**Venous thromboembolism is linked to severity of disease in COVID-19 patients: A systematic literature review and exploratory meta-analysis**

Rashmi Srivastavaa, Rizwana Parveena, Pinki Mishraa, Nilanjan Sahaa, Ram Bajpaib, Nidhi Bharal Agarwala

aCentre for Translational and Clinical Research, School of Chemical & Life Sciences, Jamia Hamdard, New Delhi-110062, India.

b School of Primary, Community and Social Care, Keele University, Staffordshine, UK

Corresponding author

Nidhi Bharal Agarwal

Centre for Translational and Clinical Research

School of Chemical & Life Sciences

Jamia Hamdard

New Delhi-110062, India

Phone: +91-9818334770

E-mail address: nidhi.bharal@gmail.com

**Abstract**

Purpose**:** Coronavirus disease-2019 (COVID-19) may predispose to venous thromboembolism (VTE) and arterial thromboembolism due to excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation. The understanding of the association might be helpful in early vigilant monitoring and better management of COVID-19 patients at a high risk. Thus, in this meta-analysis we aim to assess the association of venous thromboembolism with severity of COVID-19 disease.

Methods: A literature search was conducted on PubMed and Cochrane Central Register of Controlled Trials using the keywords “COVID-19 and thromboembolism” and “COVID-19 and embolism”, till 20 February 2021. Thirteen studies including 6648 COVID-19 patients were incorporated in this systematic review and exploratory meta- analysis.

Results: The analysis revealed nearly three times more risk of intensive care unit (ICU) care in patients with venous thromboembolism (VTE) compared to non-VTE patients (RR: 2.78; 95% CI: 1.75- 4.39; p <0.001; *I2:* 65.1 %). Patients with pulmonary embolism and deep vein thrombosis are at increased risk of being admitted to ICU (RR: 2.21; 95% CI: 1.86-2.61; p<0.001; *I2:*41.2%) and (RR: 2.69; 95 % CI: 2.37-3.06; p <0.001; *I2*: 0.0 %), respectively. The quality assessment indicated that the included studies were of fair quality.

Conclusions: Our findings suggest that venous thromboembolism either deep vein thrombosis or pulmonary embolism may have a negative effect on the health status of COVID-19 patients. The study highlights the need to consider measures for reducing thromboembolism risk among COVID-19 patients.

Keywords: COVID-19, venous thromboembolism, deep vein thrombosis, pulmonary embolism, SARS-CoV-2

**Review criteria:**

* We conducted a systematic review and meta-analysis of the studies describing the incidence of venous thromboembolism in COVID-19 patients requiring ICU care.
* We searched PUBMED and Cochrane Central Register of Controlled Trials using the keywords “COVID-19 and thromboembolism” and “COVID-19 and embolism” till 20 February 2021.
* We pooled dichotomous outcomes as risk ratios and continuous outcomes as mean differences with 95% confidence intervals, both under the random- or fixed-effects model.

**Message for the clinic:**

* The study highlights the need to consider measures for reducing thromboembolism risk among COVID-19 patients.
* Precise knowledge of the incidence of thrombotic complications in COVID-19 patients is important for decision making with regard to intensity of thromboprophylaxis.
* The understanding of the association might be helpful in early vigilant monitoring and better management of COVID-19 patients at a high risk.

1. **Introduction**

Coronavirus disease-2019 (COVID-19), a viral illness caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can lead to coagulation dysfunction in patients with severe COVID-19 infection 1. Venous thromboembolism (VTE) is a recurrent complication in COVID-19 patients 2 and results in poor prognosis 1. COVID-19 may predispose to both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation 3–6. Many of the hospitalized COVID-19 patients are elderly, suffering from severe infectious illness and are immobile in an intensive care unit (ICU) setting. Therefore, a relatively high incidence of venous thromboembolism among patients diagnosed with COVID-19 is expected due to the severity of their disease and distinctive risk factors 7.

However, so far there have been only few studies describing venous thromboembolism either deep vein thrombosis or pulmonary embolism in patients with COVID-19 infection 8–11. A high incidence of venous thromboembolism in COVID-19 patients has been reported in various studies 1,12–14. A retrospective study reported high prevalence of deep vein thrombosis and associated adverse outcomes in COVID-19 patients 15. Another prospective study demonstrated very high incidence of deep vein thrombosis in COVID-19 patients requiring ICU admission 16. A cohort study observed a high risk for venous thromboembolism in COVID-19 patients requiring ICU care 14.

