Venous Thromboembolism in Hospitalized COVID-19 Patients: A Systematic Review

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Abstract

Background: Coagulopathy associated with COVID-19 infection and venous thromboembolism (VTE) have emerged as significant contributors to morbidity in the Covid-19 pandemic. We performed a systematic review to estimate VTE incidence in hospitalized patients and to analyze characteristic factors in the VTE cohort.

Methods: We performed a systematic literature search in PubMed with title search terms of “COVID-19” or “SARS-CoV-2” or “Novel Coronavirus 2019” and “venous thromboembolism” or “deep vein thrombosis” or “pulmonary embolism” or “thrombosis” or “thromboembolic” or “anticoagulation” or “heparin” or “thromboprophylaxis” to identify primary research studies that report the rate of venous thromboembolism in patients hospitalized with COVID-19 infection who are treated with standard dose pharmacologic VTE prophylaxis, high dose pharmacologic VTE prophylaxis, treatment dose anticoagulation, no anticoagulation or no documentation. A supplementary search was performed with Google Scholar using the same search terms and journal article references were reviewed to identify additional studies. Studies of adult populations that were published in a PubMed peer reviewed journal from 6/22/2019 to 6/22/2020 were included for review. Data collected for each included study design, population studied, VTE event rate, VTE diagnostic strategy, VTE prophylaxis or treatment strategy, hemostatic lab abnormalities, and clinical outcomes including ICU level of care and survival.
We excluded studies with arterial thrombosis, myocardial infarction or ischemic stroke, pediatric and fetal populations, and reviews, case reports, letters to the editor or any study that had not yet undergone peer review. Clinical outcomes data for the included studies were pooled, and we conducted a systematic review and meta-analysis with a random effects model to measure a single group summary for VTE incidence as our primary outcome.12 Confidence intervals were determined by the Adjusted Wald method. Secondary outcomes included a single group summary for mortality with the same methodology as the primary outcome and patient demographics with clinical characteristics using descriptive statistics with weighted mean and weighted standard deviation. Assessment of variables associated with VTE incidence was conducted using univariate linear regression and multivariate linear regression. Assessment of binary variables associated with VTE occurrence was conducted using multiple logistic regression. Estimation of differences in continuous variables between patients with VTE and patients without VTE was conducted using the z-Test (two sample for weighted means with weighted variance). Data were compiled using Google Sheets and Microsoft Excel.
Cedars Sinai Hospital Institutional Review Board requirement for approval was waived as this is a systematic literature review.

Results: The initial PubMed literature review returned 212 journal articles of which 12 studies were included in our review. The supplementary Google Scholar and journal article research identified an additional 2 studies to include in our review. In total, 14 studies were included in our review.6,9,13-24 (Figure 1).
Studies included were observational (Table 1) and predominantly based on experience at a single center (Single Center N = 10, Multi-Center N = 4). The total patient sample size was 1677 patients (range 26 to 388) and represented a multinational patient population (China N = 272, France N = 206, Italy N = 415, Netherlands N = 382, Spain N = 156, United States N = 44). The weighted median study duration was 37.2 ± 17.4 days and 3 studies reported a median length of stay (LOS) (weighted mean LOS 9.5 ± 1.8 days) with patients receiving both ICU and Non-ICU level of care (Table 2). 5 studies (N = 352) did not report the patient status (eg discharged alive, expired or admitted) at completion of the study period. For the other 9 studies, there were 244 designated Non-Survivors, 717 designated Discharged Alive, 369 designated Admitted, and 20 designated Unknown.

13 studies reported utilization of VTE chemoprophylaxis or treatment anticoagulation. 83.2% of patients (N = 1306) received anticoagulation and 17.8% of patients (N = 279) did not receive anticoagulation. Of patients who received anticoagulation, standard dose VTE prophylaxis was most common (52.9%, N = 691). Patients were also prescribed high dose VTE prophylaxis (6.4%, N = 84), or treatment anticoagulation (15.1%, N = 197). In 25.6% of patients prescribed anticoagulation the dosage or intensity was not specified (N = 334). VTE diagnosis was determined by systematic screening in 7 studies, 1 of which also implemented systematic screening for PE. For 7 other studies, VTE diagnosis was made by usual practice. 3 studies exclusively screened for DVT and did not report PE.

