Peer Review File
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Reviewer A

Comment 1:

The small number of studies included and the heterogeneity of the studies makes the result of the meta-analysis hard to interpret. Each of their models was probably constructed differently and included different predictors so not sure how to interpret the results of such a meta-analysis.

Reply 1: Thank you for your comments, which is highly appreciated. We completely understand and share your concerns about the limited number of studies and the heterogeneity among them. However, it should be noted that despite our awareness of these limitations, we felt it imperative to conduct this meta-analysis due to a significant gap in the current literature. Our primary intention was not to provide a conclusive answer but rather to provide insights into this field and offer potential directions for future research. By consolidating previous studies, we hope to highlight both the consistencies and discrepancies in findings, which might serve as a guide for further investigations. Although we recognize the challenges posed by heterogeneity, we also believe our analysis could provide a perspective on the current state of knowledge in the field of venous thrombosis. We will make sure to further emphasize the preliminary nature of our findings in our manuscript and articulate the need for more comprehensive, standardized research in subsequent works. (see details in Page 15-16, Line 295-304) in the tracked version of the manuscript.

Change in the text 1:

Our study has several limitations. Firstly, the study was based on a relatively small dataset comprising only six studies. Thus, it is difficult to identify more pneumonia-specific risks factors, especially from prospective cohorts. Secondly, the primary studies did not contain relevant data, such as clinical manifestations, laboratory metrics,

or thromboprophylaxis details, due to their absence or inadequacy. Thirdly, our analysis did not have enough specificity as we were unable to perform subgroup analyses based on the severity of pneumonia due to insufficient data. Given these constraints, there is an urgent requirement for more multicenter, well-designed original studies with superior rigor and breadth to validate and potentially enhance our results.

Comment 2: *The English language also needs some editing as some sentences are hard to understand or have grammar errors (e.g. line 70-71, to the global burden of what?; line 82-84; line 88 'critically ill' being used as a noun etc)*

Reply 2: Thanks for the careful and kind suggestions. We are very sorry for the mistakes in this manuscript and inconvenience they caused in your reading. We have revised our manuscript carefully with the help from a native speaker.

Change in the text 2:

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), has become a substantial contributor to the global burden of disease. (see details in Page 5, Line 68-70) in the tracked version of the manuscript. Several studies have indicated that advancing age, cancer, elevated D-dimer levels upon admission(10), critical illness(11,12) may serve as independent risk factors for VTE in COVID-19 patients. (see details in Page 6, Line 87-90) in the tracked version of the manuscript.

Reviewer B

Comment 1:

Interesting paper (meta-analysis), clear and well written. The methods seem corrected. in support of the results there are nice figures and tables. I would suggest to short the abstract and the discussion. It is need of minor check for language.

Reply 1: Thank you for your kind feedback and appreciation of our work. We value your constructive suggestions and agree on the importance of conciseness in both the abstract and the discussion. We have revisited the abstract and shorten the discussion section while ensuring that key insights and implications remain intact. Unnecessary details have been pruned for brevity. We have also undertaken a thorough language review to rectify any error and ensure the manuscript meets the journal's standards.

Change in the text 1:

Abstract (see details in Page 3-4, Line 37-62) in the tracked version of the manuscript. Discussion (see details in Page 12-16, Line 233-304) in the tracked version of the manuscript.

Reviewer C

Comment 1: *The first line of the introduction is quite unclear. The authors mentioned the global burden but were unclear about what is being referred to. In addition, VTE doesn't just comprise PE and DVT*

Reply 1: We sincerely thank the reviewer for careful reading. We have made an addition to this sentence. In addition, regarding the definition of VTE, we adopted the authoritative guidelines (*Kearon, C., et al., Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 2012. 141(2 Suppl): p. e419S-e496S.)* and comprehensive reviews (*Khan, F., et al., Venous thromboembolism. LANCET, 2021. 398(10294): p. 64-77*) currently available in the VTE field, which include DVT and PE. In particular, DVT most often occurs in the leg vein but can also develop in the splanchnic, cerebral, and arm veins. (see details in Page 5, Line 68-70) in the tracked version of the manuscript.

