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BRIEF REPORT

Venous thromboembolism in critically ill patients with pneumonia in the pre-COVID-19 era: Data from a large public database

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Abstract

Background: The magnitude of venous thromboembolism (VTE) risk in severe COVID-19 is a matter of debate because of study heterogeneity, changes in VTE management, and scarce evidence of VTE risk in critically ill patients with pneumonia in the pre-COVID-19 era.

Objectives: To evaluate VTE risk in the pre-COVID-19 era in a large intensive care unit (ICU) database.

Patients/Methods: Data from consecutive pneumonia patients admitted to the ICU were retrieved from the Medical Information Mart for Intensive Care III. VTE risk was described in the entire cohort and in subgroups.

Results: Among 6842 pneumonia patients admitted to the ICU, 486 patients were diagnosed with VTE after a median of 3 (IQR 1–11) days in the ICU. The 30-day cumulative incidence of VTE was 7% and remained at this level across different age groups, sex, and type of ICU. After adjusting for death, the overall cumulative incidence of VTE was 5%. A total of 1788 patients received thromboprophylaxis (of 2958 for whom that data were available). VTE occurred in 10.7% (95% CI 9.0–12.6) of patients without thromboprophylaxis and in 6.4% (95% CI 5.4–7.6) of those with thromboprophylaxis. Mortality was 20.6% among patients with VTE and 19.2% among those without VTE.

Conclusions: In the pre-COVID-19 era, VTE risk in ICU patients with pneumonia was high and decreased with thromboprophylaxis. These findings can serve as comparators for future studies aiming at evaluating the impact of COVID-19 or other emerging infections on VTE risk.

KEYWORDS
anticoagulants, COVID-19, pneumonia, prophylaxis, venous thromboembolism

Essentials

- Evidence of venous thromboembolism (VTE) risk in critically ill patients with pneumonia in the pre-COVID-19 era is scarce.
- In this study, the VTE risk in pneumonia patients from a large intensive care unit database was described.
- The proportion of patients with a VTE event was high, at 7%, in this population.
- This VTE risk is comparable to that recently reported by trials with severe COVID-19 patients.

1 | INTRODUCTION

A high risk of venous thromboembolism (VTE), largely pulmonary embolism (PE), is a hallmark of COVID-19, particularly in patients requiring admission to intensive care units (ICUs). However, the precise magnitude of this risk is still a matter of debate, as evidenced by the large heterogeneity in the frequency of PE in series from China, Europe, and the Americas, with figures varying from 6% to 50%.[1,2] Moreover, demonstrations of the association of D-dimer levels with both the severity of COVID-19 and the risk of VTE,[3–5] coupled with clinical evidence that the use of anticoagulants could be beneficial to these patients,[6,7] also prompted renewed interest in the clinical meaning of D-dimer measurements in the course of pneumonia.[8]

These observations resulted in changes in how VTE is being diagnosed and managed in COVID-19 patients and in how D-dimers are being used in the critical care setting. In regard to the former, a higher index of suspicion lowered the threshold for computed tomography pulmonary angiograms and compression ultrasound.[9,10] For the latter, D-dimer levels are being measured with an unprecedented frequency, and the results used to support the indication for computed tomography pulmonary angiograms even in patients who would not otherwise be investigated for PE and even to support empiric diagnosis of PE in patients with limitations to perform these assays.

Nevertheless, there is great uncertainty about the role of VTE as a major determinant of mortality in COVID-19 and about D-dimer as a biomarker of disease severity or of an underlying hypercoagulable state. Moreover, few studies have addressed the risk of VTE in patients with pneumonia in the ICU in the pre-COVID-19 era, such that a complete overview of the previous scenario on VTE suspicion, diagnosis, and risk is lacking. The lack of this information represents a challenge for the precise estimation of VTE risk in COVID-19 and in other emerging infectious diseases. Here, we retrieved data from a large public database of consecutive patients admitted to the ICU (Medical Information Mart for Intensive Care III [MIMIC-III])[11] and filtered patients who presented an underlying diagnosis of pneumonia to describe the frequency of VTE and its association with clinical outcomes in critically ill patients with pneumonia.