Several studies have demonstrated higher incidence of venous thromboembolism in COVID-19 patients 1,14,17,18, however, the effect of the incidence of venous thromboembolism on prognosis of the disease needs further exploration. Precise knowledge of the incidence of thrombotic complications in COVID-19 patients is important for decision making with regard to intensity of thromboprophylaxis 13. The understanding of the association might be helpful for clinicians in early vigilant monitoring and better management of COVID-19 patients at a high risk. Thus, in the present exploratory meta-analysis we aimed to assess the association of venous thromboembolism with severity of disease in COVID-19 patients.

1. **Materials and methods**

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines extension for scoping reviews 19 was followed for designing and reporting this systematic literature review.

**2.1 Data sources and searches**

We searched PubMed and Cochrane Central Register of Controlled Trials until 20 February, 2021 using the keywords “COVID-19 and thromboembolism” and “COVID-19 and embolism”. Grey literature was searched on Clinical Trial Registry of India, Clinicaltrials.gov, Google Scholar and reference list of eligible articles.

**2.2 Inclusion and exclusion**

The studies describing the incidence of thromboembolism according to disease severity were included. We excluded duplicate publications, reviews, editorials, case reports, letters, meta-analysis, protocols, studies in language other than English and studies not reporting the required data. First author (RS) searched data and screened articles for eligibility. Senior author (RP) double checked all the included articles and any dispute was resolved by consensus.

**2.3 Quality assessment**

Two reviewers (RS and RP) assessed the quality of data in the included studies using the National Institute of Health (NIH) quality assessment tools developed by National Heart, Lung, and Blood Institute 20. We preferred the NIH tool because it is comprehensive and widely accepted for an exhaustive assessment of data quality. We rated the generalquality of included studies nearly as good, fair and poor, and incorporated them within theresult of meta-analysis.

**2.4 Data extraction**

Data was inputted into a standardized data extraction table (Excel) and independently checked by a second reviewer (RP) for accuracy. The following variables were extracted: name of the first author, year of publication, study design, age, gender, number of patients in ICU and non- ICU care with comorbidities as well as prognosis. The disease was considered severe if the patient with COVID-19 required ICU care.

**2.5 Data synthesis**

We performed an exploratory meta-analysis to understand the magnitude and direction of effect estimate. Relative risk (RRs) was calculated and presented with respective 95% confidence intervals (CIs). Mantel-Haenszel random-effects meta-analysis using DerSimonian and Laird method was used to pool RRs 21. Heterogeneity between studies was assessed using the *χ2*-based Cochran's Q statistic (p<0.1 considered as the presence of heterogeneity) and I-squared (*I2*) statistics (>50% representing moderate heterogeneity) 21. Forest plot was produced, and subgroup analysis was conducted according to study design. The 95% prediction interval (PI) was calculated which estimates the uncertainty bounds for a new study evaluating that same association by considering between-study heterogeneity. Publication bias was not assessed as total number of studies were less than ten for a given outcome 21. P-value <0.05 was set as statistical significance for comparing study level effects.

1. **Results**

**3.1 Search Results**

The systematic search yielded a total of 1607 publications. Out of 1607 studies, 920 studies were found using the keywords” COVID-19 and thromboembolism”, 686 studies with keywords “COVID-19 and embolism”. One study was found from the other source. After removing duplicates, 1200 articles were found to be potential publications for screening. After the application of predefined inclusion and exclusion criteria, a total of thirteen studies were included for the meta-analysis (Figure 1).

**3.2 Study characteristics**

The incidence of venous thromboembolism either deep vein thrombosis or pulmonary embolism was reported in ICU care and non-ICU care in twelve studies 12,14–17,22–28 and one study reported the incidence of venous thromboembolism either deep vein thrombosis or pulmonary embolism in survivors and non survivors group 1. Among the thirteen included studies, a total of 6648 patients were enrolled, including 3973 males and 2675 females. The baseline characteristics of the subjects included in these studies are provided in Table 1.

