

## ORIGINAL PAPER

## Infectious Diseases

# Effect of age of COVID-19 inpatient on the severity of the disease: A meta-analysis

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**Abstract**

**Background:** Clinical symptoms of adults and paediatric inpatients with COVID-19 disease are conflicting. This meta-analysis was conducted to assess the effect of age of COVID-19 inpatient on the severity of the disease.

**Methods:** A systematic literature search up to January 2021 was performed and 5 studies included 910 inpatients with COVID-19 disease at the baseline of the study; 773 of them were adult inpatients, and 137 of them were paediatric inpatients. They reported a comparison between adults and children with COVID-19 in the level of symptomatic severity, clinical features, computed tomography (CT) results and laboratory results. Odds ratio (OR) with 95% confidence intervals (CIs) were calculated assessing the effect of age of COVID-19 inpatient on the severity of the disease using the dichotomous method with a random or fixed-effect model.

**Results:** Adults with COVID-19 disease had significantly lower number of mild cases (OR, 0.18; 95% CI, 0.04-0.77,  $P = .02$ ); higher number severe cases (OR, 4.90; 95% CI, 2.03-11.83,  $P < .001$ ); higher number of cases with fever (OR, 4.14; 95% CI, 2.31-7.43,  $P < .001$ ); and higher number of cases with CT positive COVID-19 disease (OR, 2.04; 95% CI, 1.17-3.55,  $P = .001$ ) compared with children. However, no significant difference was found between adults and children in number of cases with shortness of breath (OR, 1.44; 95% CI, 0.41-5.04,  $P = .57$ ); dry cough (OR, 1.77; 95% CI, 0.64-4.93,  $P = .27$ ); leukopenia (OR, 0.89; 95% CI, 0.47-1.66,  $P = .71$ ); lymphopenia (OR, 0.96; 95% CI, 0.49-1.88,  $P = .91$ ); high platelets (OR, 0.41; 95% CI, 0.17-1.02,  $P = .05$ ); and high D-dimer (OR, 0.82; 95% CI, 0.43-1.56,  $P = .54$ ).

**Conclusions:** Adults with COVID-19 disease have a much higher level of symptomatic severity, fever and CT-positive COVID-19 disease than children. However, as shown in our results, the laboratory data were similar in both groups.

## 1 | INTRODUCTION

A new SARS-CoV-2 infection appeared in December 2019 in Wuhan and spread rapidly all over the world.<sup>1</sup> The World Health Organization has called it COVID-19 disease and confirmed it as a pandemic.<sup>2</sup> Children are more prone to pneumonia infection than

adults, which may cause deadly outcomes.<sup>3,4</sup> During the current COVID-19 pandemic, it was reported that infants are less susceptible to such a violent virus.<sup>5,6</sup> So, the number of paediatric inpatients with COVID-19 disease was much lower than the number of adult inpatients.<sup>7,8</sup> However, there is no proper explanation for this phenomenon. Numerous studies and meta-analyses reported

Shaoqing Chai and Yan Li both are the first authors, they contributed equally.

the demographics, clinical characters, laboratory indicators and computed tomography imaging characteristics of the adult with COVID-19 disease.<sup>9,10</sup> But because of the inadequate number of children with COVID-19 disease, a few meta-analysis studies concentrated on children with COVID-19 disease.<sup>11-13</sup> Though, they did not compare their children's results to adults because of the lack of comparative studies. Further compassion between adults and children on the clinical features of COVID-19 disease is urgently needed to help in the clinical diagnosis and management of the subjects, of different ages, infected with SARS-CoV-2. This meta-analysis aimed to assess the effect of age of COVID-19 inpatient on the severity of the disease.

## 1.1 | Methods

The study performed here followed the meta-analysis of studies in the epidemiology statement,<sup>14</sup> which was conducted following an established protocol.

## 1.2 | Study selection

Studies included were observation studies assessing the effect of age of COVID-19 inpatient on the severity of the disease. Only human studies in any language were considered. Inclusion was not limited by study size. Publications excluded were review articles and commentary and studies that did not deliver a measure of an association. Figure 1 shows a schematic diagram of the study procedure. The articles were integrated into the meta-analysis when the following inclusion criteria were met:

1. The study was observational.
2. The target population was subjects with COVID-19 disease.
3. The intervention programme was based on the effect of age of COVID-19 inpatient on the severity of the disease.
4. The study included a comparison between adults and children.