The combined estimate of VTE incidence was 26.9% (SE 3.1; 95% CI 20.8-33.1) (Figure 2). Occurrence of VTE (N = 377) was more often attributed to DVT (N = 262) and less often PE (N = 116). 10 The combined estimate of mortality incidence was 24.4% (SE 7.1, 95% CI 10.5-38.2). Absolute values were Non-Survivors N = 244, Discharged Alive N = 717, Admitted N = 369, and Unknown N = 20.

Systematic screening for VTE (r2 0.34, p = 0.03) and study duration (r2 -0.33, p = 0.03) were both correlated with VTE incidence. There were no associations with VTE and mortality, percentage of patients prescribed anticoagulation, gender, age, or d-dimer. Multivariate linear regression for intensity of VTE prophylaxis and VTE incidence was not significant (r2 0.64; F = 0.25) nor was a model that included percentage of patients prescribed VTE prophylaxis or anticoagulation, percentage of patients in the ICU, gender, age, d-dimer level, study duration and implementation of systematic screening for VTE (r2 0.67; F = 0.58).

5 studies compared clinical characteristics and outcomes for patients with VTE (N = 157) to patients without VTE (N = 296). D-dimer was significantly increased in patients with VTE compared to patients without VTE (5.62 ± 0.9 vs. 1.43 ± 0.6, p = 0.00006).VTE was decreased in patients receiving anticoagulation (either VTE prophylaxis or treatment anticoagulation) (OR 0.58; 95% CI 0.36 to 0.92, p = 0.02) and was increased in patients receiving ICU level of care during their admission (OR 6.38; 95% CI 3.67 to 11.11; p = 0.0000). There was no difference in VTE rates for non-survivors compared to survivors (OR 2.02; 95% CI 0.98 to 4.19; p = 0.058).

Conclusion: Despite utilization of background anticoagulation, VTE incidence was historically high. Future studies will provide additional data to guide optimal VTE prophylaxis and diagnostic strategies.

Objective: We performed a systematic review of VTE in the setting of patients hospitalized with COVID-19 infection and summarized the potential treatment effects in VTE management of VTE these patients. Our aim was to estimate the observed incidence of hospitalized VTE patients and analyze patient characteristics in the VTE cohort.

Conclusions: Coagulopathy associated with COVID-19 infection has emerged as a meaningful contributor to morbidity in the COVID-19 pandemic with early reports of a significantly increased incidence of VTE. We performed a systematic review to estimate the observed incidence of hospitalized VTE patients with COVID-19 infection. Despite utilization of background VTE prophylaxis and anticoagulation, VTE incidence is historically high. Future studies will provide additional data and generate insights to guide therapeutic decision making and optimize VTE prophylaxis and diagnostic strategies.

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Background

Coagulopathy associated with COVID-19 infection has emerged as a significant contributor to morbidity in the COVID-19 pandemic. Though the incidence of coagulopathy is unknown, COVID-19 associated coagulopathy has been described as having a unique hemostatic signature.[1,2,3] Typical reported abnormalities include mildly prolonged Prothrombin Time (PT/INR) and activated partial thromboplastin time (aPTT), mild thrombocytopenia, and elevated d-dimer and fibrinogen.[3,4] Generally, COVID-19 associated coagulopathy results in a prothrombotic state and is non-consumptive or progresses to hemorrhage.[5] As such, observational studies and autopsy reports have focused on characterizing thrombotic complications, including venous thromboembolism (VTE).