**3.3 Quality assessment**

We assessed the quality of data in the included studies using the NIH quality assessment tools. The quality assessment indicated that most of the included studies were of fair quality. All the studies clearly stated the research question or the objective, the study population was clearly specified and defined, all the subjects were selected from similar populations. The detailed result of the quality assessment is provided in *Supplementary file 1*.

**3.4 Association between venous thromboembolism and disease severity**

In order to assess the association between venous thromboembolism and disease severity, four cohort studies qualified for inclusion in quantitative analysis. The pooled estimate of four cohort studies with substantial heterogeneity revealed nearly three times more risk of ICU care requirement in patients with venous thromboembolism (VTE) compared to non-VTE patients (RR: 2.78; 95% CI: 1.75- 4.39; p<0.001; *I2:* 65.1 %) (Figure 2, Supplementary Figure 2). The mortality outcome was assessed in one retrospective study indicative of higher risk of VTE in ICU patients (RR: 50.19; 95% CI: 3.05- 832.75; p <0.001).

**3.5** **Association between pulmonary embolism and disease severity**

To assess the association between pulmonary embolism and disease severity, eight studies (four cohort and retrospective studies) qualified for inclusion in quantitative analysis. The pooled estimate of four cohort and retrospective studies with substantial heterogeneity study showed that patients with pulmonary embolism are at nearly three times increased risk of being admitted to ICU (RR: 2.21; 95% CI: 1.86-2.61; p<0.001; *I2:*41.2%) (Figure 2). The subgroup pooled analysis of four cohort studies demonstrated nearly two times higher risk of ICU care in patients with pulmonary embolism (RR: 1.97; 95% CI: 1.44-2.70; p<0.001; *I2:* 57.6 %) (Supplementary Figure 2). The subgroup pooled estimate of four retrospective studies highlighted that patients with pulmonary embolism are around three times higher risk of being admitted to ICU (RR: 2.39; 95 % CI: 1.91-2.99; p <0.001; *I2*: 37.8%) (Supplementary Figure 2).

**3.6** **Association between deep vein thrombosis and disease severity**

For the outcome, in order to assess the association between deep vein thrombosis and disease severity, five studies (three cohort studies and two retrospective studies) qualified for inclusion in quantitative analysis. The pooled estimate of three cohort and two retrospective studies demonstrated around three times higher risk of deep vein thrombosis in ICU patients (RR: 2.69; 95 % CI: 2.37-3.06; p <0.001; *I2*: 0.0 %) (Figure 2). The subgroup pooled analysis of three cohort studies highlighted higher risk of requiring ICU care in patients with deep vein thrombosis (RR: 2.57; 95 % CI: 1.53-4.30; p <0.001; *I2*: 30.7%) (Supplementary Figure 2). The subgroup pooled estimate of two retrospective studies showed that the need for ICU care was higher in patients with deep vein thrombosis (RR: 2.61; 95 % CI: 2.19-3.11; p <0.001; *I2*: 1.1%) (Supplementary Figure 2).

1. **Discussion**

Recent evidence on COVID-19 postulated that the high mortality observed among COVID-19 patients may be partly due to unrecognized pulmonary embolism and pulmonary in situ thrombosis 1,13. Several studies have demonstrated higher incidence of venous thromboembolism in COVID-19 patients, 17,18 however, the effect of the incidence of venous thromboembolism on severity of disease needs further exploration. Thus, the present meta-analysis was conducted to assess the association of venous thromboembolism either pulmonary embolism or deep vein thrombosis with disease severity in COVID-19 patients. The present meta-analysis demonstrated a high incidence of pulmonary embolism, deep vein thrombosis and venous thromboembolism in patients requiring ICU care.

The present meta-analysis demonstrated positive association between COVID-19 and incidence of pulmonary embolism in ICU patients. Whyte at al., performed a cohort study on 214 COVID-19 patients and revealed that the overall proportion of patients with pulmonary embolism was 5.4%, increasing to 16.2% in ICU patients. Pulmonary embolism was diagnosed in 3.5% patients receiving ward-based care. The higher incidence of pulmonary embolism in ICU patients is consistent with previous studies (16.7–47%) 28. A cohort study reported high incidence of pulmonary embolism in the critically ill COVID-19 patients, also it was found to be one of the major thrombotic complications in this study 13. Therefore, pulmonary thromboembolism may be considered in COVID-19 patients with sudden onset of oxygenation deterioration, respiratory distress, and reduced blood pressure as these patients are often immobile and present with an acute inflammatory state 29.