Change in the text 1: Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), has become a substantial contributor

to the global burden of disease.

Comment 2: *In line 75, I think the word is et al, rather than, etc.*

Reply 2: We were really sorry for our careless mistakes. Thank you for your correction. We have fixed the error. (see details in Page 5, Line 74-75) in the tracked version of the manuscript.

Change in the text 2: M. Schmidt et al.(4) reported that patients with respiratory tract infections had highest incidence rate ratio….

Comment 3: *Line 78/79: Risk remains higher during the 26-week observation is quite unclear.*

Reply 3: Thanks for your valuable comments. We have revised the expression. (see details in Page 5, Line 77-78) in the tracked version of the manuscript.

Change in the text 3: This elevated rate ratio persisted throughout a 26-week follow-up period.

Comment 4: *There is a major bias in the study inclusion criteria. It appears the study inclusion criteria were not prespecified prior to starting the review. This also probably explains why the study was not registered on any of the publicly available SR &MA registers. Overall the methodology described by the authors raises some serious bias concerns.*

Reply 4: We feel very grateful for your professional review work on our article. We have revised the inclusion and exclusion criteria and improved the flowchart figure of summarizing evidence search and study selection (Figure 1) to for better presentation and clarity. (see details in Page 7, Line 114-119) in the tracked version of the manuscript.

Furthermore, in line with your recommendation, we have completed the registration of our study on the PROSPERO platform. As soon as we receive the registration number, we will ensure it's incorporated into the manuscript promptly.

Change in the text 4:

They reached a consensus with the inclusion criteria as follows: (1) the study design was case control or cohort study; (2) patients with pneumonia and VTE; (3) studies presented in English only. Studies were excluded: (1) studies that did not report relevant risk factors; (2) patients diagnosed with COVID-19; (3) research lacking full text, with incomplete information, or posing inability to conduct data extraction.

Comment 5: *I will encourage the authors to pay particular attention to the English sentence structures, tenses, and word choices (a few examples include lines 131, 134,154)*

Reply 5: Thank you for your careful review. We are very sorry for the mistakes in this manuscript and inconvenience they caused in your reading. The manuscript has been thoroughly revised and rewritten with the help from a native English speaker. We hope it can meet the journal's standard.

Change in the text 5:

OR (95%Cl) was used to analyze the risk factors of subtype of cardiovascular and cerebrovascular disease. (see details in Page 8, Line 132-133) in the tracked version of the manuscript.

I^2 was used to evaluate heterogeneity. If the heterogeneity test was $P \geq 0.1$ and $I^2 \leq 50\%$, it indicated that there was homogeneity between studies,…(see details in Page 8, Line 134-135) in the tracked version of the manuscript.

A total of six studies were included in this meta-analysis, consisting of two case-control studies(20,21) and four cohort studies(16-19), with a total sample size of 162,011 patients. (see details in Page 9, Line 156-158) in the tracked version of the manuscript.

Comment 6: *I have concerns with the search strategy used in this present study. I will encourage the authors to share the MEDLINE search strategy as a representative.*