Potential approaches to treatment are continuing to develop with increasing experience with COVID-19 infection. Institutions have described updated VTE prophylaxis protocols aimed to more aggressively prevent clots.[1,2,6] For example, some describe utilization of standard dose VTE prophylaxis with heparin or low molecular weight heparin for all patients hospitalized with COVID-19 infection. Others deploy high dose or empiric treatment anticoagulation for high risk patients which is variably defined (E.g. Intensive Care Unit (ICU) level of care, clinical deterioration, rising d-dimer) and based on historical data in other high risk populations (E.g. bariatric surgery, 3rd trimester pregnancy).[1,2,6] In fact, early experience indicates that high risk patients (E.g. Sepsis Induced Coagulopathy score ≥ 4 or D-dimer > 3 times the upper limit of normal (ULN)) are most likely to benefit from VTE prophylaxis.[7] However, evidence-based treatment protocols are needed to further improves in Covid-19 patients with venous thromboembolism.l[1,2]

The mechanism of COVID-19 associated coagulopathy is not fully understood. However, the intense and sustained cytokine-mediated inflammatory response to SARS-CoV-2 infection is likely etiologic. As an example, elevated fibrinogen levels have been found to be associated with elevated interleukin-6 (IL-6) levels, while d-dimer also rises in parallel with c-reactive protein (CRP).[8] Further, inflammatory markers directly activate the clotting system as does tissue hypoxia both on top of direct endothelial cell injury and subsequent dysfunction by SARS-CoV-2 cellular entry.[7,9]

Serologic markers may be associated with severity of infection and may also be predictors of increased morbidity and coagulopathy. For example, d-dimer is a biomarker that increases as a result of thrombosis (eg microvascular thrombosis, DVT or PE) or systemic activation of hemostasis (eg Disseminated Intravascular Coagulation) and is associated with severe COIVD-19 and mortality.[10] Tang et al demonstrated that d-dimer elevation on admission and rising to at least 3-4 times ULN over the course of the hospital stay was associated with increased mortality.[4] Other hemostatic markers such as PT and aPTT prolongation, elevated fibrinogen degradation product and low platelets have also been associated with severe COVID-19 and mortality.[4,11] Governing bodies have recommended that d-dimer, PT, platelets and fibrinogen be measured in patients with Covid-19 infection for risk stratification and prognosis.[1,2]

We performed a systematic review of VTE in the setting of patients hospitalized with COVID-19 infection and summarized the potential treatment effects in VTE management of VTE these patients. Our aim was to estimate the observed incidence of hospitalized VTE patients and analyze patient characteristics in the VTE cohort.

Methods

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Discussion

In this review, we identified and evaluated 14 studies to assess the incidence of venous thromboembolism in hospitalized patients with COVID-19.[10] Our estimated VTE incidence of 26.9% is higher than what has been previously described in the placebo arms (VTE 5% to 15%) of clinical trials that evaluated VTE prophylaxis in medically ill patients, as well as in French controls admitted to the ICU with ARDS (4.8%), influenza (7.5%) or any cause (6.1%).[2,21] One explanation for this finding may be the consistently elevated coagulopathy associated with COVID-19 infection.[1,2,3] Though all 14 studies reported VTE incidence, there was variation in sample size, study duration, hospital length of stay, level of care, and VTE prophylaxis and diagnostic strategies. Risk factors for VTE were not reported. This may explain the degree of variation among individual studies around the summary estimate as well as the differences in degree of weighted impact. Further, more than a quarter of the

patients included in our systematic review were still hospitalized at the time of study completion. Without including the entire duration of hospitalization for COVID-19 patients, the VTE incidence we report may be an underestimate.

Though the patient populations we evaluated encompassed Asia, Europe and North America, demographics and clinical characteristics were similar and consistent with previous reports for patients with COVID-19 infection.[10] Accordingly, a high proportion of patients were candidates for anticoagulation and received anticoagulation during their hospitalization. Although the odds of VTE were lower in patients who received anticoagulation, there was no observed association between VTE incidence and anticoagulation intensity. Our review supports the increasingly standard practice of prescribing VTE prophylaxis for hospitalized COVID-19 patients.[1,2] However, future studies will be needed to guide recommendations for the optimal VTE prophylaxis strategy in this cohort of patients. Further research into the pathophysiology of hypercoagulability in these patients may also better inform the most optimal prophylaxis strategy.

