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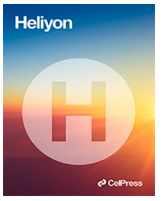

Research article

# Comparison of inflammatory markers, coagulation indicators and outcomes between influenza and COVID-19 infection amongst children: A systematic review and meta-analysis

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ABSTRACT

*Background:* Influenza and COVID-19 patients share similar features and outcomes amongst adults. However, the difference between these diseases is not explored in paediatric age group especially in terms of inflammatory markers, coagulation profile and outcomes. Hence, we did this review to compare the inflammatory, coagulation features and outcomes between influenza and COVID-19 infected children.

*Methods:* Literature search was done in PubMed Central, Scopus, EMBASE, CINAHL, Cochrane library, Google Scholar & ScienceDirect from November 2019 to May 2022. Risk of bias assessment was done through Newcastle Ottawa scale. Meta-analysis was done using random-effects model and the final pooled estimate was reported as pooled odds ratio (OR) or standardized mean difference (SMD) along with 95 % confidence interval (CI) depending on the type of outcome.

*Results:* About 16 studies were included with most studies having higher risk of bias. Influenza paediatric patients had significantly higher erythrocyte sedimentation rate (ESR) (pooled SMD = 0.60; 95%CI: 0.30–0.91; $I^2$ = 0 %), lactate dehydrogenase (LDH) (pooled SMD = 2.01; 95%CI: 0.37–3.66; $I^2$ = 98.4 %) and prothrombin time (PT) (pooled SMD = 2.12; 95%CI: 0.44–3.80; $I^2$ = 98.3 %) when compared to paediatric COVID-19 patients. There was no significant difference in terms of features like CRP, procalcitonin, serum albumin, aPTT, mortality and need for mechanical ventilation.

*Conclusion:* Inflammatory markers like ESR, LDH and PT was significantly higher in influenza patients when compared to COVID-19 in children, while rest of the markers and adverse clinical outcomes were similar between both the groups. Identification of these biomarkers has helped in understanding the distinctness of COVID-19 and influenza virus and develop better management strategies.

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## 1. Introduction

Public health specialists have been long anticipating a possibility of the emergence of a pandemic potential extremely contagious respiratory virus. When the COVID-19 infection started circulating in late 2019, it was compared with seasonal & pandemic influenza viruses immediately. This was mainly because of the similar features shared between these viruses in terms of clinical presentations like fever, sore throat, cough to severe form of lung infection [1,2]. Both COVID-19 and influenza virus have demonstrated same transmission route and ease of human-to-human transmission via the route of the respiratory droplets [3]. However, COVID-19 has certain clinical characteristics like loss of taste and smell, which are different from other influenza viruses [3]. Though, several effective vaccines are now available for the COVID-19 infection, search is still on for the perfect treatment practices. However, influenza can be easily detected, treated and prevented using vaccines [2].

Influenza amongst children acts as a major source of virus carriers [4]. In addition, children were found to have a higher risk of severe influenza condition, despite lower rate of infection compared to the adults [4,5]. A contrasting finding was found in COVID-19 infection, where the deaths amongst children were found to be rare when compared to the influenza virus infection. Primary COVID-19 management takes mostly a supportive form, though there are several experimental antiviral drugs are being evaluated [6,7]. Hence, either prevention or early diagnosis and management of children infected with the influenza virus is very crucial.

Despite the ongoing efforts to manage and mitigate the effects of both viruses, there remains a critical gap in our understanding of how these viruses compare, particularly in the pediatric population. This review aims to fill a significant void in current research by comparing inflammatory markers and outcomes between influenza and COVID-19 in children. The importance of identifying distinctive inflammatory markers and understanding their implications cannot be overstated, as these markers hold the key to unlocking novel management strategies and therapeutic interventions tailored to the unique challenges posed by each virus.

Furthermore, the paucity of data on coagulation indicators and outcomes between the two infections in children highlights an urgent need for research in this area. Coagulation abnormalities have been a notable concern in adult patients with COVID-19, suggesting potential unique risks that could also be present in pediatric cases. By delving into these comparisons, this study not only seeks to delineate the clinical and pathophysiological distinctions between COVID-19 and influenza in children but also aims to lay the groundwork for more effective, targeted approaches to treatment and prevention in this highly susceptible group.

Identifying these markers will help us understand more about the distinctness of the COVID-19 and influenza virus and develop better management strategies addressing all these factors. Hence, we did this review to compare the inflammatory markers and outcomes between influenza and COVID-19 patients in paediatric age group.

## 2. Methods

### *2.1. Eligibility criteria*

#### *2.1.1. Study design*

Observational studies of any nature i.e., cohort or case-control or cross-sectional analytical studies were eligible for inclusion. Full-text articles published in peer-reviewed journals were included, while case reports or case series or conference abstracts or unpublished grey literature were excluded.

#### *2.1.2. Study participants*

Studies reporting the outcomes in both influenza and COVID-19 paediatric patients as a separate group were eligible for incorporation into review.

#### *2.1.3. Exposure*

Studies assessing the difference in terms of inflammatory markers and outcomes between the influenza and COVID-19 patients in paediatric age group.