## 1.3 | Identification

A protocol of search strategies was prepared according to the PICOS principle,<sup>15</sup> and we defined it as follow: P (population): subjects with COVID-19 disease; I (intervention/exposure): effect of age of COVID-19 inpatient on the severity of the disease; C (comparison): adults compared with children; O (outcome): level of symptomatic severity, clinical features, CT results and laboratory results; and S (study design): no restriction.<sup>16</sup>

First, we conducted a systematic search of OVID, Embase, Cochrane Library, PubMed, Google Scholar databases till January 2021, using a blend of keywords and similar words for COVID-19,

### What's known

- Clinical symptoms of adults and paediatric inpatients with COVID-19 disease are conflicting.
- This meta-analysis was conducted to assess the effect of age of COVID-19 inpatient on the severity of the disease.

### What' new

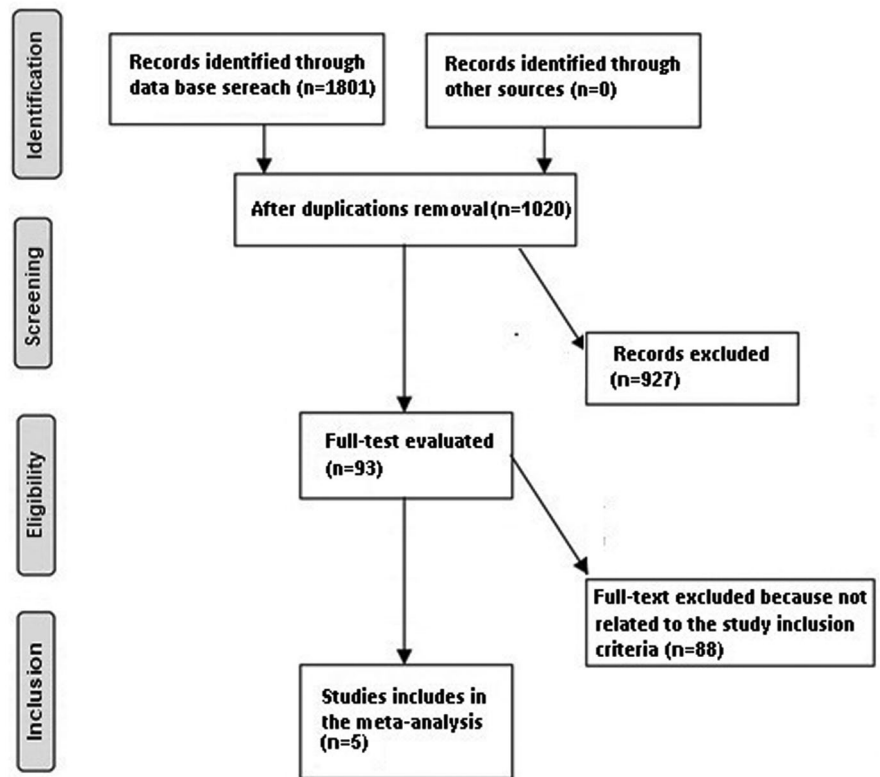
- Adults with COVID-19 disease have a much higher level of symptomatic severity, fever and CT-positive COVID-19 disease than children.
- However, as shown in our results, the laboratory data were similar in both groups.

SARS-CoV-2, adults, children, level of symptomatic severity, clinical features, computerised tomography and laboratory results, as shown in Table 1. All identified studies were pooled in an EndNote file, duplicates were omitted and the title and abstracts were reviewed to exclude studies that did not report an association of effect of age of COVID-19 inpatient on the severity of the disease.

## 1.4 | Screening

Data were abridged on the following bases; study-related and subject-related characteristics onto a standardised form; last name of the primary author, period of study, year of publication, country, region of the studies and study design; population type, the total number of subjects, demographic data, clinical and treatment characteristics, categories, qualitative and quantitative method of evaluation, information source, outcome evaluation and statistical analysis.<sup>17</sup> When there were different data from one study based on the assessment of the effect of age of COVID-19 inpatient on the severity of the disease, we extracted them independently. The risk of bias in these studies; individual studies were evaluated using the two authors independently assessed the methodological quality of the selected studies. The "risk of bias tool" from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 was used to assess methodological quality.<sup>18</sup> In terms of the assessment criteria, each study was rated and assigned to one of the following three risks of bias: low: if all quality criteria were met, the study was considered to have a low risk of bias; unclear: if one or more of the quality criteria were partially met or unclear, the study was considered to have a moderate risk of bias; or high: if one or more of the criteria were not met, or not included, the study was considered to have a high risk of bias. Any inconsistencies were addressed by a re-evaluation of the original article.