In our review, systematic screening for VTE was correlated with VTE incidence. However, the clinical significance of positive studies is unknown (E.g. asymptomatic venous clot or superficial venous clot). Study duration was negatively correlated with VTE incidence which was not expected, likely reflecting heterogeneity in studied patient populations, including severity of illness, length of stay, prevalence of VTE risk factors, and anticoagulation and diagnostic strategies.

Five studies reported data for patients with VTE compared to patients without VTE. The d-dimer level was significantly elevated in patients with VTE, which is consistent with previous studies and supports the prognostic value of d-dimer as a serum biomarker for assessing VTE risk in a hospitalized patient with COVID-19.[1,2] Additionally, the odds of VTE were higher in patients in the ICU and lower in patients on anticoagulation. However, these studies did not specify the intensity of VTE prophylaxis or dosage. No other patient subgroups who may be at increased VTE risk (E.g. comorbidities, pregnancy) were identified. There was no difference in mortality in these sub-groups of patients, and therefore the impact of VTE on survival remains unknown and likely confounded by differences in patient populations.

The strengths of our analysis are inclusion of populations from across the globe, overall sample size, and consistency among studies in reporting data for VTE incidence, level of care and strategies for VTE prophylaxis as well as diagnostic strategy.

There are several noteworthy limitations in our study. First, the studies included in our analysis are observational. Given that there are no randomized clinical trials at this time, it is difficult to eliminate confounding variables when assessing VTE and clinical associations. Furthermore, the included studies are heterogeneous with respect to reporting of patient demographics, clinical characteristics, method of VTE diagnosis, and strategy for anticoagulation. These studies suggest increased incidence of late or delayed VTE risk.[6] Further, the studies did not consistently report duration of illness, severity of illness, hospital length of stay, risk factors for VTE, or presence of other Non-VTE indications for anticoagulation. Most importantly, a significant proportion of patients included in our analysis were still hospitalized at the time that the study was completed.

Future potential areas of research include arterial thrombosis, impact of hypercoagulability

risk factors, occurrence of late-term thrombosis post discharge, and the presence of long-term coagulopathy. As worldwide cases continue to surge, VTE risk in non-hospitalized patients with less acute and non-pneumonia COVID-19 infection also warrant further investigation. Wearable technology is actively being investigated to monitor COVID-19 infection in the community and at home. Examples include the DETECT Health Study, COVIDENTIFY Study and TemPredict Study. A proposed framework exists to develop novel clinical indications for wearable technology, such as early detection of VTE in ambulatory patients based on potential physiologic or wearable markers that could signal increased VTE risk or association. However, feasibility studies would need to be conducted to validate novel use cases.[25]

Conclusion

Coagulopathy associated with COVID-19 infection has emerged as a meaningful contributor to morbidity in the COVID-19 pandemic with early reports of a significantly increased incidence of VTE. We performed a systematic review to estimate the observed incidence of hospitalized VTE patients with COVID-19 infection. Despite utilization of background VTE prophylaxis and anticoagulation, VTE incidence is historically high. Future studies will provide additional data and generate insights to guide therapeutic decision making and optimize VTE prophylaxis and diagnostic strategies.

