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

Cardiovascular Revascularization Medicine 31 (2021) 34–40

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Does Pulmonary Embolism in Critically Ill COVID-19 Patients Worsen the In-Hospital Mortality: A Meta-Analysis

Tanveer Mir [a,*], Hassan Bin Attique [b], Yasar Sattar [c], Neelambuj Regmi [d], Muhammad Shayan Khan [e], Haris Youns [a], Basharat Qayoom [f], Michael T. Jerger [d], M. Chadi Alraies [g]

[a] Internal Medicine Detroit Medical Center, Wayne State University, Detroit, USA
[b] Internal Medicine, University of Connecticut, Farmington, USA
[c] Icahn School of Medicine at Mount Sinai Elmhurst Hospital, New York, USA
[d] Department of Pulmonary and Critical Care, Detroit Medical Center/Wayne State University, USA
[e] Mercy Saint Vincent Medical Centre, Toledo, OH, USA
[f] Government Medical College, Srinagar, India
[g] Detroit Medical Center, Detroit, MI, USA

ARTICLE INFO

Article history:
Received 9 October 2020
Received in revised form 18 November 2020
Accepted 23 November 2020

Keywords:
Coronavirus
Pulmonary embolism
Critically ill patients

ABSTRACT

Background: Mortality in critically ill COVID (coronavirus disease) patients secondary to pulmonary embolism (PE) has conflicting data. We aim to evaluate the mortality outcomes of critically ill patients with and without PE (WPE).

Methods: Three studies were identified after a digital database search on PE in ICU (intensive care unit) patients until September 2020. The primary outcome was mortality. Outcomes were compared using a random method odds ratio and confidence interval of 95%.

Results: A total of 439 patients were included in the study. Diabetes, hypertension, and renal replacement requirement had no statistically significant association between PE and WPE, $p = 0.39$, $p = 0.23$, and $p = 0.29$ respectively. The study revealed that males have higher odds of PE, OR-1.98, 95%CI-1.01-3.89; $p = 0.05$. In-hospital mortality results were comparable between PE and WPE after subgroup analysis and correction of heterogeneity, $p = 0.25$.

Conclusion: PE in critically ill COVID patients had similar in-hospital mortality outcomes as WPE patients. The findings are only hypotheses generated from observational studies and need future randomized, prospective clinical trials for a definitive conclusion.

1. Introduction

Coronavirus, the pandemic infected worldwide with clinical presentations from asymptomatic cases to severe respiratory distress, multi-organ dysfunction, and death [1]. Respiratory distress secondary to COVID-19 in critically ill patients is multifactorial. The pulmonary causes of respiratory distress in a critically ill patient can be secondary to acute respiratory distress syndrome (ARDS) or ventilation-perfusion mismatch in lungs [2,3]. Cardiac causes of hypoxia, from pulmonary edema, can be secondary to multiple coronaviruses-related cardiac injuries including myocarditis, arrhythmias, stress-induced cardiomyopathy, and myocardial ischemia [4]. COVID-19 related ARDS have distinct features, despite meeting the Berlin definition of ARDS, of relatively well-preserved lung mechanics and severity of hypoxemia [3]. Pulmonary embolism worsens the ventilation-perfusion mismatch and hypoxia [5]. Coronavirus patients are at a high risk of venous thromboembolism, including pulmonary embolism, which can worsen ventilation-perfusion mismatch and hence hypoxia. The prevalence of pulmonary embolism in critically ill patients has been reported from 15% to 28.57%. COVID being a procoagulant state, cases of venous thromboembolism have been reported even if the patients were on prophylactic or therapeutic anticoagulation. A meta-analysis by Hasan et al. reported a prevalence of venous thromboembolism in critically ill patients of 31% and the patients were either on prophylactic or therapeutic anticoagulation [6]. The prevalence of PE in critically ill COVID patients has been reported higher than COVID patients not admitted to intensive care units [7]. There are conflicting results on mortality in critically ill COVID patients with and without pulmonary embolism. Since pulmonary embolism has a high prevalence in critically ill COVID patients and PE would worsen hypoxia in such critically ill patients with COVID ARDS, we aimed to do a database search to evaluate the pulmonary embolism outcomes and association of any comorbidity with PE in critically ill COVID patients admitted to ICU.