2 | MATERIALS AND METHODS

This study was performed using data extracted from MIMIC-III1 v 1.4, a large database of unidentified high-quality data from more than 40,000 unique patients admitted to ICUs at the Beth Israel Deaconess Medical Center between 2001 and 2012. The database contains detailed medical information, such as demographics, vital signs, diagnoses, laboratory test results, caregiver notes, and mortality. The MIMIC-III project was approved by both the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Requirement for individual patient consent was not needed because all protected health information was deidentified before the release of the publicly accessible database. One author (M.P.) was granted access to the database after completing a course on human research (CITI Program record ID 30832492) and was responsible for data extraction. This was a retrospective cohort study designed in accordance with the Reporting of Studies Conducted using Observational Routinely Collected Health Data statement.[12]

The study population consisted of all patients with a documented diagnosis of pneumonia admitted to any of the five ICUs included in the MIMIC-III database. These patients were identified when International Classification of Diseases, 9th edition (ICD-9), codes encompassing pneumonia were listed in the diagnoses table, which relates the diagnoses (ICD-9 codes) to specific admissions. A detailed list of the ICD-9 codes encompassing pneumonia used to identify patients with pneumonia is shown in Table S1. Although there is a free text diagnosis column in the admissions table, it is usually assigned by the admitting clinician and does not use a systematic ontology. Therefore, as advised on the MIMIC-III v1.4 documentation, this information was not used to stratify patients. The ICD-9 codes used to define the population were those related to bacterial, viral, or unspecified pneumonia. To handle diagnosis multiplicity, we excluded admissions that had both viral and bacterial pneumonia diagnoses during the same ICU stay. Patients younger than age 16 years or older than 90 years were excluded. Consecutive admissions from the same patient were included as different admissions, and therefore, their diagnoses were handled separately. Data were extracted using Structure Query Language with an open-source multiplatform database tool for developers, DBeaver version 7.0.4.

The primary outcome was the occurrence of VTE during the ICU stay. Secondary outcomes included the frequency of PE and deep venous thrombosis (DVT) and mortality during the ICU stay. These outcomes were identified when their ICD-9 codes were listed in any of the diagnostic fields. A detailed list of the ICD-9 codes used to identify patients with VTE is shown in Table S2. The quick score sequential organ failure assessment score was calculated as previously described.[13] We also retrieved data on the type of ICU where the patient was hospitalized, laboratory parameters, such as peripheral blood count, fibrinogen, and D-dimer, and VTE prophylaxis.

Consistent data on thromboprophylaxis were available only after 2018. Before 2018, data on fluid administration were registered in the MIMIC-III database in two distinct critical care information systems that stored data in different ways (https://mimic.mit.edu/docs/iii/about/io/); therefore, the retrieval of such data before 2018 from the database is complex and could not be performed.

2.1 | Statistical analysis

The proportion (and 95% CI) of patients with VTE and death was estimated as the total number of patients with events over the total number of patients at risk (ICU patients with pneumonia) during the ICU hospitalization period. These parameters were estimated for the entire study population and by type of ICU and thromboprophylaxis use. The cumulative incidence of VTE during ICU hospitalization was estimated using the traditional Kaplan–Meier method and Gray's test for competing risk. Statistical analyses were performed using SPSS software (IBM version 26.0) and RStudio.