The present meta-analysis demonstrated positive association between COVID-19 ICU patients and deep vein thrombosis. A systematic literature review of four prospective studies conducted on patients requiring critical care reported the rate of objectively confirmed deep vein thrombosis which ranged from 13% to 31% and suggested a potential role for thromboprophylaxis in patients requiring critical care 30. A retrospective study reported 18.2 % incidence of deep vein thrombosis in COVID-19 ICU patients 15. Various cohort studies have reported 32 % 14, 13 % 16 and 4.1 % 25 incidence of deep vein thrombosis in COVID-19 ICU patients.

The present meta-analysis demonstrated positive association between COVID-19 ICU patients and venous thromboembolism. Malas et., al conducted a systematic review involving 8271 SARS-CoV-2 patients determining the overall incidence of VTE to be 21%. Among ICU patients the VTE rate was as high as 31%. Patients who developed VTE were at 74% increased odds of death compared to those who did not. 18 Collectively, several cohort studies have reported 47 % 14 and 8.3 % 25 incidence of venous thromboembolism in COVID-19 ICU patients. A retrospective study reported an incidence of 25 % of venous thromboembolism in COVID-19 hospitalized patients 1.

There are various mechanisms explaining the risk of venous thromboembolism either deep vein thrombosis or pulmonary embolism or both in COVID-19 patients. One such mechanism explains that the virus can bind to the endothelial cells via angiotensin 2 receptors, which are most commonly found in the alveolar epithelial cells, followed by endothelial cells – a process which may ultimately damage blood vessels and increase the risk of thrombogenicity 2. However, apart from the severe COVID-19 patients in ICUs, those hospitalized in hospital wards share common predisposing factors for venous thromboembolism, namely strict and long isolation and subsequently immobilization. Any severe infection can predispose to venous thromboembolism. However, it appears that in COVID-19 additional mechanisms might contribute to increased venous thromboembolism risk, including endothelial damage, microvascular thrombosis and occlusion, or even autoimmune mechanisms 31. Another mechanism explains that the abnormal expression of T cell associated mRNA can lead to venous thromboembolism 32. This meant that older patients with more underlying diseases were more likely to develop immune dysfunction and have a higher risk of venous thromboembolism because of their poor immunity 1.

There are several limitations worth mentioning. First, most studies included a relatively small number of cases with poor description of patient characteristics, which limited the possibility to explore the effects of concomitant risk factors on the incidence of VTE. Second, the lack of randomization and the little data provided on the incidence of VTE stratified by use, type, dose, and duration of anticoagulation (i.e. prophylactic, intermediate, or therapeutic dose) precluded subgroup analysis on the effects of pharmacological prophylaxis. Third, the nature of the data available in the individual studies did not allow the meta-analysis to be stratified by some clinically relevant variables such as thromboprophylaxis status, race, and healthcare access/quality to assess their effect on the incidence of VTE and mortality.

To conclude, our findings suggest that venous thromboembolism either deep vein thrombosis or pulmonary embolism may have a negative effect on the health status of COVID-19 patients. However, large incidence studies demonstrating the consequences of venous thromboembolism are urgently needed for decision making with regard to the intensity of thromboprophylaxis.

**Authorship:**

Conception and design- Rashmi and Rizwana; acquisition of data- Rashmi and Rizwana; analysis and interpretation of data- Pinki and Ram; drafting the manuscript- Rashmi and Pinki; revised manuscript critically for important intellectual content- Nilanjan and Nidhi; final approval of the version to be published- Nidhi and Rizwana; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved- Rashmi and Nidhi

**Acknowledgement:** None.

**Disclosures:**

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of Interest Statement:**

No potential conflicts of interest to declare in relation to this publication.