**FIGURE 1** Schematic diagram of the study procedure



**TABLE 1** Search strategy for each database

Database	Search strategy
Pubmed	#1 "COVID-19"[MeSH Terms] OR "SARS-CoV-2"[All Fields] OR "adults"[All Fields] OR "children"[All Fields] #2 "clinical features"[MeSH Terms] OR "COVID-19"[All Fields] OR "computerized tomography"[All Fields] OR "laboratory results"[All Fields] #3 #1 AND #2
Embase	'COVID-19'/exp OR 'SARS-CoV-2'/exp OR 'adults'/exp OR children #2 'clinical features'/exp OR 'ICBG'/exp OR 'computerized tomography'/exp OR laboratory results #3 #1 AND #2
Cochrane library	(COVID-19):ti,ab,kw (SARS-CoV-2):ti,ab,kw OR (adults):ti,ab,kw (Word variations have been searched) #2 (children):ti,ab,kw OR (clinical features):ti,ab,kw OR (computerized tomography):ti,ab,kw OR (laboratory results):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

### 1.5 | Eligibility

The main outcome focused on the assessment of the effect of age of COVID-19 inpatient on the severity of the disease, we extracted them independently to form a summary.

### 1.6 | Inclusion

Sensitivity analyses were limited only to studies reporting the level of symptomatic severity, clinical features, computerised tomography results and laboratory results of children with COVID-19 disease

compared with adults; we extracted them independently. For sub-category and sensitivity analysis, we used comparisons between adults and children.

### 1.7 | Statistical analysis

The dichotomous method with a random-effect model or fixed-effect was used to calculate the odds ratio (OR) and 95% CI. The  $I^2$  index was calculated; the  $I^2$  index is between 0% and 100%. Values of about 0%, 25%, 50% and 75% indicate no, low, moderate and high heterogeneity, respectively.<sup>19</sup> When  $I^2$  was higher than 50%,

we chose the random effect model; when it was lower than 50%, we used the fixed-effect model. A subcategory analysis was completed by stratifying the original evaluation per outcome categories as described before. In this analysis, a *P*-value for differences between subcategories of  $<.05$  was considered statistically significant. Publication bias was evaluated quantitatively using the Egger regression test (publication bias considered present if  $P \geq .05$ ), and qualitatively, by visual examination of funnel plots of the logarithm of ORs versus their standard errors (SE).<sup>15</sup> All *P*-values were two tailed. All calculations and graphs were performed using reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

## 2 | RESULTS

A total of 1801 unique studies were identified. Most of them were either showing data for adults only or children only. That made our studies much harder. Only 5 studies were found, conducted in 2020

**TABLE 2** Characteristics of the selected studies for the meta-analysis

Study	Country	Total	Adults	Children
Pierce <sup>18</sup>	USA	125	60	65
Chen <sup>19</sup>	China	61	47	14
Du <sup>20</sup>	China	67	53	14
Han <sup>21</sup>	China	32	25	7
Luo <sup>22</sup>	China	625	588	37
	Total	910	773	137