Reply 6: We apologize for the lack of clarity. We have added the search strategy in supplementary file. The following search strategy was used: ((((((("Pulmonary Embolism"[Mesh]) OR (Pulmonary Embolisms[Title/Abstract])) OR (Pulmonary Thromboembolisms[Title/Abstract])) OR (Pulmonary Thromboembolism[Title/Abstract])) OR ((((((((((("Venous Thrombosis"[Mesh]) OR (Phlebothrombosis[Title/Abstract])) OR (Phlebothromboses[Title/Abstract])) OR (Venous Thromboses[Title/Abstract])) OR (Deep Vein Thrombosis[Title/Abstract])) OR (Deep Vein Thromboses[Title/Abstract])) OR (Deep-Venous Thrombosis[Title/Abstract])) OR (Deep-Venous Thromboses[Title/Abstract])) OR (Deep-Vein Thrombosis[Title/Abstract])) OR (Deep-Vein Thromboses[Title/Abstract])) OR (Deep Venous Thrombosis[Title/Abstract])) OR (Deep Venous Thromboses[Title/Abstract]))) AND ((((((((((((((((((("Pneumonia"[Mesh]) OR (Pneumonias[Title/Abstract])) OR (Lobar Pneumonia[Title/Abstract])) OR (Lobar Pneumonias[Title/Abstract])) OR (Pneumonias, Lobar[Title/Abstract])) OR (Pneumonia, Lobar[Title/Abstract])) OR (Experimental Lung Inflammation[Title/Abstract])) OR (Experimental Lung Inflammations[Title/Abstract])) OR (Inflammation, Experimental Lung[Title/Abstract])) OR (Lung Inflammation, Experimental[Title/Abstract])) OR (Lung Inflammations, Experimental[Title/Abstract])) OR (Pneumonitis[Title/Abstract])) OR (Pneumonitides[Title/Abstract])) OR (Pulmonary Inflammation[Title/Abstract])) OR (Inflammation, Pulmonary[Title/Abstract])) OR (Inflammations, Pulmonary[Title/Abstract])) OR (Pulmonary Inflammations[Title/Abstract])) OR (Lung Inflammation[Title/Abstract])) OR (Inflammation, Lung[Title/Abstract])) OR (Inflammations, Lung[Title/Abstract])) OR (Lung Inflammations[Title/Abstract]))) AND (((((risk factor[Title/Abstract]) OR (risk factors[Title/Abstract])) OR (predictive factor[Title/Abstract])) OR

(predictors[Title/Abstract])) OR (predictor[Title/Abstract])). (see details in Page 1, Line 1-27) in the supplementary file.

Change in the text 6:

Detailed search strategy was listed in Supplementary file …(see details in Page 7, Line 109-110) in the tracked version of the manuscript.

Comment 7: *The discussion section needs a lot of improvement.*

Reply 7: Thanks for pointing this out. We have worked on refining the discussion sections to be more concise while ensuring they still capture the essence of our findings.

Change in the text 7:

Discussion (see details in Page 12-16, Line 233-304) in the tracked version of the manuscript.

Comment 8: *In the conclusion section, the authors, mentioned "eligible clinical trials" which is incongruent with the preceding information.*

Reply 8: Thanks for your careful comments. We have corrected this error to make the article more rigorous. (see details in Page 16, Line 306) in the tracked version of the manuscript.

Change in the text 8:

Through systematically reviewing the eligible studies, the present meta-analysis…

Comment 9: *The inclusion of just 6 observational studies means the current topic although interesting is not well studied and might not be ripe for a metanalysis. One can argue that information gotten from pooling data from just 2-3 observational studies is quite very weak at best.*

Reply 9: Thank you for underlining this deficiency. We understand the potential limitations of pooling data from a small number of observational studies. However, our primary intent was to consolidate the available evidence and highlight the need for further research. We appreciate your feedback and will consider adding further discussion on this matter to emphasize the preliminary nature of our findings and to underscore the need for more comprehensive studies in the future. We have also improved the discussion of the limitations of our analysis. (see details in Page 15-16, Line 295-304) in the tracked version of the manuscript.

Change in the text 9:

Our study has several limitations. Firstly, the study was based on a relatively small dataset comprising only six studies. Thus, it is difficult to identify more pneumonia-specific risks factors, especially from prospective cohorts. Secondly, the primary studies did not contain relevant data, such as clinical manifestations, laboratory metrics, or thromboprophylaxis details, due to their absence or inadequacy. Thirdly, our analysis did not have enough specificity as we were unable to perform subgroup analyses based on the severity of pneumonia due to insufficient data. Given these constraints, there is an urgent requirement for more multicenter, well-designed original studies with superior rigor and breadth to validate and potentially enhance our results.