#### *2.1.4. Outcome*

*Inflammatory markers*: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, serum albumin.

*Coagulation indicators*: prothrombin time (PT), activated partial thromboplastin time (APTT)

*Outcomes*: Severity (need for mechanical ventilation) and Mortality.

#### *2.1.5. Search strategy*

Search strategy is described in the **Supplementary Appendix** and it was done in the following databases: PubMed Central, Scopus, EMBASE, CINAHL, Cochrane library and search engines: Google Scholar & ScienceDirect. Medical subject headings (MeSH) and the free-text words (with the appropriate Boolean operators "OR" & "AND") utilized in the search are also reported in the **Supplementary Appendix**. Timeline restriction for the search was November 2019 (starting point of reports about COVID-19 infection) till May 2022. Additional filters in terms of language (English) and study design (observational studies) were also placed during the search. Bibliographies of the studies included in the review were again hand-searched to identify any missed-out articles during the search.

*2.1.6. Study records screening*

We managed to retrieve studies using Rayyan and eliminated duplicates, following which remaining studies were screened. Two independent reviewers (YY and QZ) did primary screening (i.e., checking title and abstract). Fairly suitable studies had their full text retrieved and the same two reviewers finalized the studies for including in analysis with additional input or expertise from third reviewer (LY). Two reviewers (QZ and LW) did data extraction using Microsoft Excel. The data form contained general study characteristics, participants, markers related details and outcomes. PRISMA guidelines was followed throughout the review process [8].

*2.1.7. Risk of bias in individual studies*

We utilized the Newcastle Ottawa Scale (NOS) to assess risk of bias [9]. The NOS is a comprehensive tool designed to assess the quality in observational studies based on three broad domains.

1. **Selection:** This domain focuses on the method used to select study participants. Criteria under this domain assess the representativeness of the cases, the selection of controls in case-control studies, and the selection of the cohort in cohort studies. It also evaluates the definition of cases and controls and the method of ascertainment of exposure, aiming to ensure that these methods are unbiased and reliable.
2. **Comparability:** This domain assesses the study groups' comparability based on the design or analysis. Studies are awarded points if they control for the most important factor(s) or any additional factor(s) that could influence the outcome. This ensures that the study's findings are not due to pre-existing differences between groups other than the exposure being studied.
3. **Outcome:** For cohort studies, this domain evaluates the assessment of the outcome, whether it was done in a way that was not biased towards the result, and the adequacy of the follow-up length for outcomes to occur. For case-control studies, it assesses the method of case ascertainment and the same assessment of exposure for cases and controls.

Each study was graded on these domains using a star system, which allows for a semi-quantitative assessment of study quality. A

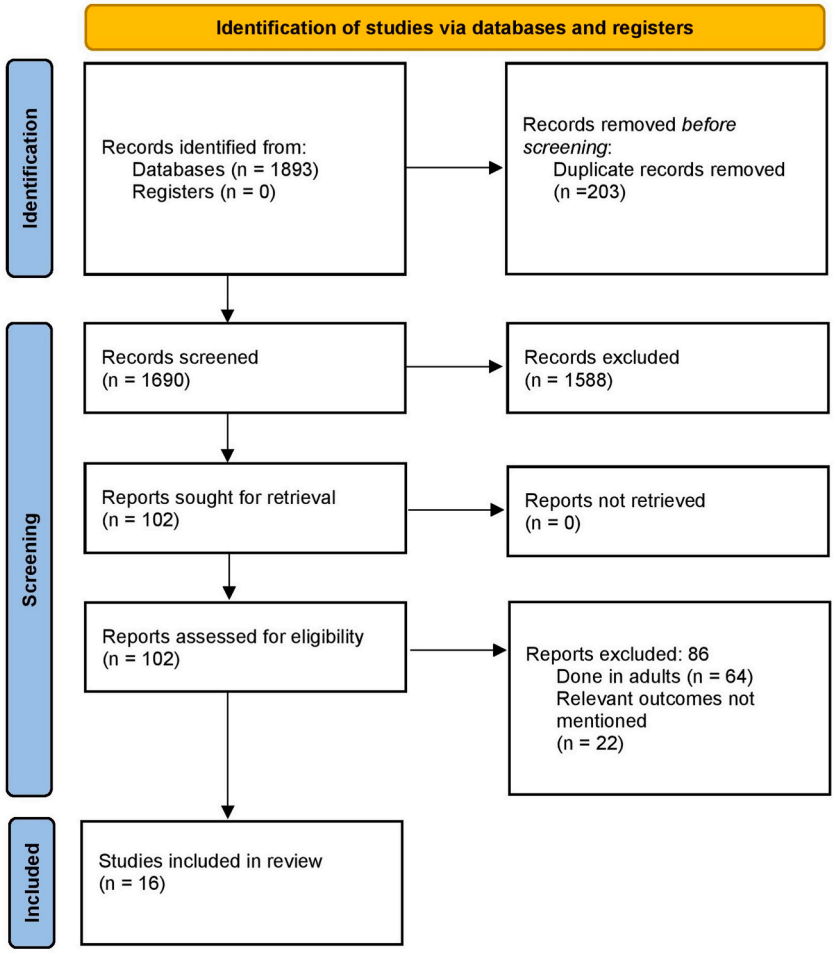


**Fig. 1.** PRISMA flowchart.

maximum of nine stars can be awarded to a study: four for Selection, two for Comparability, and three for Outcome. Studies achieving higher stars are considered to be of higher quality and lower risk of bias.