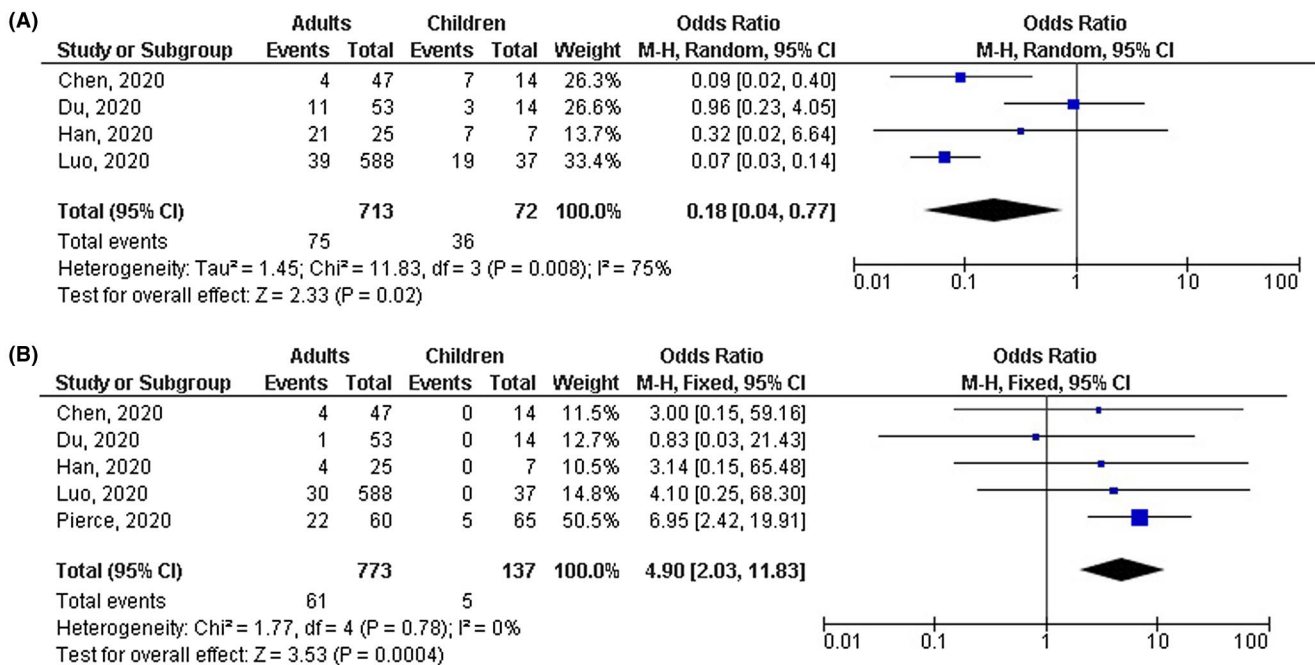
and most of them were from China, comparing adults with children and fulfilled the inclusion criteria.<sup>20-24</sup> Details of the included studies are shown in Table 2.

The 5 studies included 910 inpatients with COVID-19 disease at the baseline of the study; 773 of them were adult inpatients, and 137 of them were paediatric inpatients.