Reviewer D

Comment 1: *Given the limited number of included studies, this paper mostly confirms previous findings and does not add much to the available literature. For instance, cancer and MV are known risk factors for TE, independently of pneumonia. Authors should focus on pneumonia-specific factors. Moreover, antithrombotic prophylaxis should be taken into account when analyzing data.*

Reply 1: Thank you for your insightful comments and suggestions. We re-examined the data and supplementary files and added chronic obstructive pulmonary disease as a

risk factor that we thought might be relevant in this context. (see details in Page 12, Line 217-220) in the tracked version of the manuscript. While we have endeavored to include more potential pneumonia-specific risk factors, the included studies unfortunately did not highlight other distinctive factors unique to pneumonia patients. We also have approached the authors of the included studies to obtain more detailed information on antithrombotic prophylaxis. Unfortunately, we were unable to obtain extensive data on anticoagulant therapy. We suspect this is partly due to a considerable percentage of patients being severely ill and at high risk of bleeding after anticoagulation, and therefore not receiving antithrombotic prophylaxis. We really appreciate your feedback and feel it's important to highlight these preliminary findings and gaps in the literature, so that future research can target these areas more specifically. So, we have emphasized these points in our revised manuscript to provide more clarity to our readers and to further contextualize our findings within the broader literature. (see details in Page 15-16, Line 295-304) in the tracked version of the manuscript.

Change in the text 1:

Chronic obstructive pulmonary disease Three studies examined the relationship between chronic obstructive pulmonary disease (COPD) and the risk of PE. The combined results revealed a notably elevated rate of DVT in patients with COPD (OR=4.73, 95%CI: 3.11-7.17, P<0.001; Figure 4E).

Our study has several limitations. Firstly, the study was based on a relatively small dataset comprising only six studies. Thus, it is difficult to identify more pneumonia-specific risks factors, especially from prospective cohorts. Secondly, the primary studies did not contain relevant data, such as clinical manifestations, laboratory metrics, or thromboprophylaxis details, due to their absence or inadequacy. Thirdly, our analysis did not have enough specificity as we were unable to perform subgroup analyses based on the severity of pneumonia due to insufficient data. Given these constraints, there is an urgent requirement for more multicenter, well-designed original studies with superior rigor and breadth to validate and potentially enhance our results.

Comment 2: *Figure 1 is missing and it is not clear (and neither it is in the text) the reason for excluding all but 6 studies. This should be made clear.*

Reply 2: We are very sorry for the mistakes in this manuscript and inconvenience they caused in your reading. Figure 1 is as follows and has been added to the manuscript. We excluded 33 reviews, 44 case reports, 1 animal trial, 126 studies related to COVID-19, 32 studies without risk factor analysis, and 59 articles for which data could not be obtained. (see details in Page 8-9, Line 148-151) in the tracked version of the manuscript.

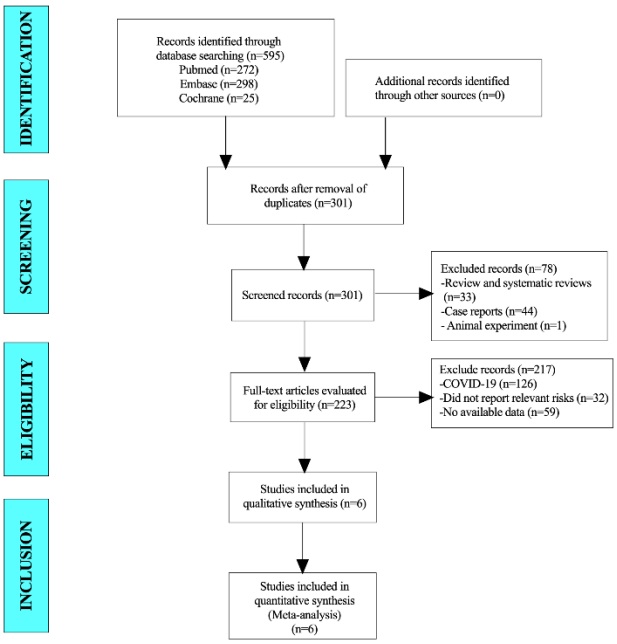

Figure 1

Change in the text 2: After reviewing the full-text, we excluded studies that reported on COVID-19, lacked risk factor analysis or had unavailable data. Finally, 6 studies(16-21) were included in the final analysis according to the inclusion and exclusion criteria. The process and the results of the literature screening are shown in Figure 1.