* Corresponding author at: Detroit Medical Center, Wayne State University, 4201 St Antoine St, Suite 2E, Detroit, MI 48201, USA.
E-mail address: gr6723@wayne.edu (T. Mir).

https://doi.org/10.1016/j.carrev.2020.11.024
1553-8389/

2. Method

2.1. Search strategy

Electronic databases, including MEDLINE (PubMed, Ovid), google scholar, and clinicaltrial.org, were searched using a combination of medical subject headings and key terms like "Pulmonary embolism," "critically ill," "COVID patients." A cross-reference check of previously published articles on this topic was also performed. For eligibility of studies, the search was restricted to English literature published from the inception of the database till September 2020. Studies with a patient population of >18 years of age with coronavirus, admitted to ICU, with and without pulmonary embolism were searched with the search keywords. Inclusion criteria of the studies were checked as per the relevance to the question of the study. Studies with no control group, insufficient data, case reports, duplicate data, conference papers, and review articles were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed to obtain studies for quantitative analysis (Fig. 1). All studies included had chest pulmonary angiography given poorly explained worsening in pulmonary or circulatory dynamics with worsening of ventilator settings.

2.2. Data extraction

Articles were screened at the level of title and abstract. The full text of potentially relevant articles was read by two independent authors. Disagreements were resolved by consensus. All extracted data from the included studies were collected into a spreadsheet and verified by a third author. Data was collected for 1) baseline characteristics: age, sex, baseline comorbidities; 2) Presence of PE, need for renal replacement therapy and use of neuromuscular blockers; 3) Primary outcome measures including mortality. The secondary outcomes were an association of diabetes, hypertension, male sex, renal replacement, and neuromuscular blocker use with pulmonary embolism in critically ill COVID patients.

2.3. Data analysis

The statistical analysis was performed using the Cochran-Mantel-Haenszel method under the random-effects model to calculate the unadjusted odds ratio (OR) for the primary and secondary endpoints. The estimated effect size was reported as a point estimate and 95% confidence interval (CI). An alpha criterion of p-value ≤0.05 was considered statistically significant. Higgins's I-squared (I^2) statistical model was used to evaluate variations in outcomes of included studies. I^2 values of 50% or less corresponded to low to moderate, and 75% or higher indicated large amounts of heterogeneity. All statistical analysis was performed using the Cochrane Review Manager version 5.3.

2.4. Quality of the included studies

The overall quality of the included studies was moderate. Two included studies were retrospective in nature, posing some theoretical risk of selection bias due to incomplete randomization and inadequate allocation concealment. However, one was a posthoc analysis from a prospective study. Reporting bias across all studies was reduced due to an adequate description of the study results (Fig. 2a, b).

3. Results

3.1. Search results and study characteristics

An initial search on multiple databases identified 187 articles, after exclusion of duplicates (50) and irrelevant (92) articles, 45 studies deemed relevant for full-text review. 42 articles were excluded due to insufficient data, case series, data comparison in noncritical patients. 3 studies finally qualified for quantitative analysis (Fig. 1).