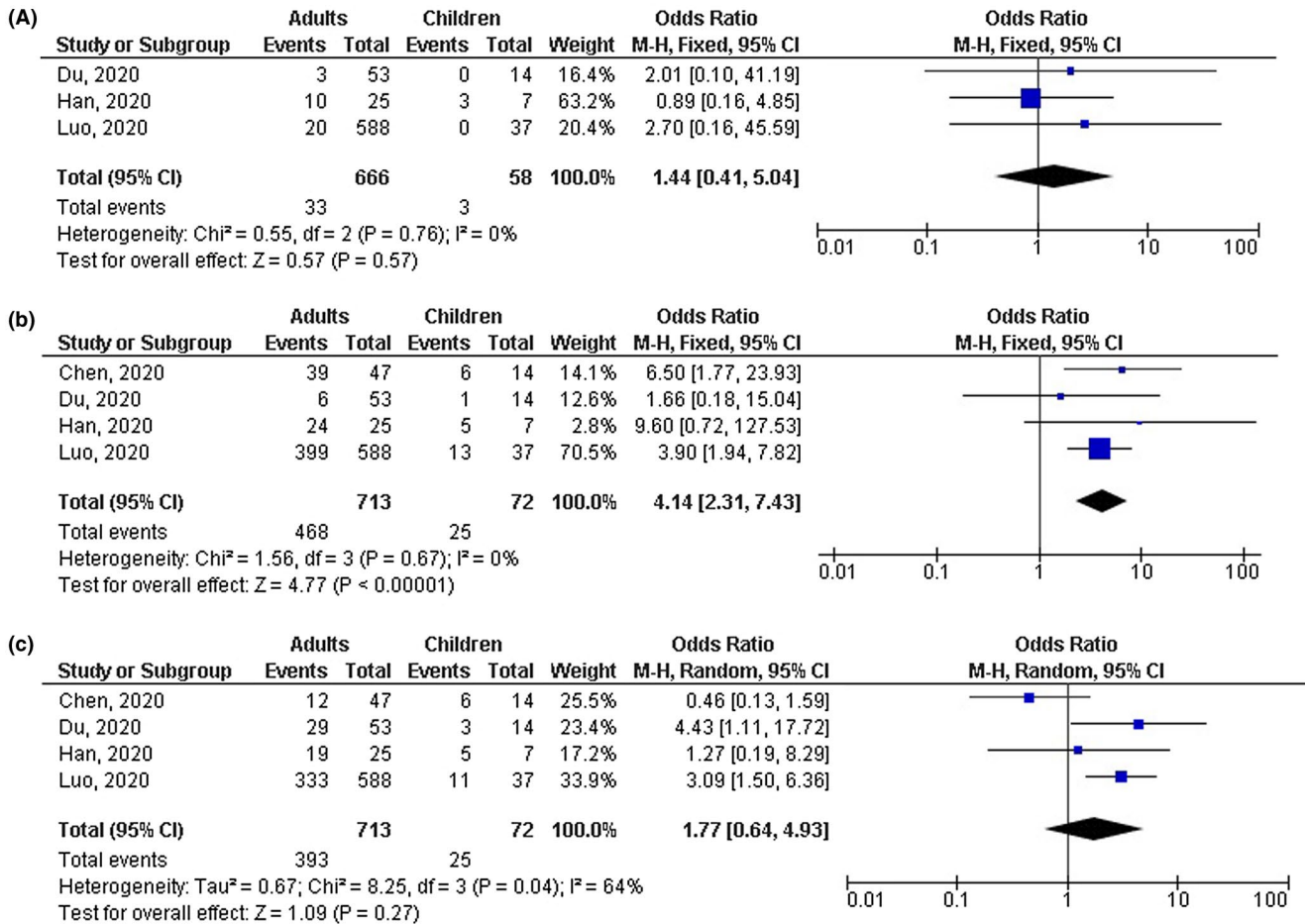
The study size ranged from 32 to 625 subjects at the start of the study. 5 studies reported data stratified comparison between subjects' age and level of symptomatic severity, 4 studies for clinical features, 4 studies for computerised tomography results and 4 studies for laboratory results.

The extent of the age outcome in subjects with COVID-19 disease was higher in adults than that in children and this was statistically significant in all populations studied.

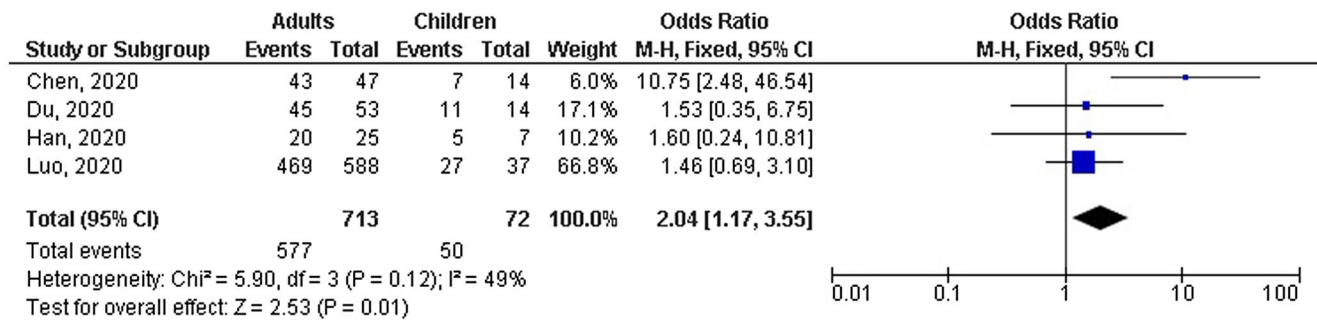
Adults with COVID-19 disease had significantly lower number of mild cases (OR, 0.18; 95% CI, 0.04-0.77,  $P = .02$ ) with high heterogeneity ( $I^2 = 75\%$ ); higher number of severe cases (OR, 4.90; 95% CI, 2.03-11.83,  $P < .001$ ) with no heterogeneity ( $I^2 = 0\%$ ); higher number of cases with fever (OR, 4.14; 95% CI, 2.31-7.43,  $P < .001$ ) with no heterogeneity ( $I^2 = 0\%$ ); and higher number of cases with CT positive COVID-19 disease (OR, 2.04; 95% CI, 1.17-3.55,  $P = .001$ ) with low heterogeneity ( $I^2 = 49\%$ ) compared with children as shown in Figures 2-4. However, no significant difference between adults and children was observed in number of cases with shortness of breath (OR, 1.44; 95% CI, 0.41-5.04,  $P = .57$ ) with no heterogeneity ( $I^2 = 0\%$ ); dry cough (OR, 1.77; 95% CI, 0.64-4.93,  $P = .27$ ) with moderate heterogeneity ( $I^2 = 64\%$ ); leukopenia (OR, 0.89; 95% CI, 0.47-1.66,  $P = .71$ ) with low heterogeneity ( $I^2 = 31\%$ ); lymphopenia (OR, 0.96; 95% CI, 0.49-1.88,  $P = .91$ ) with low heterogeneity ( $I^2 = 25\%$ ); high platelets (OR, 0.41;