The assessments were independently performed by two reviewers (YY and QZ), with disagreements resolved through discussion or the input of a third reviewer. This dual-review process ensures a thorough and unbiased evaluation of each study included in our review.

## 3. Statistical analysis

Meta-analysis was done using STATA software version 17. Random-effects (DerSimonian and Laird) model was utilized.[15] Pooled odds ratio (OR) was the summary outcome for dichotomous outcomes and standardized mean differences (SMD) for reporting of continuous outcomes. The final estimates are represented using forest plots.

Heterogeneity assessment was done using $I^2$ statistic and chi square test of heterogeneity.[15] P value $< 0.05$ in chi square test and $I^2$ value higher than 75 percent is indicative of high heterogeneity. Publication bias examination was done through funnel plot and Egger test. The shape of funnel plot being asymmetrical and Egger test p-value $<0.05$ is indicative of publication bias. Sensitivity analysis or leave one out analysis was done to identify whether the final estimate is robust to single study changes.

## 4. Results

### 4.1. Study selection

Overall, 1893 records were found and amongst them, 102 full-text manuscripts were retrieved. After matching these full text with inclusion criteria, 16 studies were included (Fig. 1) [10–25].

**Table 1**
Characteristics of the included studies (N = 16).

| Author | Year of publication | Country | Study design | Sample size in COVID-19 group | Sample size in influenza group | Influenza type | Mean age (in years) |
|---|---|---|---|---|---|---|---|
| Akkoc | 2021 | Turkey | Retrospective | 32 | 22 | Influenza A & B | COVID - 15.3<br>Influenza - 1.4 |
| Asseri | 2021 | Saudi Arabia | Retrospective | 73 | 34 | H1N1 | COVID - 1<br>Influenza - 3 |
| Hedberg | 2021 | Sweden | Retrospective cohort | 101 | 871 | Influenza A & B | COVID - 7<br>Influenza - 2 |
| Laris-González | 2021 | Mexico | Retrospective | 133 | 295 | Influenza A & B | COVID - 5.3<br>Influenza - 3.7 |
| Li | 2020 | China | Retrospective | 57 | 59 | Influenza A | COVID -18.7 months<br>Influenza - 21.8 months |
| Liang | 2021 | China | Retrospective | 45 | 45 | Influenza A | COVID - 2.6<br>Influenza - 2.6 |
| Liu | 2020 | China | Retrospective | 24 | 67 | Any influenza | COVID – 54 months<br>Influenza – 35 months |
| Liu | 2021 | China | Retrospective | 248 | 337 | Influenza A & B | COVID – 6.96<br>Influenza – 2.67 |
| Liu | 2021 | China | Case control study | 171 | 35 | Influenza A | COVID – 6.7<br>Influenza – 1 |
| Piroth | 2021 | France | Retrospective cohort | 1227 | 8942 | Seasonal Influenza | NR |
| Pokorska-Śpiewak | 2021 | Poland | Prospective | 15 | 32 | Any influenza | COVID – 128 months<br>Influenza – 112 months |
| Siddiqui | 2021 | Turkey | Retrospective | 206 | 411 | Influenza A & B | COVID – 7.75<br>Influenza – 4 |
| Song | 2020 | USA | Retrospective | 54 | 291 | Influenza A & B | COVID - 8.3<br>Influenza – 3.9 |
| Sousa | 2020 | Brazil | Cross-sectional | 2590 | 659 | Any influenza | NR |
| Yilmaz | 2021 | Turkey | Retrospective | 164 | 46 | Influenza A & B | COVID – 93.9 months<br>Influenza – 87.5 months |
| Zhao | 2020 | China | Observational control | 23 | 240 | Influenza A | COVID – 5.7<br>Influenza – 5.7 |

**Table 2**
Quality assessment of the included studies (N = 16).

| S. N. | Author and year | Representativeness | Sample size justification | Non-response | Ascertainment of exposure | Control for confounding | Assessment of outcome | Statistical tests | Overall Quality |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Akkoc 2021 | 0 star | 0 star | 0 star | * | * | * | * | Satisfactory |
| 2. | Asseri 2021 | 0 star | * | * | * | * | * | * | Good |
| 3. | Hedberg 2021 | 0 star | 0 star | * | 0 star | 0 star | * | * | Poor |
| 4. | Laris-González 2021 | 0 star | * | 0 star | 0 star | 0 star | * | 0 star | Poor |
| 5. | Li 2020 | 0 star | 0 star | 0 star | * | * | * | * | Satisfactory |
| 6. | Liang 2021 | 0 star | 0 star | 0 star | * | ** | * | * | Satisfactory |
| 7. | Liu 2020 | 0 star | * | * | * | 0 star | * | 0 star | Poor |
| 8. | Liu 2021 | 0 star | 0 star | * | * | 0 star | * | * | Poor |
| 9. | Liu 2021 | 0 star | 0 star | 0 star | 0 star | 0 star | * | * | Poor |
| 10. | Piroth 2021 | 0 star | 0 star | 0 star | 0 star | 0 star | * | 0 star | Poor |
| 11. | Pokorska-Śpiewak 2021 | * | 0 star | 0 star | * | ** | * | * | Good |
| 12. | Siddiqui 2021 | 0 star | 0 star | * | 0 star | 0 star | * | * | Poor |
| 13. | Song 2020 | 0 star | 0 star | * | 0 star | 0 star | * | * | Poor |
| 14. | Sousa 2020 | 0 star | 0 star | 0 star | 0 star | 0 star | 0 star | * | Poor |
| 15. | Yilmaz 2021 | 0 star | 0 star | 0 star | * | 0 star | * | * | Poor |
| 16. | Zhao 2020 | 0 star | 0 star | * | * | 0 star | 0 star | * | Poor |