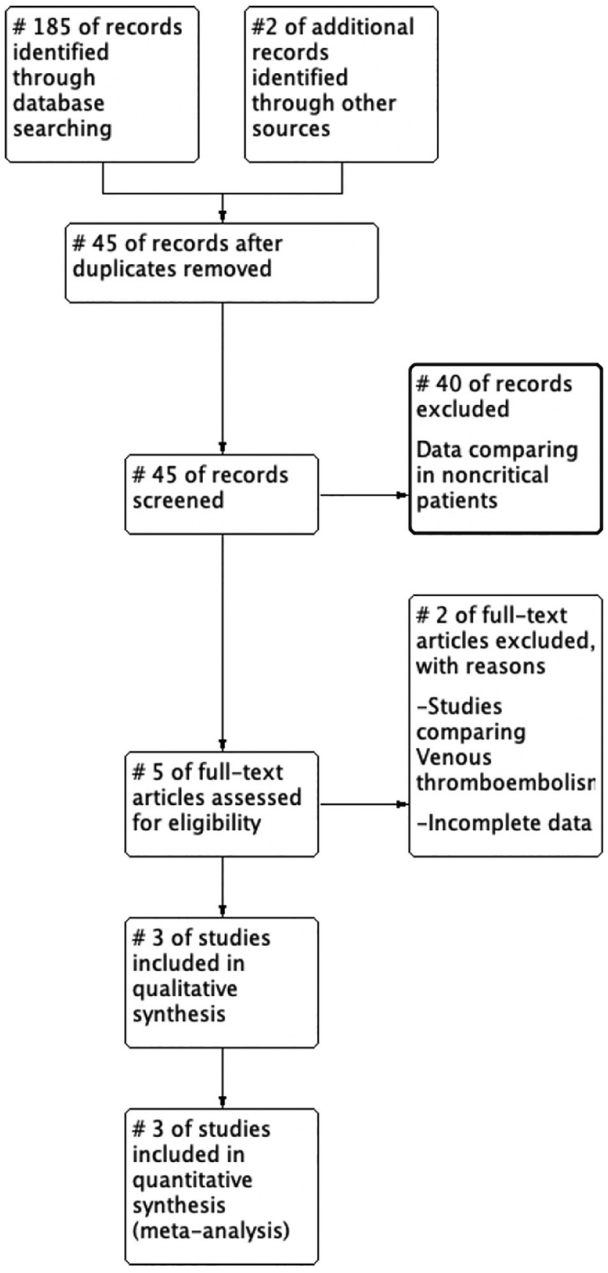


Fig. 1. PRISMA flow chart for selection of studies.

The included studies recruited a total of 439 patients: (PE 82 and WPE 357). The mean age of the included population was 63.3 ± 3.43 years for the WPE group and 60.67 ± 3.43 years for the PE group, comprising mostly of male patients (77%). The mean proportion of baseline characteristics of patients with and without PE included diabetes mellitus (23.17% vs. 26.61%), hypertension (54.88% vs 59.94%), respectively. The renal replacement was required in 29.26% in PE vs. 19.88% of WPE patients. Neuromuscular blocking agents were used in 92.75% of PE patients vs. 83.63% WPE. The baseline characteristics including comorbidities are given in Table 1.

3.2. Pooled results

Diabetes was studied in 439 patients. Diabetes had no relation with PE in critically ill COVID patients, OR 0.77, 95%CI = 0.42–1.41; $p = 0.39$

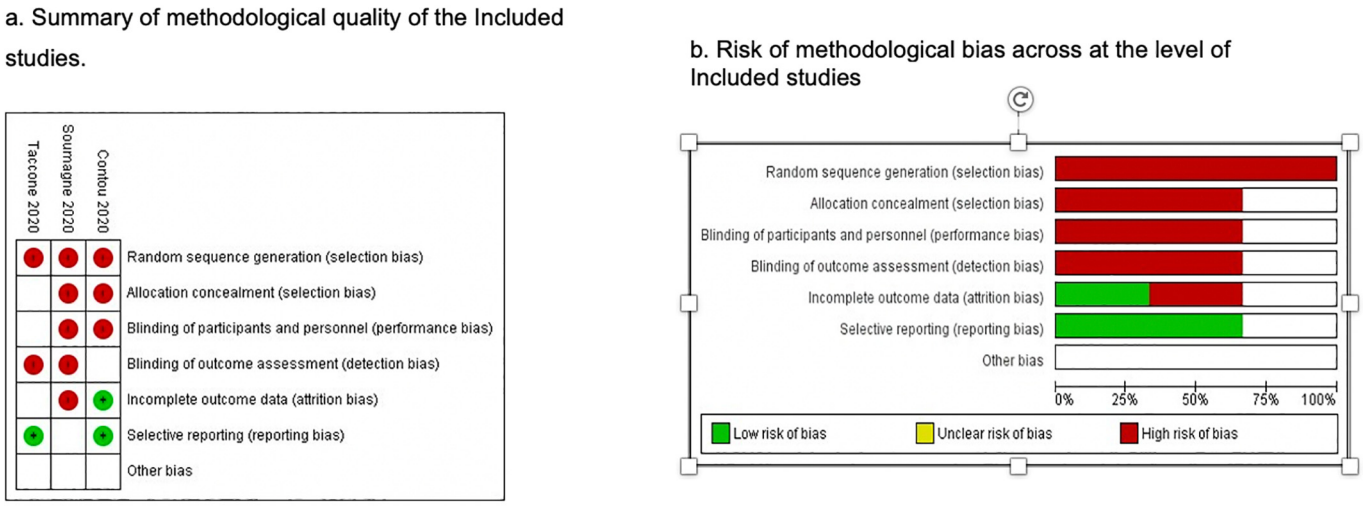


Fig. 2. a. Summary of methodological quality of the included studies. b. Risk of methodological bias across at the level of included studies.