**FIGURE 2** Forest plot of the effect of age on (A) number of mild cases, (B) number of severe cases



**FIGURE 3** Forest plot of the effect of age on (A) number of cases with shortness of breath, (B) number of cases with fever, (C) number of cases with shortness of dry cough

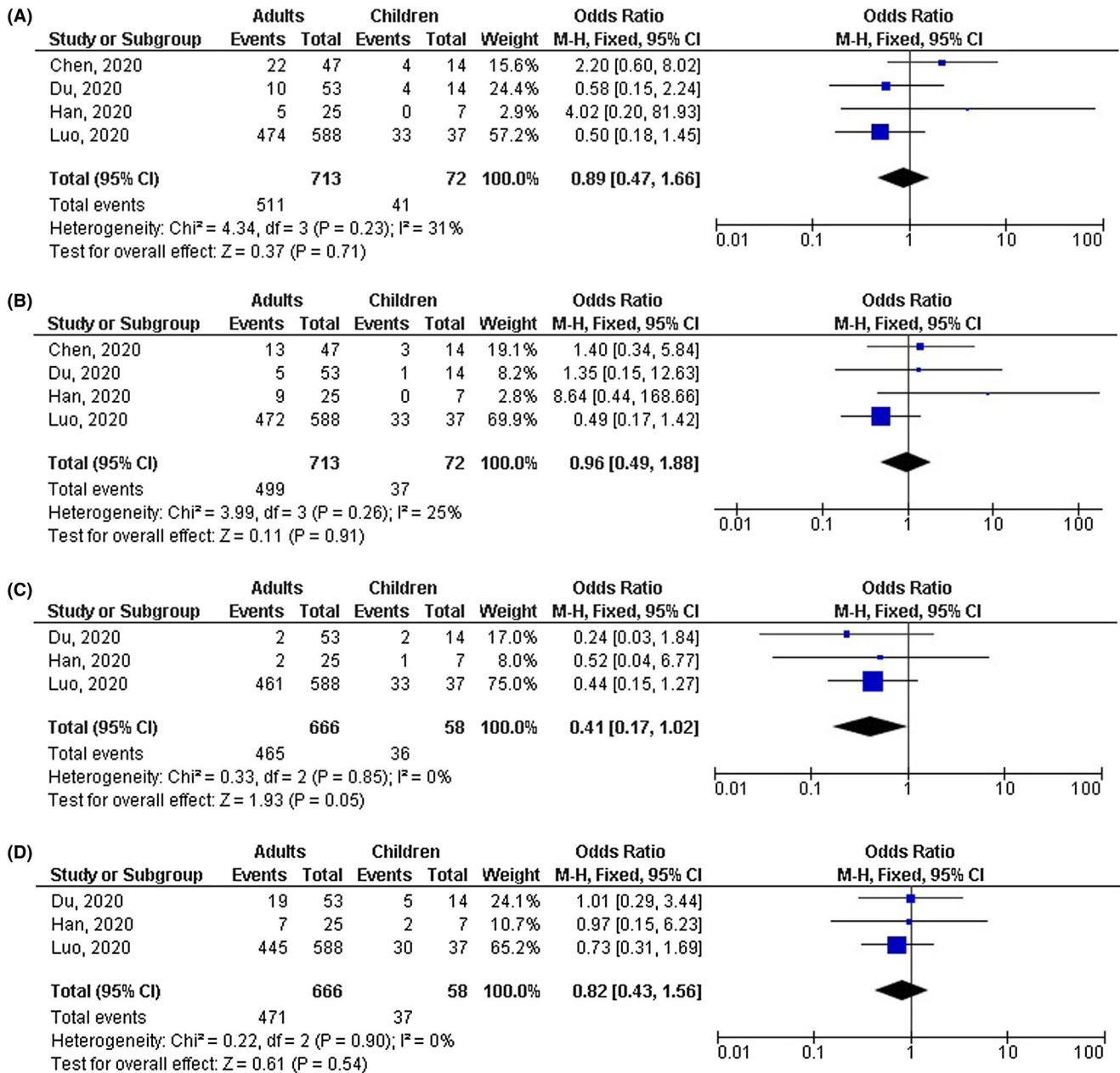


**FIGURE 4** Forest plot of the effect of age on the number of cases with CT positive results

95% CI, 0.17-1.02,  $P = .05$ ) with no heterogeneity ( $I^2 = 0\%$ ); and high D-dimer (OR, 0.82; 95% CI, 0.43-1.56,  $P = .54$ ) with no heterogeneity ( $I^2 = 0\%$ ) as shown in Figures 3 and 5.

A stratified analysis of studies that did and did not adjust for the effect of ethnicity and gender on the results was not performed because no studies reported or adjusted for this factor.

Based on the visual inspection of the funnel plot as well as on quantitative measurement using the Egger regression test, there was no evidence of publication bias ( $P = .87$ ). However, most of the included studies were assessed to be of a low methodological quality. All studies did not have selective reporting bias, and no articles had incomplete outcome data and selective reporting.



**FIGURE 5** Forest plot of the effect of age on (A) number of cases with leukopenia, (B) number of cases with lymphopenia, (C) number of cases with shortness of high platelets, (D) number of cases with shortness of dry high D-dimer

### 3 | DISCUSSION

This meta-analysis study based on 5 studies included 910 inpatients with COVID-19 disease at the baseline of the study; 773 of them were adult inpatients, and 137 of them were paediatric inpatients.<sup>20-24</sup>

The extent of poor outcome in the symptomatic severity, fever and CT positive in adults with COVID-19 disease was higher than that in children and this was statistically significant in all populations studied.<sup>20-24</sup> However, no significant difference between adults and children was observed in shortness of breath, dry cough and all the laboratory data. Although, the low  $P$ -values of the high platelet outcomes ( $P = .05$ ) suggest that the insignificant difference found

between adults and children could turn into significant if more studies comparing adults COVID-19 cases to children. Though, the analysis of outcomes should be done with caution because of the small number of the study found (5 studies) and the low sample size in most of the selected studies (3 studies  $\leq 100$  subjects) in our meta-analysis; suggesting the need for more studies to validate these findings or possibly to significantly influences confidence in the effect evaluation.

This finding suggests that adults with COVID-19 disease have a much higher level of symptomatic severity, clinical features and CT results than children. Also, request more comparative studies rather than the hundreds of observational studies available that just

describe the COVID-19 patients' status. The reasons for these findings are likely multi-factorial.<sup>20-24</sup>

To our knowledge, this is the first meta-analysis comparing adults and children with COVID-19. Though, the analysis of outcomes should be with caution because of the low number of studies in our meta-analysis, the small sample size of the selected studies, and the potential risk of bias.