### 4.2. Characteristics of the included studies

All the studies except Pokorska-Śpiewak et al., 2021 [20] were retrospective studies. Majority of the included studies (6 out of 16) were based in China followed by Turkey (3 studies). The sample sizes ranged from 39 to 10,169 with overall sample size of the review of 17,529 participants. The mean age in COVID-19 group ranges from 1 to 11 years and influenza group from 1 to 9 years. Most studies

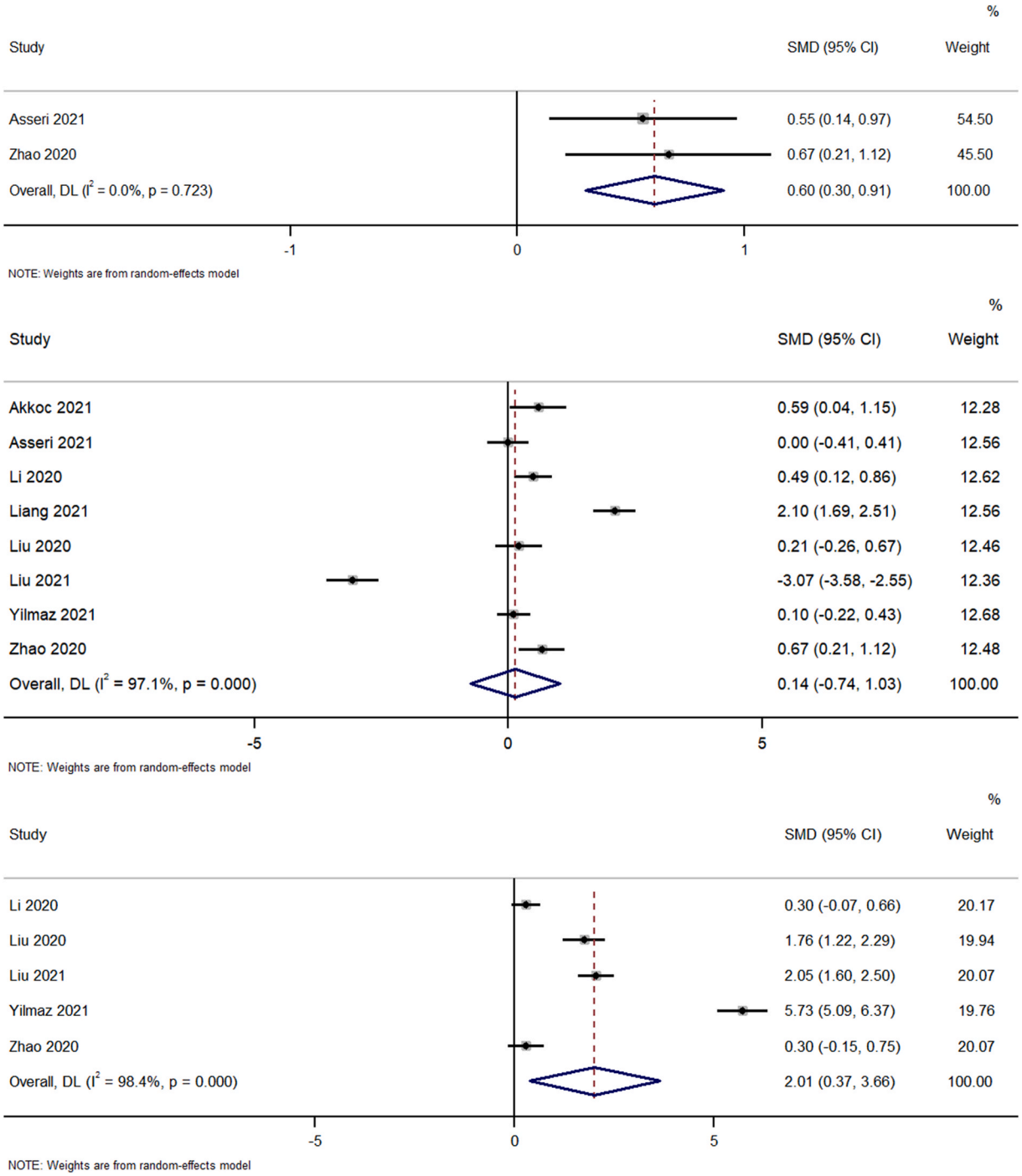


**Fig. 2.** A: Forest plot showing the difference in ESR between paediatric COVID-19 and influenza patients. Fig. 2B: Forest plot showing the difference in CRP between paediatric COVID-19 and influenza patients. Fig. 2C: Forest plot showing the difference in LDH between paediatric COVID-19 and influenza patients. Fig. 2D: Forest plot showing the difference in procalcitonin between paediatric COVID-19 and influenza patients. Fig. 2E: Forest plot showing the difference in serum albumin between paediatric COVID-19 and influenza patients.