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Figures and Tables

Figure 1. Study selection flowchart showing inclusion and exclusion criteria

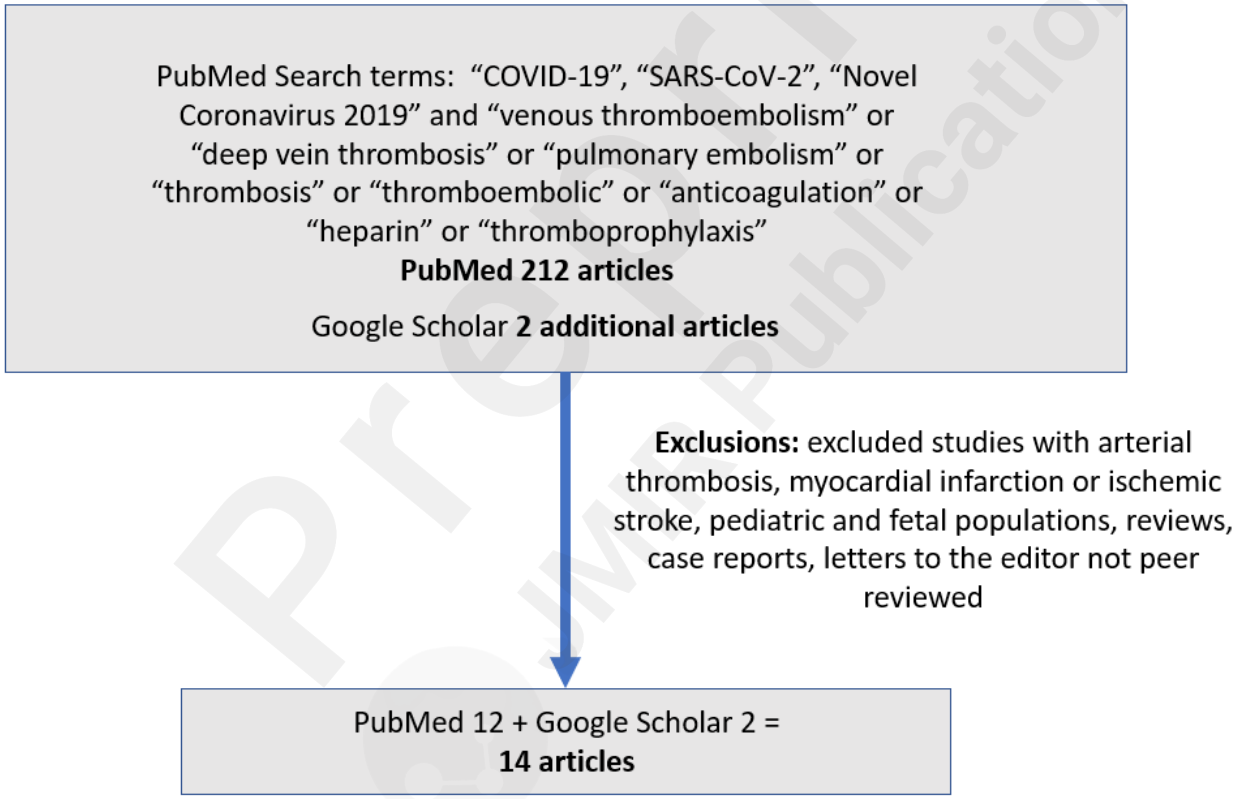


Table 1. Summary of Included Studies

Study	Study Design	Oxford Level of Evidence	Sample Size (#)	Study Duration (Days)
Lodigiani C, et al 2020	Prospective cohort	3	388	57
Llitjos JF, et al 2020	Retrospective historical	4	26	23