**REFERENCES**

1. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421-1424. doi:10.1111/jth.14830

2. Tal S, Spectre G, Kornowski R, Perl L. Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? *Acta Haematol*. Published online May 12, 2020:1-8. doi:10.1159/000508233

3. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. Published online March 26, 2020:m1091. doi:10.1136/bmj.m1091

4. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

5. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061. doi:10.1001/jama.2020.1585

6. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

7. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID‐19 patients: emerging evidence and call for action. *Br J Haematol*. 2020;189(5):846-847. doi:10.1111/bjh.16727

8. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020;41(19):1858. doi:10.1093/eurheartj/ehaa254

9. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089-1098. doi:10.1007/s00134-020-06062-x

10. Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med*. Published online May 6, 2020:M20-2003. doi:10.7326/M20-2003

11. Xie Y, Wang X, Yang P, Zhang S. COVID-19 Complicated by Acute Pulmonary Embolism. *Radiol Cardiothorac Imaging*. 2020;2(2):e200067. doi:10.1148/ryct.2020200067

12. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute Pulmonary Embolism Associated with COVID-19 Pneumonia Detected by Pulmonary CT Angiography. *Radiology*. Published online April 23, 2020:201544. doi:10.1148/radiol.2020201544

13. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147. doi:10.1016/j.thromres.2020.04.013

14. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID‐19. *J Thromb Haemost*. Published online May 5, 2020:jth.14888. doi:10.1111/jth.14888

15. Zhang L, Feng X, Zhang D, et al. Deep Vein Thrombosis in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19) in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation*. Published online May 18, 2020:CIRCULATIONAHA.120.046702. doi:10.1161/CIRCULATIONAHA.120.046702

16. Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res*. 2020;192:23-26. doi:10.1016/j.thromres.2020.05.018

17. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis*. 2020;50(1):211-216. doi:10.1007/s11239-020-02146-z

18. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine*. 2020;29:100639. doi:10.1016/j.eclinm.2020.100639

19. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467. doi:10.7326/M18-0850

20. NIH. Study Quality Assessment Tools. National Heart, Lung and Blood Institute. Accessed June 9, 2020. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

21. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. Accessed June 9, 2020. https://training.cochrane.org/handbook

22. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA*. 2020;324(8):799-801. doi:10.1001/jama.2020.13372

23. Fauvel C, Weizman O, Trimaille A, et al. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J*. 2020;41(32):3058-3068. doi:10.1093/eurheartj/ehaa500

24. Leonard-Lorant I, Delabranche X, Severac F, et al. Acute Pulmonary Embolism in COVID-19 Patients on CT Angiography and Relationship to D-Dimer Levels. *Radiology*. Published online April 23, 2020:201561. doi:10.1148/radiol.2020201561

25. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14. doi:10.1016/j.thromres.2020.04.024

26. Poyiadi N, Cormier P, Patel PY, et al. Acute Pulmonary Embolism and COVID-19. *Radiology*. Published online May 14, 2020:201955. doi:10.1148/radiol.2020201955

27. Trimaille A, Curtiaud A, Marchandot B, et al. Venous thromboembolism in non-critically ill patients with COVID-19 infection. *Thromb Res*. 2020;193:166-169. doi:10.1016/j.thromres.2020.07.033

28. Whyte MB, Kelly PA, Gonzalez E, Arya R, Roberts LN. Pulmonary embolism in hospitalised patients with COVID-19. *Thromb Res*. 2020;195:95-99. doi:10.1016/j.thromres.2020.07.025

29. Scialpi M, Scialpi S, Piscioli I, Battista Scalera G, Longo F. Pulmonary thromboembolism in critical ill COVID-19 patients. *Int J Infect Dis*. 2020;95:361-362. doi:10.1016/j.ijid.2020.04.056

30. Geerts W, Cook D, Selby R, Etchells E. Venous thromboembolism and its prevention in critical care. *J Crit Care*. 2002;17(2):95-104. doi:10.1053/jcrc.2002.33941

31. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. *N Engl J Med*. 2020;382(17):e38. doi:10.1056/NEJMc2007575

32. Duan Q, Gong Z, Song H, et al. Symptomatic Venous Thromboembolism Is a Disease Related to Infection and Immune Dysfunction. *Int J Med Sci*. 2012;9(6):453-461. doi:10.7150/ijms.4453