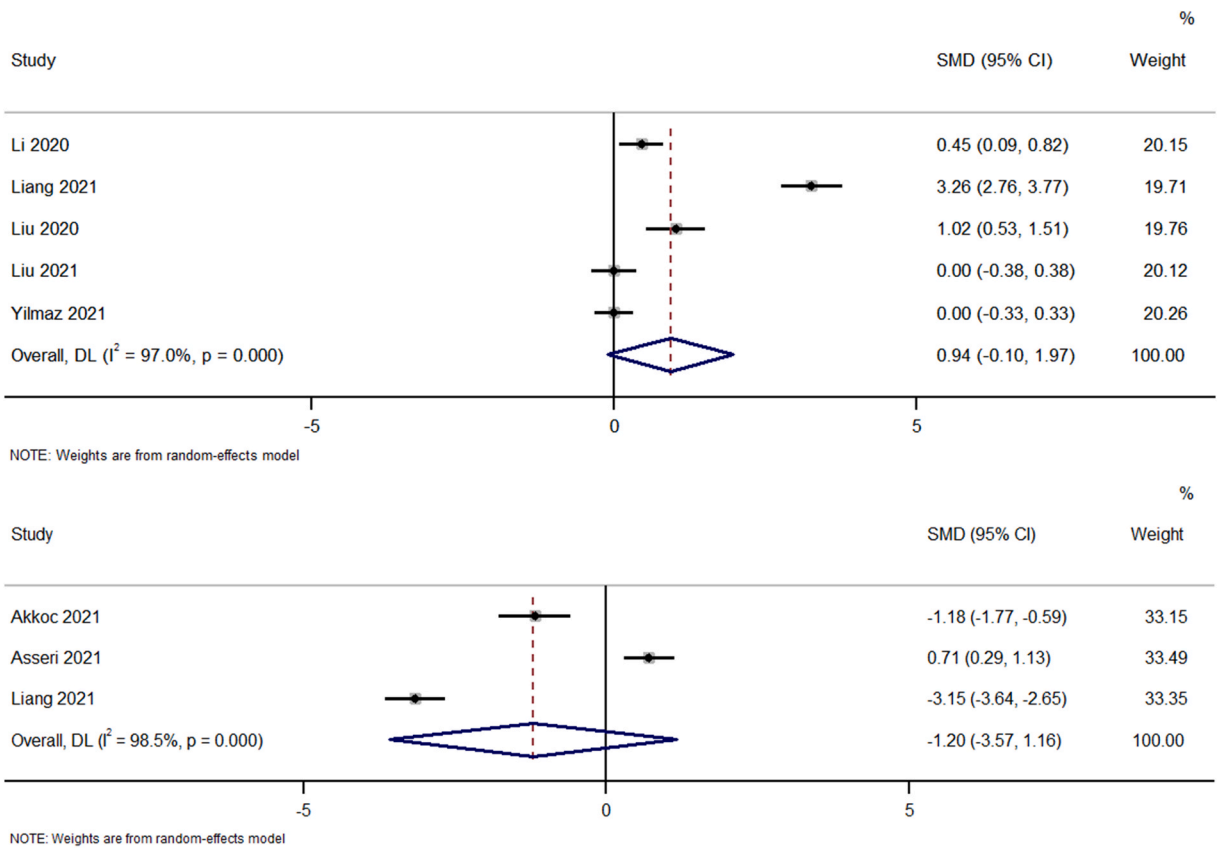


**Fig. 2.** (*continued*).

were conducted among both influenza A & B patients (Table-1). Most studies (11 studies) had higher risk of bias (Table-2).

### *4.3. Inflammatory markers*

#### *4.3.1. ESR*

Two studies highlighted the variation in ESR levels between children with COVID-19 and those with influenza. The aggregated SMD was 0.60 (95%CI: 0.30 to 0.91; I2 = 0 %), showing that pediatric influenza patients had elevated ESR levels compared to those with COVID-19 (Figure-2A).

#### *4.3.2. CRP*

Eight studies explored the differences in CRP levels. The combined SMD was 0.14 (95%CI: −0.74 to 1.03; I2 = 97.1 %), suggesting no substantial variation in CRP levels between the two groups of paediatric patients (p = 0.76) (Figure-2B).

#### *4.3.3. LDH*

Five research works reported on LDH level differences. The consolidated SMD was 2.01 (95%CI: 0.37 to 3.66; I2 = 98.4 %), revealing elevated LDH levels in pediatric influenza patients in contrast to those with COVID-19 (Figure-2C).