Children are much easier infected at school and playgrounds,<sup>25</sup> much less aware of the proper protection measures about SARS-CoV-2 infection spread<sup>26</sup> and much less aware of the proper way to handle COVID-19 disease patients at home.<sup>27</sup> Hence, children can serve as a great source of infection to their families since mostly they have asymptomatic SARS-CoV-2 infection.<sup>25,26</sup> Several studies and consensus have been published describing the proper diagnosis, management and prevention of COVID-19 disease.<sup>25,28,29</sup> However, COVID-19 disease still infecting and taking the life of millions of people.<sup>30</sup> This disease required further description of the effect on different ages, gender and ethnicity. It has been shown previously and validated in our meta-analysis that adults are more susceptible to SARS-CoV-2 infection than children. However, as shown in our results, the laboratory data were similar in both groups. These results are confusing and require a proper explanation of why symptoms and severity are high in adults and laboratory data are similar in both groups since most of the present explanations are suggestions. The reasons why paediatric inpatients are milder than adult inpatients are still unidentified. However, one of the suggested reasons is the existence of cross-reaction between SARS-CoV-2 and any of childhood vaccines.<sup>30</sup> That could be valid since some relations were made between the Bacillus Calmette-Guérin vaccine, one of the childhood vaccinations in most of the countries in the world, and the lower severity of the COVID-19 disease.<sup>30</sup> Another explanation was based on the risk factors and the co-morbid conditions that mostly occur in adults compared with children. A meta-analysis study has shown that smoking, which mostly occurs in adults, could stimulate the development of COVID-19 disease making the smoking subjects suffer more from COVID-19 disease.<sup>31</sup> Also, the co-morbid diseases which occur more in adults than in children could add some reasons why adults are much more susceptible to COVID-19 disease than children.<sup>32,33</sup> However, still all of these explanations are suggestions. This meta-analysis showed the effect of age of COVID-19 inpatient on the severity of the disease. Yet, further studies are needed to validate these potential relationships and explain the mechanism of the effect of age of COVID-19 inpatient on the severity of the disease. These studies must comprise larger with more homogeneous samples. Well-conducted studies are needed to assess these factors and the combination of different childhood vaccination, gender, ethnicity and other variants of subjects; since our meta-analysis study could not answer whether different ethnicity and gender are associated with the results.<sup>34-39</sup>

In summary, the data suggest that adults with COVID-19 disease may be at higher risk of the poor level of symptomatic severity, clinical features and computerised tomography results than children.

However, the laboratory data were similar in both groups. From the study presented here, we recommend the use of further comparative studies to validate these findings.

### 3.1 | Limitations

There may be selection bias in this study since so many of the studies found were excluded from the meta-analysis. However, the studies excluded did not satisfy the inclusion criteria of our meta-analysis. Also, we could not answer whether the results are associated with ethnicity and gender or not. The study designed to assess the effect of age of COVID-19 inpatient on the severity of the disease was based on data from previous observational studies, which might cause bias induced by incomplete details. The meta-analysis was based on 5 observational studies; 3 of them had a small sample size ( $n < 100$ ). Variables including ethnicity, sex, nutritional status and comorbidity, for example diabetes mellitus, hypertension or obesity of subjects were also the possible bias-inducing factors. Some unpublished articles and missing data might lead to a bias in the pooled effect. Also, some important paediatric cohorts were not included because of the low number of studies found in this meta-analysis, given that only studies comparing children to adults were included. The sample sizes varied considerably across studies and four of the five included studies were conducted in China; non-coverage of different geographical areas.

## 4 | CONCLUSIONS

Adults with COVID-19 disease have a much higher level of symptomatic severity, fever and CT-positive COVID-19 disease than children. However, as shown in our results, the laboratory data were similar in both groups. From the study presented here, we request further comparative studies between adults and children with COVID-19 to validate these findings and find any possible explanation for the insignificant difference in laboratory results. Though, the analysis of outcomes should be done with caution because of the small number of the study found (5 studies) and the low sample size in most of the selected studies (3 studies  $\leq 100$  subjects) in our meta-analysis; suggesting the need for more studies to validate these findings or possibly to significantly influences confidence in the effect evaluation.

## 5 | DATA AVAILABILITY STATEMENT

The datasets analysed during this study are available from the corresponding author on reasonable request.

## ACKNOWLEDGEMENTS

Not applicable.

**DISCLOSURE**

The authors declare that they have no competing interests.

**AUTHOR CONTRIBUTIONS**

Conception and design: Xiaoxiao Xu, Mohamed EA Abdelrahim. Administrative support: All authors. Provision of study materials or subjects: All authors. Collection and assembly of data: Shaoqing Chai, Yan Li, Xuemei Li, Jie Tan. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors. All authors have read and approved the manuscript.

**IRB APPROVAL**

Not required for this study.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

**CONSENT FOR PUBLICATION**

Not applicable.

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