*Table-1 Baseline characteristics*

| **Author, year** | **Study Design** | **Age** | **No. of patients** | **Sex N (%)** | | **Prognosis** | | | | **Comorbidities N (%)** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **Males** | **Females** | **Discharged** | **Continued Hospitalization** | **Transferred to another Hospital** | **Death** |  |  |
| Middeldorp, 2020 | Cohort | 61 (14) | 198 | 130 (66) | 68 (34) | 136 (69) | 16 (8) | 8 (4) | 38 (19) | Active cancer | 7 (3.5) |
| Grillet, 2020 | Retrospective | 66 (13) | 100 | 70 | 30 | NA | NA | NA | NA | Cardiovascular Disease | 39 |
|  |  |  |  |  |  |  |  |  |  | Chronic Respiratory Insufficiency | 15 |
|  |  |  |  |  |  |  |  |  |  | T2DM | 20 |
|  |  |  |  |  |  |  |  |  |  | Malignancy | 20 |
| Zhang, 2020 | Retrospective | 63 (14) | 143 | 74 (51.71) | 69 (48.25) | 92 (64.3) | 19 (13.3) | NA | 32 (22.4) | HTN | 56 (39.2) |
|  |  |  |  |  |  |  |  |  |  | DM | 26 (18.2) |
|  |  |  |  |  |  |  |  |  |  | CAD | 17 (11.9) |
|  |  |  |  |  |  |  |  |  |  | Malignancy | 7 (4.9) |
|  |  |  |  |  |  |  |  |  |  | Cerebal Infarction | 5 (3.5) |
|  |  |  |  |  |  |  |  |  |  | Chronic Liver Disease | 5 (3.5) |
|  |  |  |  |  |  |  |  |  |  | CKD | 4 (2.8) |
| Lorant, 2020 | Retrospective | 64 (22) | 106 | 70 (66) | 36 (34) | NA | NA | NA | NA | NA |  |
| Demelo, 2020 | Cohort | 68.1 (14.5) | 156 | 102 (66) | 54 (34) | NA | NA | NA | NA | Active Cancer | 16 (10.3) |
| Lodigiani, 2020 | Cohort | 66 | 388 | 264 (68) | 124 (32) | NA | NA | NA | NA | HTN | 183 (47.2) |
|  |  |  |  |  |  |  |  |  |  | DM | 88 (22.7) |
|  |  |  |  |  |  |  |  |  |  | Dyslipidemia | 76 (19.6) |
|  |  |  |  |  |  |  |  |  |  | Chronic Renal Dysfunction | 61 (15.7) |
|  |  |  |  |  |  |  |  |  |  | Active Cancer | 25 (6.4) |
| Poyiadi, 2020 | Retrospective | 62 (16) | 328 | 148 (45) | 180 (55) | NA | NA | NA | NA | Cancer History | 14 |
|  |  |  |  |  |  |  |  |  |  | DM | 38 |
|  |  |  |  |  |  |  |  |  |  | HTN | 61 |
|  |  |  |  |  |  |  |  |  |  | COPD | 13 |
|  |  |  |  |  |  |  |  |  |  | CHF | 9 |
| Cui, 2020 | Retrospective | 59.9 | 81 | 37 (46) | 44 (54) | 9 (11) | 64 (79) |  | 8 (10) | HTN | 20 (25) |
|  |  |  |  |  |  |  |  |  |  | DM | 8 (10) |
|  |  |  |  |  |  |  |  |  |  | CHD | 10 (12) |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  | Coronary Heart Disease | 10 (12) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Bilalogu et al, 2020 | Retrospective Study | 64 | 3334 | 2014 (60.4) | 1320 (39.6) | NA | NA | NA | NA | Myocadial Infarction | 195 |
|  |  |  |  |  |  |  |  |  |  | Congestive Heart failure | 279 |
|  |  |  |  |  |  |  |  |  |  | HTN | 1676 |
|  |  |  |  |  |  |  |  |  |  | Diabetes | 1246 |
|  |  |  |  |  |  |  |  |  |  | Hyperlipidemia | 1285 |
|  |  |  |  |  |  |  |  |  |  | Coronary artery disease | 617 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Fauvel et al, 2020 | Cohort Study | 64 | 1240 | 721 (58.1) | 519 (41.9) | NA | NA | NA | 151 (12.2) | HTN | 559 (45.4) |
|  |  |  |  |  |  |  |  |  |  | Diabetes | 268 (21.7 |
|  |  |  |  |  |  |  |  |  |  | Dyslipidemia | 316 (25.6) |
|  |  |  |  |  |  |  |  |  |  | Cardiovascular disease | 19 (1.6) |
|  |  |  |  |  |  |  |  |  |  | COPD | 77 (6.2) |
|  |  |  |  |  |  |  |  |  |  | CKD | 126 (10.3) |
|  |  |  |  |  |  |  |  |  |  | Stroke | 94 (7.7) |
|  |  |  |  |  |  |  |  |  |  | Peripheral arterial disease | 60 (4.9) |
|  |  |  |  |  |  |  |  |  |  | Atrial fibrillation | 117 (9.5) |
|  |  |  |  |  |  |  |  |  |  | CHF | 117 (9.5) |
|  |  |  |  |  |  |  |  |  |  | CAD | 133 (10.7) |
|  |  |  |  |  |  |  |  |  |  | Malignancy | 167 (13.7) |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Trimaille et al, 2020 | Cohort Study | 62.2 | 289 | 171 (59.2) | 118 (40.8) | 236 (88.7) | NA | NA | 24 (8.3) | NA | NA |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Whyte et al, 2020 | Cohort Study | 63.5 | 214 | 129 | 85 | NA | 36 | NA | 31 | Malignancy | 16 |
|  |  |  |  |  |  |  |  |  |  | Haemoptysis | 12 |
| Artifoni et al, 2020 | Cohort Study | 64 | 71 | 43 (60.6) | 28 (39.4) | NA | NA | NA | NA | HTN | 32 (60) |
|  |  |  |  |  |  |  |  |  |  | Diabetes | 14 (20) |
|  |  |  |  |  |  |  |  |  |  | Cancer | 4 (6) |