3 | RESULTS AND DISCUSSION

In total, 6842 patients requiring intensive care and with a diagnosis of pneumonia were identified. The demographic characteristics and clinical parameters of the hospitalization are shown in Table 1. Most patients (56.9%) were men older than 60 years of age who were hospitalized in a medical ICU (57.4%). Pneumonia was caused by bacteria in 32.6% of the patients and by viruses in 2.3% of them; in most patients, the cause of pneumonia was not specified or unknown (65.1%). During ICU hospitalization, 542 VTE events were detected in 486 patients (7% of the patients). The median time elapsed between ICU admission and a VTE event was 3 (IQR 1–11) days of ICU. DVT accounted for 59% (320 events) of all reported VTE events, and PE accounted for the remaining 41% (222 events). The mean length of ICU stay was 15.6 days (SD 15.2), and 19.2% of the patients died during the ICU stay.

In the entire cohort of ICU patients with pneumonia, the 30-day crude cumulative incidence of VTE was 7.0% (95% CI 6.8–7.1); adjusted for competing risk (death) was 5.0% (95% CI 4.9–5.1). Table 2 demonstrates the 30-day cumulative incidence of VTE (crude and adjusted considering death) in the entire cohort and in the subgroups. Figure 1 illustrates the 30-day crude cumulative incidence of VTE and mortality among critically ill patients with pneumonia hospitalized in different types of ICUs, and Figure S1 shows the competing risk by death adjustments. All-cause mortality was 20.6% among patients with VTE and 19.2% among those without VTE. In a subgroup analysis, 2958 patients with available data on prophylaxis were included, of which 1788 (60.4%) received VTE prophylaxis and 1170 (39.6%) did not receive this treatment. Thromboprophylaxis mostly started within 2 days of ICU stay (median 2 days, IQR 1–4 days). Unfractionated heparin was administered to 94.9% of the patients, enoxaparin to 4.6%, and fondaparinux to 0.6%. VTE events were approximately two times more likely to occur in patients without thromboprophylaxis (10.7% of patients with VTE; 95% CI 9.0–12.6) than in those who received this treatment (6.4%; 95% CI 5.4–7.6). By day 15, the death-adjusted cumulative incidence of VTE was 8.4% (95% CI 7.8–9.0) among patients without thromboprophylaxis and 6.0% (95% CI 5.4–6.6) among those who receive thromboprophylaxis. The death-adjusted 30-day crude cumulative incidence of VTE was at 9.0% in both groups.

Respiratory infections have long been associated with an increased risk of VTE, which may persist for months after the infection is resolved.[14] A large cohort study aimed at evaluating VTE risk among surgical patients demonstrated that the diagnosis of pneumonia was associated with a two- to three-fold increase in the rates of postsurgical VTE.[15] The diagnosis of pneumonia was also shown to be an independent risk factor for VTE in surgical ICU patients.[16] In patients undergoing major general surgery, VTE events occurred in 6.0% of those with preoperative pneumonia; in these cases, the most prevalent thrombotic event was DVT (4.8% of the patients).[17]

TABLE 1 Demographic and clinical characteristics of 6842 ICU patients with pneumonia from the Medical Information Mart for Intensive Care III database

	All patients ($n = 6842$)
Age, y, mean ± SD	64.7 ± 15.9
Male, *n* (%)	3896 (56.9)
Ethnicity	
White	4930 (72.1%)
Black	667 (9.7%)
Hispanic/Latino	250 (3.7%)
Asian	167 (2.4%)
Type of ICU[a]	
Medical ICU, *n* (%)	3926 (57.4%)
Trauma surgical ICU, *n* (%)	896 (13.1%)
Cardiac care unit, *n* (%)	31 (0.5%)
Surgical ICU, *n* (%)	440 (6.4%)
Cardiac surgery recovery unit, *n* (%)	874 (12.8%)
Quick SOFA score, mean ± SD	1.94 ± 0.73
Thromboprophylaxis, *n* (%)[b]	1788 (60.5%)
Venous thromboembolism during ICU hospitalization, *n* (%)	486 (7%)[c]
Deep vein thrombosis, *n* (% of VTE events)	320 (59%)
Pulmonary embolism events, *n* (% of VTE events)	222 (41%)
Length of ICU stay in days, mean ± SD	15.6 ± 15.2
Death during ICU hospitalization, *n* (%)	1321 (19.3%)

Abbreviations: ICU, intensive care unit; SOFA, score sequential organ failure assessment score; VTE, venous thromboembolism.