(Heterogeneity 0%) (Fig. 3a). Hypertension was studied in 439 patients and did not show any association with PE, OR-0.73, 95%CI-0.44-1.22; $p = 0.23$ (Fig. 3b). Male sex was more associated with PE in critically ill COVID patients, OR-1.98, 95%CI-1.01-3.89; $p = 0.05$ (Heterogeneity 0%) (Fig. 3c). Renal replacement therapy had comparable results for PE and WPE, OR = 1.37, 95%CI-0.77-2.45; $p = 0.29$. The heterogeneity of the test was 0% (Fig. 4a). Neuromuscular blocker use had comparable results between the PE and WPE group with OR of 1.39, 95%CI 0.60–3.24; $p = 0.44$ (Fig. 4b).

3.3. Primary outcome

The overall mortality was with higher Odds for PE than WPE (OR = 1.54) with $p < 0.05$, however, without statistical significance; 95%CI = 0.36–6.61, and heterogeneity of the test was 75%. A subgroup analysis was done given high heterogeneity. After excluding Contou et al., mortality results were comparable for PE and WPE group [OR = 0.72, 95% CI = 0.41–1.26; $p = 0.25$]. The heterogeneity of the test was 0% (Fig. 5).

3.4. Publication bias

The publication bias was illustrated graphically with funnel plotting. The vertical axis of the plot used standard error to estimate the sample size of the study, plotting large population studies on top and smaller at the bottom. The horizontal spread reflected the power and effect size of the included studies. On visual assessment, our funnel plot was symmetrical, indicating that the limited scatter was due to sampling variation and not publication bias; Fig. 6.

4. Discussion

Our study revealed a higher prevalence of pulmonary embolism in male patients admitted with severe COVID to ICU. The study did not reveal any association between comorbidities like diabetes, hypertension with pulmonary embolism, $p = 0.39$, and $p = 0.23$ respectively. The requirement for renal replacement therapy was comparable between the two groups, $p = 0.29$. Interestingly the pulmonary embolism did not result in the overall worsening of mortality in critically ill COVID patients who had PE than patients who did not had a pulmonary embolism ($p = 0.25$).

Contou et al., in their retrospective study on 92 critically ill patients with ARDS, 26 underwent chest pulmonary angiography, and 16 were positive, 61.53% of screened patients (17% of the total number). PE was bilateral in 3 patients and unilateral in 13. Higher mortality was reported in patients with PE with $p = 0.04$ [8]. Taccone et al., studied 49 critically ill intensive care unit (ICU) admitted patients with severe hypoxia who underwent chest pulmonary angiography. The study concluded that 15% of ICU admitted patients develop PE. However, mortality results were not statistically significant [2]. Soumagne et al., in their post hoc study, reported the prevalence of 15% in critically ill patients admitted to ICU who were on mechanical ventilation. PE increased the duration of mechanical ventilation than patients without PE [9].

The major limitation of all these studies was the inclusion of the smaller scale population and being relatively underpowered to assess the mortality outcomes in critically ill patients with PE.