Data is presented as Median (IQR) or number (%).

No., number; NA, not available; IQR, inter quartile range; T2DM, Diabetes Mellitus type 2; DM, Diabetes Mellitus; HTN, Hypertension; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CHD, Coronary Heart Disease; CHF, Coronary Heart Failure; COPD, Chronic obstructive pulmonary disease.

Figure 1: PRISMA Flow diagram of study selection

Additional records identified through other sources (n=1)

Records identified through database searching (n=1606)

**Identification**

Duplicates records removed (n=407)

Records screened (n=1200)

**Screening**

Records excluded based on exclusion criteria (n=371)

Review (n=390)

Commentary (n=220)

Summary article (n=10)

Editorial (n=89)

Studies in other language (n=2)

Case reports (n=105)

**Eligibility**

Records retrieved for more detailed evaluation (n=13)

Total records included in the final analysis (n=13)

**Included**

n, number.

Figure-2: Relative risk of ICU admission in venous thromboembolism (Figure 2a), pulmonary embolism (Figure 2b), and deep vein thrombosis subgroups (Figure 2c).



*Supplementary File 1- Quality assessment of included studies*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Criteria** | Middeldorp et al, 2020 | | Cui et al, 2020 | | Grillet et al, 2020 | | Zhang et al, 2020 | | Lorant et al, 2020 | | Demelo et al, 2020 | | Lodigiani et al, 2020 | | Poyiadi et al, 2020 | | Bilalogu et al, 2020 | | Fauvel et al, 2020 | | Trimaille et al, 2020 | | Whyte et al, 2020 | | Artifoni et al, 2020 | |
|  | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) | Yes/No | Other (CD,NR,NA) |
| 1. Was the research question or objective in this paper clearly stated? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 2. Was the study population clearly specified and defined? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 3. Was the participation rate of eligible persons at least 50%? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 10. Was the exposure(s) assessed more than once over time? |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |
| 12. Were the outcome assessors blinded to the exposure status of participants? |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |
| 13. Was loss to follow-up after baseline 20% or less? |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |  | NA |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  | Yes |  |

**Supplementary Figure 2**: Relative risk of ICU admission by study design in venous thromboembolism, pulmonary embolism, and deep vein thrombosis

(a) Venous Thromboembolism (b) Pulmonary Embolism



(c) Deep Vein Thrombosis