[a]Data not available in 675 admissions.

[b]Data available for 2958 patients.

[c]542 VTE events were identified.

TABLE 2 30-day cumulative incidence of VTE in critically ill patients with pneumonia hospitalized in ICU, according to the age group, sex, and quick SOFA score (crude and adjusted considering death)

	Crude 30-day cumulative incidence of VTE during ICU stay (95% CI)	Competing risk-adjusted 30-day cumulative incidence of VTE during ICU stay (95% CI)
All patients	7.0% (6.8; 7.1)	5.0% (4.9; 5.1)
Age group, y		
16-29	10.9% (10.1; 11.7)	9.1% (8.3; 9.9)
30-39	4.0% (3.4; 4.6)	3.1% (2.5; 3.7)
40-49	8.6% (7.8; 9.4)	6.6% (5.8; 7.4)
50-59	8.1% (7.5; 8.7)	5.9% (5.3; 6.5)
60-69	6.6% (6.0; 7.2)	4.3% (3.7; 4.9)
>70	6.6% (6.0; 7.2)	3.7% (3.1; 4.3)
Sex[a]		
Women	6.6% (6.0; 7.2)	4.3% (3.71; 4.89)
Men	7.5% (6.9; 8.1)	4.9% (4.31; 5.49)
Quick SOFA[a]		
Negative qSOFA Score (<2)	4.6% (4.0; 5.2)	3.4% (2.8; 4.0)
Positive qSOFA Score (≥2)	7.4% (6.8; 8.0)	4.8% (4.2; 5.4)

Abbreviations: CI, confidence interval; q, quick; SOFA, score sequential organ failure assessment score; VTE, venous thromboembolism.

[a]Data on sex and quick SOFA was missed in 5 and 134 VTE patients, respectively.

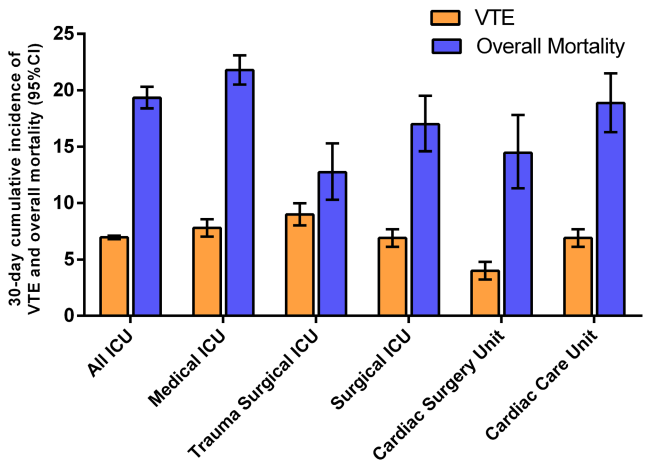

FIGURE 1 Cumulative incidence of VTE and in-ICU mortality. Crude 30-day cumulative incidence of VTE and overall mortality among critically ill patients with pneumonia hospitalized in an ICU. ICU, intensive care unit; VTE, venous thromboembolism

In medically ill patients, case–control studies revealed that the risk of VTE and PE are, respectively, 2.5- to five-fold[18–23] and eight-fold[21] higher among patients with pneumonia than in controls. This risk is more pronounced within the first 2 weeks of acute respiratory infection[23] but may persist for up to 3 months.[18,21,23] Despite the many studies demonstrating the association between respiratory infections and VTE, evidence on the absolute risk of VTE in critically ill patients with pneumonia is scarce. Population-based cohort studies demonstrated that the incidence of VTE after pneumonia is 0.12% per year,[24] which is very similar to the overall risk of VTE in the general population.[25] Nevertheless, in more severe cases, when hospitalization resulting from community-acquired pneumonia is necessary, VTE risk increases to 1.1% within 90 days of admission.[26] In a recent cohort study that included 90 patients with adult respiratory distress syndrome caused by bacterial pneumonia, 44.4% of the patients (n = 40) were diagnosed with DVT after an ultrasound scan; the number of proximal DVT cases, however, was small (3%).[27]