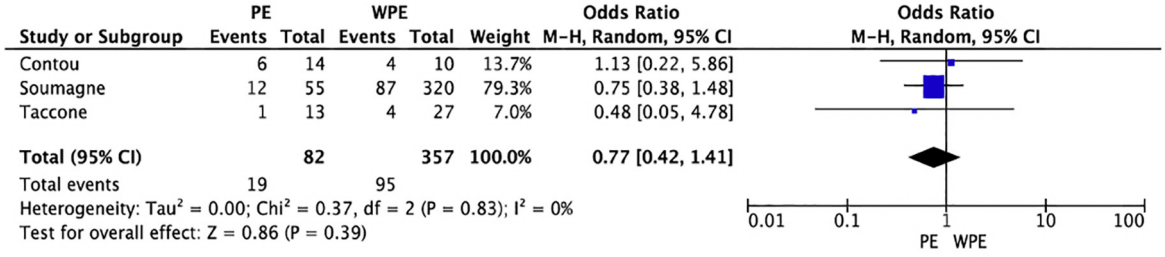
COVID is a hypercoagulable state caused by vascular endothelial damage [10]. All patients included in this meta-analysis were on antithrombotics, either prophylactic or therapeutic. Venous thromboembolism was reported in patients despite being on antithrombotics, however, rates were less in patients on higher doses of antithrombotics [2,8,9]. Klok et al. reported a high prevalence of thrombotic complications in critically ill COVID patients, 31% (95% confidence interval [95% CI] 20–41%), with PE being the predominant one, 87% [11]. They reported higher results of all-cause mortality in patients with thrombotic complications. Our study did not reveal any statistically significant difference in mortality for patients who had PE than patients without PE in critically ill COVID patients ($p = 0.25$).

Thromboprophylaxis in critically ill COVID patients would decrease the incidence of venous thromboembolism. There are no uniform anticoagulation guidelines for anticoagulation prophylaxis among different societies worldwide. American College of Cardiology recommends Enoxaparin 40 mg daily or equivalent doses of low molecular weight heparin (LMWH) can be administered with consideration of

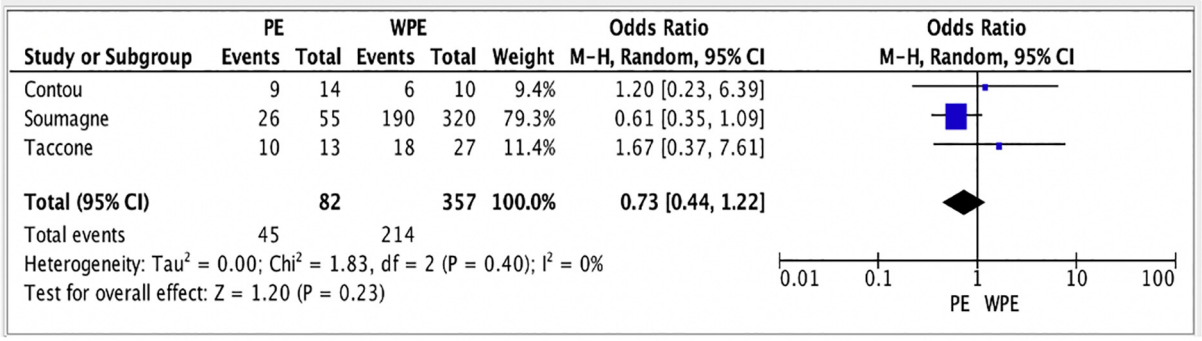
Table 1
Baseline characteristics of individual studies.

Study	Year	n PE/WPE	Diabetes PE/WPE	Male PE/WPE	Hypertension PE/WPE	Age PE
Contou	2020	14/10	06/04	14/8	09/06	63/63
Soumagne	2020	55/320	12/87	46/242	26/190	61. ± 9.1/63.9 ± 10.3
Taccone	2020	13/27	01/04	17/10	10/18	58/63

a. Forest plot comparing diabetes for PE and WPE. The odds of association of diabetes were comparable between the two groups.



b. Forest plot comparing Hypertension for PE and WPE. The odds of association of hypertension were comparable between the two groups.



c. Forest plot comparing sex distribution for PE and WPE. The odds of association of PE with male sex in critically ill COVID patients is higher and statistically significant than WPE.