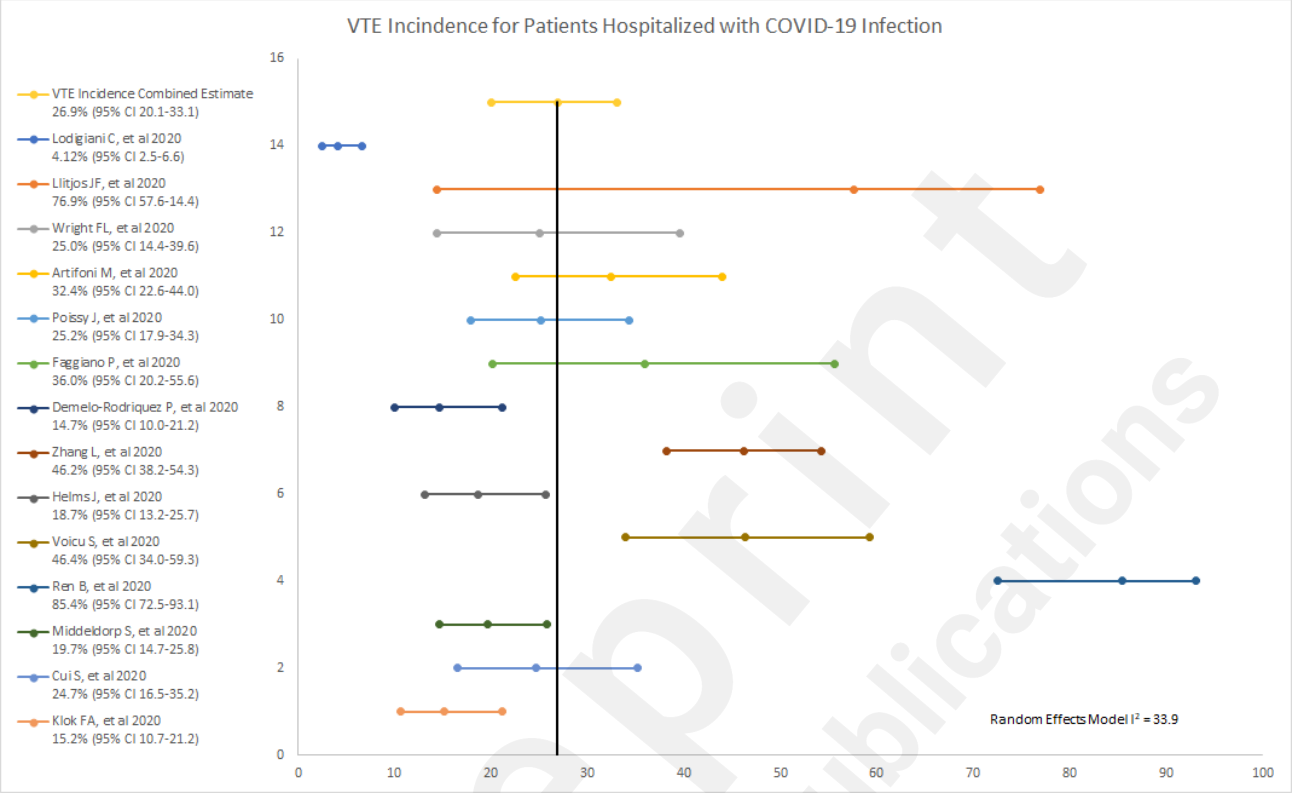
	cohort			
Wright FL, et al 2020	Retrospective historical cohort	4	44	29
Artifoni M, et al 2020	Retrospective historical cohort	4	71	16
Poissy J, et al 2020	Case-series	4	107	33
Faggiano P, et al 2020	Retrospective historical cohort	4	25	14
Demelo-Rodriquez P, et al 2020	Prospective cohort	4	156	14
Zhang L, et al 2020	Cross-sectional cohort	4	143	31
Helms J, et al 2020	Prospective cohort with historical controls	3	150	28
Voicu S, et al 2020	Prospective cohort	4	56	21
Ren B, et al 2020	Cross-sectional cohort	4	48	2
Middeldorp S, et al 2020	Prospective cohort	4	198	59
Cui S, et al 2020	Retrospective historical cohort	4	81	52
Klok K, et al 2020	Retrospective historical cohort	4	184	29