In our study, the cumulative incidence of VTE was 7% (95% CI 6.8–7.1) among patients with pneumonia admitted to the ICU, and DVT was the most prevalent thromboembolic event (accounting for 59% of all VTE events). Furthermore, the risk of VTE was higher without thromboprophylaxis, and was reduced by 50% with thromboprophylaxis in the first 2 weeks of ICU hospitalization. The diagnosis of VTE did not substantially affect the risk of death. These numbers provide an estimation of the absolute risks of VTE associated with respiratory infections among ICU patients.

Finally, the number of patients with a D-dimer result in our study was very low (n = 453; 7%), which underscores that, in the pre-COVID-19 era, the use of D-dimers in the ICU was limited. Indeed, D-dimer indication for VTE diagnosis in high-risk patients is controversial because in the setting of increasing prevalence of VTE, the negative predictive value of the test is decreased.

Knowing the magnitude of the association between pneumonia in critically ill patients and VTE is essential for the evaluation of VTE risk in COVID-19. Although very high incidence rates of VTE were reported in the early phases of the COVID-19 pandemic,[2] further research showed considerably lower rates of VTE. VTE rates in randomized trials aimed at evaluating different VTE prophylaxis strategies ranged from 6% to 11% in critically ill patients, regardless of the type of anticoagulant regimen.[28,29] It is worth noting that the

risk of VTE reported in our study is as high as that reported in recent COVID-19 studies.

Some limitations to our study may affect the generalizability of the results. We only evaluated data during the ICU stay, and VTE events occurring in the ward or after discharge were not available. Additionally, it is not possible to retrieve the underlying diagnosis because of a limitation in the MIMIC database, and most cases were defined as unspecified pneumonia. Data on thromboprophylaxis were available only for those hospitalized after 2009 (approximately 47% of the entire cohort); therefore, this parameter had to be evaluated in a subgroup analysis. The impact of D-dimer levels on VTE risk and mortality was not evaluated because this test was available for less than 10% of the patients. Finally, the identification of patients with pneumonia and VTE was based on ICD-9 codes registered by the medical staff during the patient's stay in the ICU. Although the use of ICD codes may result in misclassification of the diagnosis, this is an inherent characteristic of studies that rely on large health care databases of "real-world" data. Our study relies on data from the MIMIC-III database, which encompasses comprehensive clinical data of more than 40,000 ICU stays. Although the main advantages of using large databases are the number of observations and the "real-world" information, there are some disadvantages, such as the reliance on ICD coding for diagnosis and the absence of individual granular data. These disadvantages, however, do not jeopardize the potential of these databases to provide relevant medical information.

In conclusion, our results demonstrate that VTE rates are high among critically ill patients with pneumonia and are possibly comparable to recently reported rates from randomized controlled trials in severe COVID-19. By bringing up the magnitude of VTE risk in a large prepandemic populational study, our findings can serve as a comparator for future studies aiming at evaluating the impact of COVID-19 or other emerging infections on VTE risk.

AUTHOR CONTRIBUTIONS

M.P. prepared the database, performed the statistical analyses, and drafted the manuscript; F.A.O. designed and performed the analyses and revised the manuscript; S.B. revised the analysis and the manuscript; E.V.D.P. was responsible for the study concept, designed the analyses, and revised the manuscript. All authors revised and approved all submitted versions of the manuscript.

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RELATIONSHIP DISCLOSURE

The authors declare no competing financial interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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