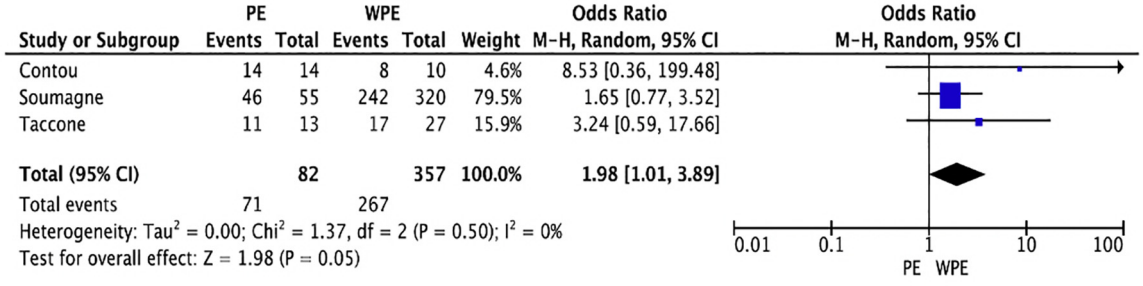


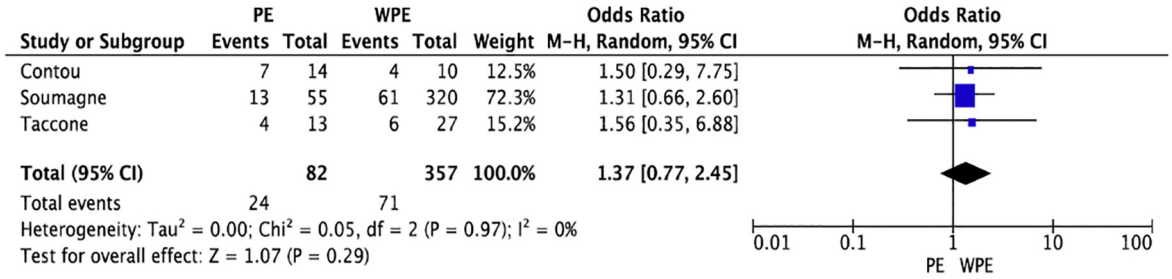
Fig. 3. a. Forest plot comparing diabetes for PE and WPE. The odds of association of diabetes were comparable between the two groups. b. Forest plot comparing Hypertension for PE and WPE. The odds of association with hypertension were comparable between the two groups. c. Forest plot comparing sex distribution for PE and WPE. The odds of association of PE with male sex in critically ill COVID patients are higher and statistically significant than WPE.

SC(subcutaneous) heparin (5000 U twice to three times per day) in patients with creatinine clearance <30 mL/min [12]. Anticoagulation forum has recommended high dose venous thromboprophylaxis for critically ill patients (LMWH 40 mg SC twice daily, LMWH 0.5 mg/kg subcutaneous twice daily, heparin 7500 SC three times daily, or low-intensity heparin infusion) [13]. Currently, there are no randomized controlled trials on in-hospital outcomes of with and without PE in critically ill COVID patients. However, randomized trials on the evaluation of the appropriate anticoagulation in COVID critically ill patients are under study which could better explain the prophylactic and therapeutic anticoagulation guidelines for critically ill COVID patients.

4.1. Limitations

Our study is constrained by the limitations of the included studies. A significant barrier was our inability to perform a stratified subgroup analysis based on the different selection criteria. The inherent heterogeneity in the observational and posthoc data limits our ability to draw

a. Forest plot comparing renal replacement therapy (RRT) for PE and WPE. The odds of association of RRT were comparable between the two groups.



b. Forest plot comparing Neuromuscular block use (NMB) for PE and WPE. The odds of association of NMB use were comparable between the two groups.

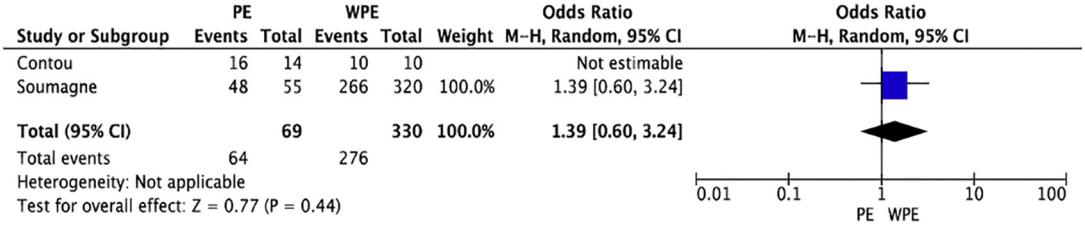


Fig. 4. a. Forest plot comparing renal replacement therapy (RRT) for PE and WPE. The odds of association of RRT were comparable between the two groups. b. Forest plot comparing neuromuscular block use (NMB) for PE and WPE. The odds of association of NMB use were comparable between the two groups.

definitive conclusions about the outcomes and associations of PE in critically ill COVID patients. The predictive odds of all the components could not be calculated due to insufficient reporting of the stratified event rates.