Table 2. Summary of Patient Clinical Characteristics and Factors

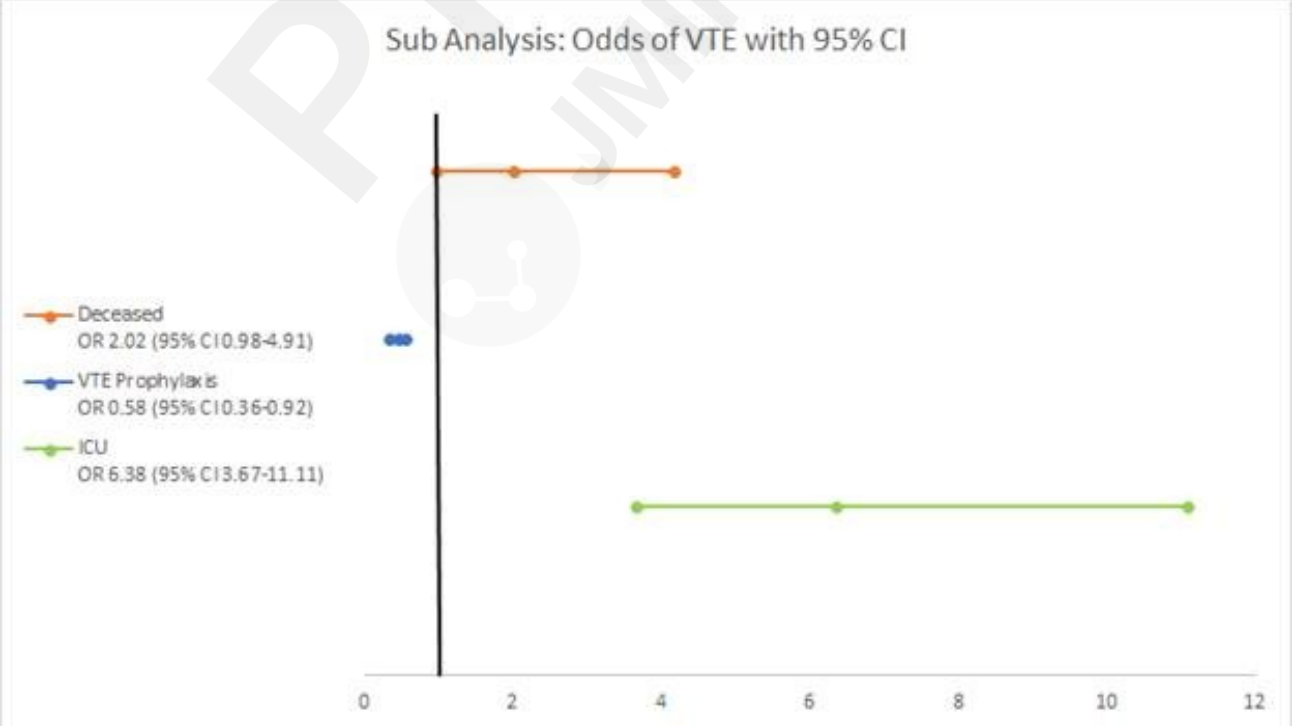
Variables	Studies Reporting Variable (#)	Sample Size (#)	Weighted Mean	Weighted Standard Deviation
Age (years)	12	1514	64.2	3.2
Male (%)	13	1570	66.8	9.4%
Female (%)	13	1570	31.2	10.0%
BMI Kg/m^2	4	339	27.7	1.2
BMI > 30 Kg/m^2	1	362	24.1	0
D-dimer ug/mL	11	998	2.1	0.9
Fibrinogen mg/dL	6	395	628.4	118.3
PT (sec)	3	268	14.4	0.9
Platelets x10^9/L	8	869	232	21.3
SOFA Score	4	291	5.9	3.1
History of VTE (%)	6	1061	8.0%	4.5%
Pre-Existing Anticoagulation (%)	4	796	25.0%	8.1%
ICU Level of Care (%)	14	1677	75.8%	53.4%

Invasive Mechanical Ventilation (%)	5	446	76.5%	55.8%

Figure 2. Forest Plot of summary estimate of VTE Incidence



Supplementary Figure: Forest Plot of VTE with anticoagulation and ICU admission



Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

KB contributed to project design, literature review, statistical analysis, manuscript writing and manuscript preparation and editing. RZ participated in manuscript preparation and manuscript writing and project design. AK participated in manuscript editing. IK contributed to project design, manuscript writing.

Supplementary Files