#### *4.3.4. Procalcitonin*

Five studies observed differences in procalcitonin levels. The summarized SMD was 0.94 (95%CI: −0.10 to 1.97; I2 = 97 %), suggesting no marked disparity in procalcitonin levels among the two paediatric groups (p = 0.08) (Figure-2D).

#### *4.3.5. Serum albumin*

Seven studies reported differences in lymphocyte count. The amalgamated SMD was −1.20 (95%CI: −3.57 to 1.16; I2 = 98.5 %), indicating no discernible difference in serum albumin levels between the two sets of paediatric patients (p = 0.32) (Figure-2E).

#### 4.3.6. Coagulation indicators

*4.3.6.1. PT.* Four studies documented differences in PT levels. The combined SMD was 2.12 (95%CI: 0.44 to 3.80; I2 = 98.3 %), showing a higher PT in pediatric influenza patients in contrast to those with COVID-19. (Figure-3A).

*4.3.6.2. aPTT.* Four articles compared aPTT levels. The aggregated SMD was 1.56 (95%CI: −0.25 to 3.36; I2 = 98.5 %), signifying no notable difference in aPTT levels among the two pediatric cohorts (p = 0.09) (Figure-3B).

*4.3.6.3. Outcomes*

*4.3.6.3.1. Mortality.* A total of 10 studies compared mortality rates between the two groups. The combined OR was 1.48 (95%CI: 0.63–3.44; I2 = 71 %), suggesting no marked variation in mortality rates between the two groups (Figure-4A). No evidence of publication bias was observed, as affirmed by the balanced funnel plot and the non-significant outcome of the Egger's test (Supplementary Fig. 1).

*4.3.6.3.2. Mechanical ventilation.* Six studies discussed the need for mechanical ventilation (a surrogate measure for disease severity). The summarized OR was 0.48 (95%CI: 0.19–1.22; I2 = 91 %), indicating no substantial difference in mechanical ventilation needs between the two patient groups (Figure-4B).

*4.3.6.3.3. Additional analysis.* Sensitivity analyses displayed no notable alterations in effect size (both in magnitude and direction), suggesting no individual study had an undue influence on the general outcome for any results. Overall, the quality of evidence is low as this review includes observational studies.

## 5. Discussion

This review was done to find the difference in inflammatory markers, coagulation indicators and outcomes between COVID-19 and influenza patients in paediatric age group. Overall, 16 studies have fulfilled the inclusion criteria of the review. Majority of the studies were done in China followed by Turkey, and other European countries like France, Poland and Sweden. All the studies except Pokorska-Śpiewak et al., 2021 [20] were retrospective studies. Most studies had higher risk of bias reflecting poorer quality.