5. Conclusion

In conclusion, PE is a highly prevalent complication in critically ill COVID patients. The prevalence of PE is higher in critically ill male patients; however, overall mortality is comparable between PE and WPE patients. The unavailability of randomized data calls for caution when interpreting the results of this meta-analysis. Future RCTs with larger patient populations might provide data to allow for more robust results and help to eventually reach a definitive conclusion.

CRediT authorship contribution statement

- Tanveer Mir contributed to concept and design of the manuscript including the acquisition, analysis and interpretation of data as primary and corresponding author. TM also revised the work critically including the final version and agreed to be accountable for all aspects of the work.
- Hassan Bin Attique had substantial contributions to the conception or design of the work, provided the majority of images and drafted the work critically including the final version and agreed to be accountable for all aspects of the work. Also he had a major contribution in evaluation of quality of the studies included in the meta-analysis.
- Yasar Sattar contributed to the analysis of cases including drafting the work for important intellectual content and final approval and agreed to be accountable for all aspects of the work.
- Neelambuj Regmi had significant contribution to the concept, the acquisition, analysis and interpretation of data for the work, drafted the work including the images and revised the final version of the manuscript to be published and agreed to be accountable for all aspects of the work.
- Muhammad Shayan Khan had substantial contributions to the conception or design of the work, provided the majority of images and drafted the work critically including the final version and agreed to be accountable for all aspects of the work.
- Haris Youns had substantial contributions to the conception or design of the work, provided the majority of images and drafted the work critically including the final version and agreed to be accountable for all aspects of the work.
- Basharat Qayoom contributed to the analysis of cases including drafting the work for important intellectual content and final approval and agreed to be accountable for all aspects of the work.
- Michael T. Jerger contributed to the analysis of cases including drafting the work for important intellectual content and final approval and agreed to be accountable for all aspects of the work. He mentored

Forest plot comparing mortality outcomes for PE and WPE. Results were comparable between the two groups.

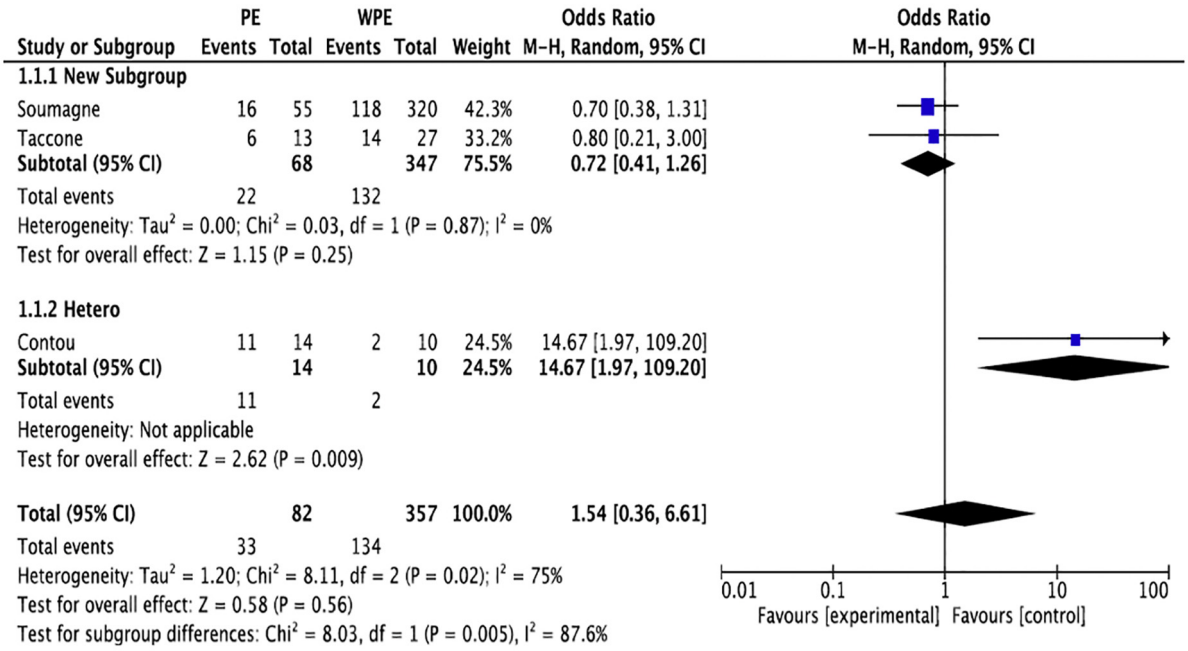


Fig. 5. Forest plot comparing mortality outcomes for PE and WPE. The results were comparable between the two groups.