Comment 3: *If possible, authors should try to increase the number of included studies, for example by contacting the corresponding authors and asking for*

unavailable/incomplete data.

Reply 3: Thank you for your suggestion. We conducted a second thorough literature search and screening, but regrettably, we did not find new studies that met our inclusion criteria. In addition, we contacted the authors of four articles with incomplete data to obtain a more comprehensive dataset. However, unfortunately, we did not receive any responses despite our efforts. We appreciate your valuable feedback and have taken all necessary measures to ensure the comprehensiveness and precision of our analysis within the limitations of the data available. (see details in Page 15-16, Line 295-304) in the tracked version of the manuscript.

Change in the text 3:

Our study has several limitations. Firstly, the study was based on a relatively small dataset comprising only six studies. Thus, it is difficult to identify more pneumonia-specific risks factors, especially from prospective cohorts. Secondly, the primary studies did not contain relevant data, such as clinical manifestations, laboratory metrics, or thromboprophylaxis details, due to their absence or inadequacy. Thirdly, our analysis did not have enough specificity as we were unable to perform subgroup analyses based on the severity of pneumonia due to insufficient data. Given these constraints, there is an urgent requirement for more multicenter, well-designed original studies with superior rigor and breadth to validate and potentially enhance our results.

Comment 4: *The risk of bias assessment should be detailed.*

Reply 4: Thank you for pointing this out. We recognize the importance of a comprehensive bias assessment beyond just publication bias. But in our manuscript, given that there were no more than 5 articles included in our study for each risk factor, conventional tests for publication bias (e.g., funnel plots or Egger's test) might not be appropriate or reliable. Numerous guidelines and methodological papers have suggested that tests for publication bias become less reliable with fewer studies,

typically recommending at least 10 studies for meaningful assessment. Thus, due to the limited number of articles that met our inclusion criteria, we believed that it wasn't necessary or statistically sound to conduct a publication bias test. We have clarified this point in our revised manuscript to ensure our rationale is well-understood. (See details in Page 8, Line 140-142) in the tracked version of the manuscript.

Change in the text 4:

Since there were no more than 5 articles in the study for each indicator, no publication bias detection was carried out in this study.

Comment 5: *English editing is recommended.*

Reply 5: Thanks for your kind suggestions. We have improved the manuscript, and made corresponding revisions including some typos, grammatical errors, and long sentences, etc. In addition, the expression of the manuscript has been improved with the help of a native English speaker.

Change in the text 5: See details in the tracked version of the manuscript.

Reviewer E

Comment 1: *I found the manuscript entitled: "Risk factors for venous thromboembolism in patients with pneumonia in the pre-COVID-19 era: a meta-analysis and systemic review" very interesting. The authors have performed a systematic review of the literature on a very clinically relevant topic. The paper is methodologically sound and its conclusions can be applied to everyday clinical practice.*

Reply 1: We appreciate the reviewer's positive evaluation of our work.

Change in the text 1: NONE.

Comment 2: *In subsection: "Baseline characteristics of the included studies" the third sentence is unintelligible - it should be rephrased.*

Reply 2: Thanks for your careful review and kind suggestion. We agree with the comment and re-wrote the sentence in the revised manuscript. (See details in Page 9, Line 156-162) in the tracked version of the manuscript.

Change in the text 2:

A total of six studies were included in this meta-analysis, consisting of two case-control studies(20,21) and four cohort studies(16-19), with a total sample size of 162,011 patients. Among these studies, four were conducted in Asia(16,18,20,21), while the remaining two were conducted in Europe(17) and America(19). Two studies focused on both DVT and PE with a total of 79548 patients, two research specifically investigated on DVT with a total of 595 patients, while the remaining two studies focused solely on PE with a total of 2,458 patients (Table 1).