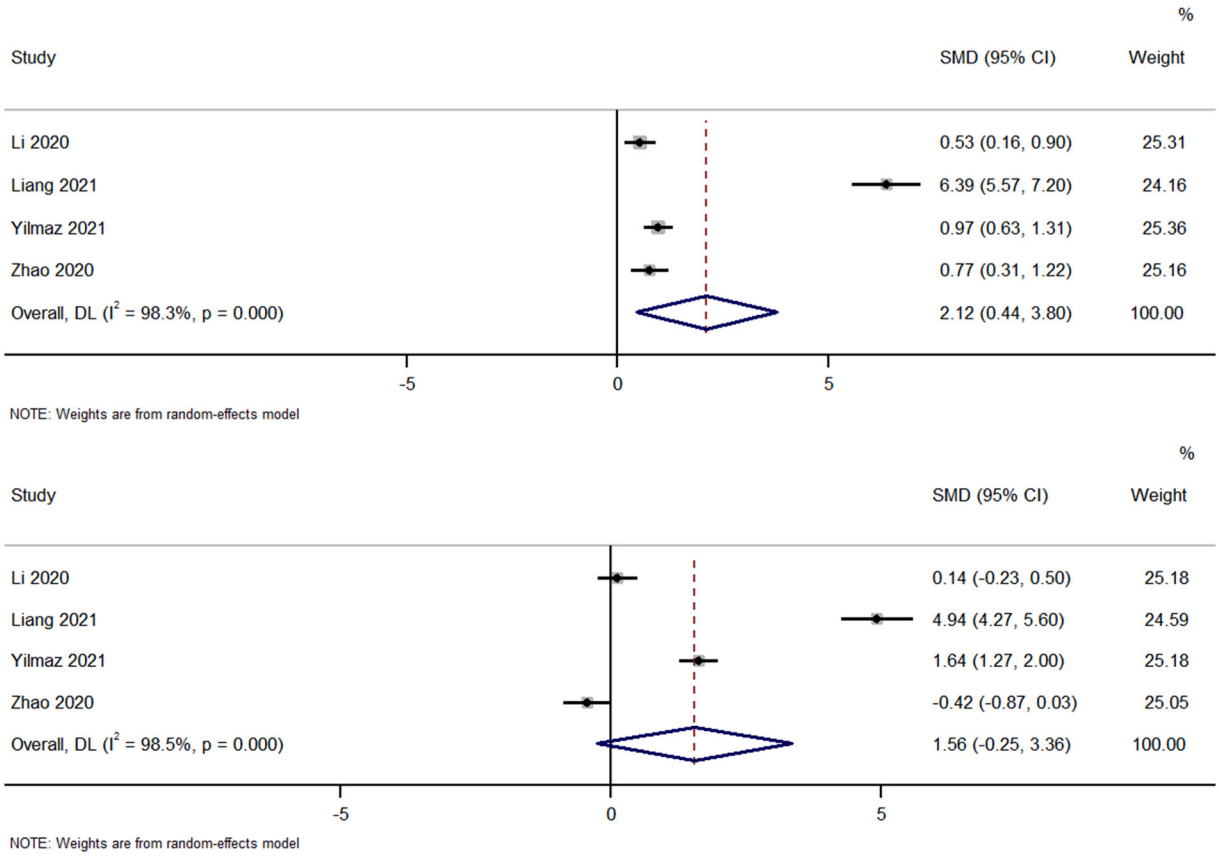


**Fig. 3.** A: Forest plot showing the difference in PT between paediatric COVID-19 and influenza patients
Fig. 3B: Forest plot showing the difference in aPTT between paediatric COVID-19 and influenza patients.

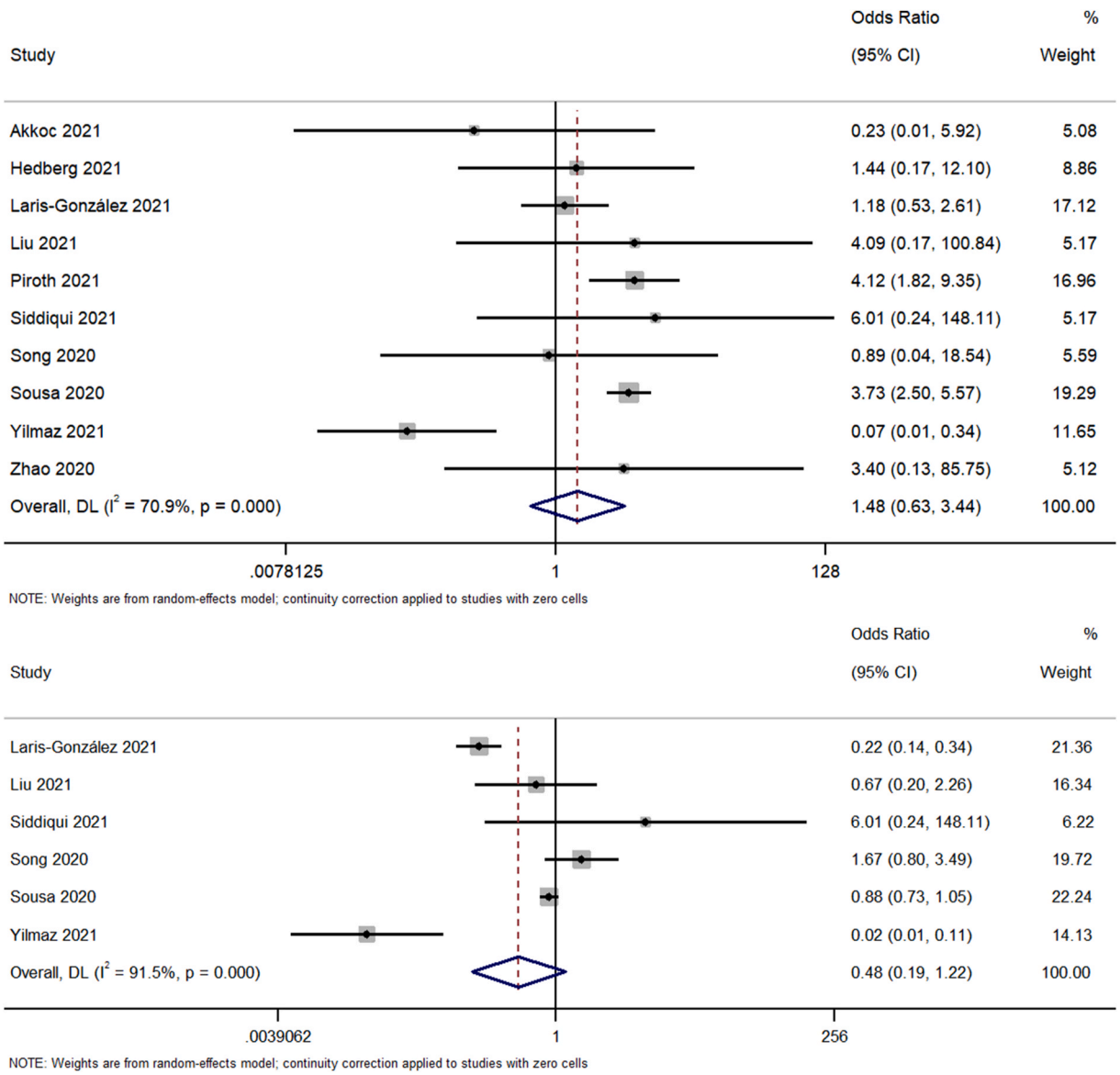


**Fig. 4.** A: Forest plot showing the difference in mortality between paediatric COVID-19 and influenza patients
Fig. 4B: Forest plot showing the difference in severity between paediatric COVID-19 and influenza patients.