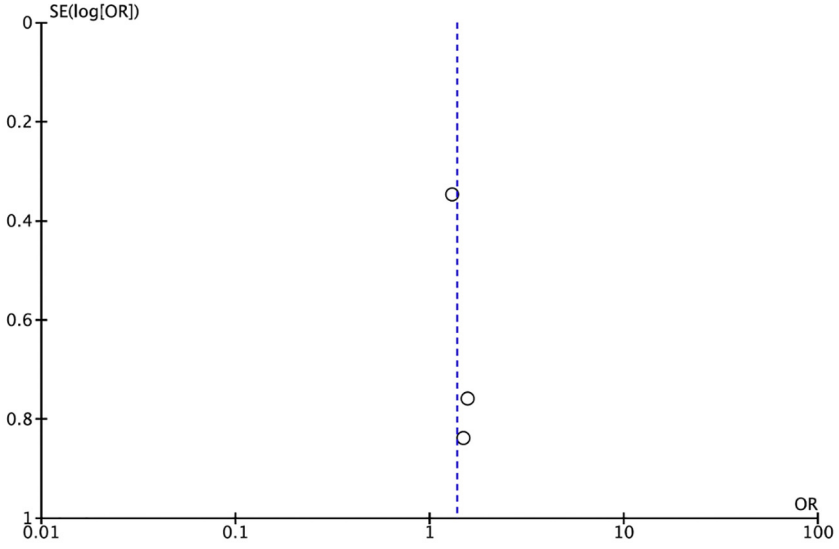


Fig. 6. Funnel plot for publication bias. No significant scatter is visible.

during the whole process.

- M Chadi Alraies had significant contribution to the concept, the acquisition, analysis and interpretation of data for the work, drafted the work including the images and revised the final version of the manuscript to be published and agreed to be accountable for all aspects of the work. He mentored during the whole process as lead mentor.

Declaration of competing interest

None. No funding was required for the project.

References

[1] Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514–23.
[2] Taccone FS, Gevenois PA, Peluso L, Pletchette Z, Lheureux O, Brasseur A, et al. Higher intensity thromboprophylaxis regimens and pulmonary embolism in critically Ill coronavirus disease 2019 patients. Crit Care Med. 2020;48:e1087–90.
[3] Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not Lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201(10):1299–300.
[4] Sattar Y, Ullah W, Rauf H, Virk HUH, Yadav S, Chowdhury M, et al. COVID-19 cardiovascular epidemiology, cellular pathogenesis, clinical manifestations and management. Int J Cardiol Heart Vasc. 2020;29:100589.

[5] Morrone D, Morrone V. Acute pulmonary embolism: focus on the clinical picture. Korean Circ J. 2018;48(5):365–81.
[6] Hasan SS, Radford S, Kow CS, Zaidi STR. Venous thromboembolism in critically ill COVID-19 patients receiving prophylactic or therapeutic anticoagulation: a systematic review and meta-analysis. J Thromb Thrombolysis. 2020;50:814–21.
[7] Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. Circulation. 2020;142(2):184–6.
[8] Contou D, Pajot O, Cally R, Logre E, Fraissé M, Mentec H, et al. Pulmonary embolism or thrombosis in ARDS COVID-19 patients: a French monocenter retrospective study. PLoS One. 2020;15(8):e0238413.
[9] Soumagne T, Lascarrou JB, Hraiech S, Horlait G, Higny J, d'Hondt A, et al. Factors associated with pulmonary embolism among coronavirus disease 2019 acute respiratory distress syndrome: a multicenter study among 375 patients. Crit Care Explor. 2020;2(7):e0166.
[10] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J. 2020;41(32):3038–44.
[11] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res. 2020;191:148–50.
[12] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(23):2950–73.
[13] Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis. 2020;1.