Type of article	Case series	46.46 (-9.21, 102.14)	89.67
			Cross-sectional	58.89 (42.80, 74.98)	97.81
			Prospective	67.97 (64.23, 71.70)	0.00
			Retrospective	67.82 (63.66, 71.98)	92.91
		Continent	America	73.92 (70.42, 77.43)	55.21
			Asia	64.96 (60.34, 69.59)	94.74
Children	Cough	Type of article	Case series	66.17 (46.33, 86.00)	53.62
			Retrospective	48.93 (39.19, 58.68)	95.27
			Cross-sectional	42.88 (7.31, 78.45)	97.52
		Continent	America	41.44 (22.8, 60.03)	94.14
			Asia	50.82 (38.60, 63.04)	96.09
			Europe	59.92 (45.51, 74.34)	84.84
Adults	Diarrhea	Type of article	Case series	9.46 (-3.38, 22.31)	0.00
			Cross-sectional	17.57 (3.33, 31.82)	97.21
			Retrospective	17.05 (13.40, 20.71)	96.03
			Prospective cohort	6.78 (2.14, 11.42)	68.51
		Continent	America	27.01 (20.80, 33.21)	88.68
			Asia	12.48 (9.24, 15.72)	96.02
Children	Diarrhea	Type of article	Retrospective	13.09 (5.51, 20.67)	93.45
			Observational study	4.03 (-0.38, 8.45)	52.26
		Continent	America	8.16 (1.27, 15.04)	55.76
			Asia	3.80 (1.61, 5.99)	35.02

			Europe	27.12 (3.55, 50.68)	93.50
Adults	Dry cough	Type of article	Retrospective	61.71 (53.94, 69.482)	95.71
			Prospective cohort	81.56 (75.63, 87.49)	Not reported
			Observational study	62.31 (33.64, 90.98)	76.84
Adults	Dyspnea	Type of article	Retrospective	48.26 (41.36, 55.15)	95.37
			Prospective cohort	57.28 (39.74, 74.83)	86.56
			Observational study	34.34 (8.33, 60.34)	98.98
		Continent	America	67.41 (63.18, 71.65)	37.63
			Asia	41.42 (34.31, 48.54)	96.44
Children	Dyspnea	Type of article	Retrospective	9.86 (0.59, 19.12)	Not reported
			Case series	0.50 (-14.92, 15.92)	95.36
		Continent	Asia	1.40 (-0.08, 2.90)	3.69
			Europe	22.48 (-3.70, 48.68)	95.33
Adults	Fatigue	Type of article	Retrospective	33.67 (28.23, 39.10)	96.36
			Prospective cohort	40.95 (34.79, 47.12)	0.00
			Observational study	32.92 (19.34, 46.51)	96.05
		Continent	America	54.25 (49.46, 59.05)	8.82
			Asia	33.19 (28.34, 38.04)	96.04
Children	Gastrointestinal symptoms	Continent	America	44.74 (-39.68, 129.16)	98.82
			Asia	19.04 (12.26, 25.83)	38.84
			Europe	49.00 (10.87, 87.12)	97.53
Adults	Headache	Type of article	Observational study	17.37 (11.57, 23.16)	84.82
			Retrospective	8.52 (6.78, 10.25)	90.30
			Prospective cohort	5.42 (3.02, 7.81)	32.03
		Continent	America	15.14 (9.89, 20.38)	89.03
			Asia	8.04 (6.41, 9.68)	89.73
Children	Headache	Type of article	Retrospective	26.52 (13.28, 39.76)	95.04
			Observational study	4.18 (1.49, 6.88)	0.00
		Continent	America	29.53 (7.80, 51.27)	91.68
			Asia	11.57 (0.11, 23.04)	94.39
			Europe	40.60 (10.69, 70.52)	88.66
Adults	Malaise	Type of article	Retrospective	47.84 (39.56, 56.11)	82.25
			Case series	16.66 (-6.49, 39.83)	Not reported
		Continent	America	58.08 (53.99, 62.17)	0.00
			Asia	29.30 (20.56, 38.03)	50.80
Adults	Myalgia	Type of article	Observational study	23.90 (13.85, 33.94)	76.00
			Retrospective	18.98 (14.84, 23.12)	94.18
			Prospective cohort	30.28 (21.73, 38.83)	80.61
		Continent	America	27.95 (25.49, 30.40)	0.00
			Asia	18.50 (14.13, 22.87)	94.63
Adults	Nasal congestion or rhinorrhea	Type of article	Observational study	5.41 (2.66, 8.16)	68.66
			Retrospective	8.87 (6.06, 11.68)	90.43
			Prospective cohort	7.39 (4.99, 9.79)	0.00

		Continent	America	14.76 (10.50, 19.03)	71.12
			Asia	4.86 (3.77, 5.96)	50.50
Adults	Nausea and vomiting	Continent	America	17.25 (15.19, 19.32)	0.00
			Asia	4.06 (3.46, 4.65)	45.65
Children	Nausea and vomiting	Continent	America	10.25 (2.11, 18.40)	65.34
			Asia	7.81 (-0.05, 15.68)	87.15
			Europe	16.40 (-1.17, 33.98)	94.03
Adults	Sore throat	Type of article	Observational study	17.53 (13.61, 21.45)	51.63
			Retrospective	9.27 (7.38, 11.17)	73.29
			Prospective cohort	5.83 (3.66, 8.00)	0.00
		Continent	America	7.89 (6.27, 9.51)	8.07
			Asia	11.07 (8.20, 13.93)	89.32
Children	Sore throat	Type of article	Retrospective	19.07 (8.99, 29.16)	94.75
			Observational study	18.63 (15.90, 53.17)	80.69
		Continent	America	26.66 (10.50, 42.81)	86.56
			Asia	3.46 (0.69, 6.22)	47.74
			Europe	22.22 (2.75, 47.20)	87.06
Adults	Sputum	Type of article	Retrospective	27.24 (19.29, 35.19)	96.91
			Prospective cohort	29.53 (23.76, 35.30)	0.00
			Descriptive study	18.40 (11.86, 48.67)	98.35
		Continent	America	22.76 (19.63, 25.88)	0.00
			Asia	28.27 (19.32, 37.22)	97.78
Adults	Shortness of breath	Type of article	Observational study	11.84 (5.51, 18.17)	87.83
			Retrospective	24.33 (8.76, 39.89)	99.56
			Prospective cohort	55.44 (19.28, 91.60)	99.51
		Continent	America	72.34 (69.50, 75.19)	0.00
			Asia	16.99 (7.93, 26.06)	99.10
Children	Shortness of breath	Type of article	Retrospective	31.24 (17.14, 45.34)	81.76
			Cohort	16.07 (11.45, 20.69)	20.16
		Continent	America	22.56 (13.13, 31.99)	86.28
			Europe	33.33 (22.73, 43.93)	0.00