Regarding the inflammatory markers, we found that the influenza patients in paediatric age group had significantly higher ESR and LDH values, both of which are key inflammatory markers that are associated with poorer prognosis leading to pneumonia and subsequently death [26–29]. ESR acts as a marker for plasma proteins, thereby indicating the prognosis of the patients [27]. LDH is a cytoplasmic enzyme that is expressed in almost all the types of cells in the body [29]. LDH is released into the blood when cells experience an injury or death, which is caused by the dehydration, drugs, chemical poisonings, bacterial toxins and ischemia. As it is expressed across various tissues or organs in higher concentration, leakage of the LDH (even from a small scale of the injured organ) might result in significantly higher level in the serum. Higher LDH value in influenza patients compared to COVID-19 again reiterates the fact that the influenza infection in paediatric age group has the possibility of causing more severe infections when compared to COVID-19 infection in children. Apart from these two markers, other inflammatory markers did not show significant difference between the two diseases in children.

Regarding the coagulation indicators, viral infections like influenza and COVID-19 activates the coagulation system through various complex mechanisms such as cytokine mediation leading to aberrant haemostasis [30]. As a result of these processes, patients with influenza and COVID-19 has possibility of reporting prolonged PT and aPTT [31,32]. However, in our review, we found that influenza patients had significantly prolonged PT and higher proportion of patients with higher-than-normal aPTT (though statistically insignificant) when compared to COVID-19 patients. This indicates that the paediatric patients with influenza are more prone to be

diagnosed with severe coagulation abnormalities when compared to paediatric COVID-19 at the point of diagnosis.

Coming to the outcomes, both severity and mortality were not significantly different between influenza and COVID-19 patients in paediatric age group. However, previous studies on adult COVID-19 patients have shown higher rate of severity and mortality especially among the adults aged ≥50 years when compared to adult influenza patients [33–35]. The possible reason behind this difference in adult population might be the presence of chronic comorbidities such as diabetes mellitus, hypertension or chronic heart disease conditions amongst middle and elderly adult age groups, skewing the adverse clinical outcome rates towards the COVID-19 patients. However, further longitudinal exploration of outcomes between the influenza and COVID-19 paediatric patients is required.

This review has certain strengths. We made a comprehensive search across various databases and search engine and followed a systematic methodology for reporting. This review also adds to the limited research available on the comparison of inflammatory markers, coagulation indicators and outcomes between paediatric influenza and paediatric COVID-19 patients. No significant change was detected in terms of the magnitude or direction of association in sensitivity analysis for any of the outcomes. No significant publication bias was also detected for the assessed outcome (mortality). These findings enhance the credibility of review results.

Despite these strengths, this review has some limitations. Significant between-study variability with substantially higher $I^2$ was found for most outcomes. We also found that most studies had higher risk of bias. This might affect the and external validity of review findings. Almost all the studies were retrospective in nature, making it difficult to establish the causal association for the identified markers, indicators and outcomes. Hence, large-scale longitudinal evidences generated for the markers and outcomes might help in producing a reliable effect size and help in making an evidence-based recommendation for developing strategies at the hospital setting.

This review underscores the critical need for differentiated diagnostic and management strategies for pediatric patients with influenza and COVID-19, given the distinct profiles of inflammatory markers and coagulation indicators observed. The findings suggest that influenza in children may lead to more severe inflammatory responses and coagulation abnormalities, highlighting the importance of vigilant monitoring and early intervention in these patients. From a public health perspective, these results underscore the necessity for targeted vaccination campaigns and preventive measures tailored to the pediatric population to mitigate the risk of severe influenza and COVID-19 infections. Additionally, the observed differences between these viral infections in children versus adults call for age-specific management strategies and public health policies to address the unique challenges posed by these diseases across different age groups.

Future research should aim to address the limitations identified in this review, particularly the need for longitudinal studies to establish causal relationships between the markers, indicators, and outcomes associated with influenza and COVID-19 in pediatric patients. Large-scale, prospective studies are essential to generate reliable effect sizes that can inform evidence-based clinical and public health strategies. Furthermore, research should explore the mechanisms underlying the differential impact of these viruses on inflammatory and coagulation pathways in children compared to adults. Understanding these mechanisms will be crucial for developing targeted therapies and preventive interventions. Finally, given the significant between-study variability observed, future studies should strive for methodological consistency to facilitate more definitive conclusions.

## 6. Conclusion

This review provides valuable insights into the differences in inflammatory markers, coagulation indicators, and outcomes between pediatric patients with influenza and COVID-19. While the severity and mortality rates did not significantly differ between the two groups, the distinct profiles of inflammatory and coagulation responses to these infections underscore the need for tailored diagnostic and management approaches. The findings highlight the importance of continued research and development of age-specific clinical and public health strategies to effectively address the challenges posed by these viral infections in the pediatric population.

## Data availability statement

All the data generated during the review is already reported within the manuscript and are obtained from the publicly available full-texts. No new data has been generated in our study.

## Ethical approval

Not required.

## Funding

None.

## CRediT authorship contribution statement

**Yutang Yang:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Data curation. **Qi Zheng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Linlin Yang:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Data curation. **Lei Wu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

Nil.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30391.

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