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ORIGINAL ARTICLE

The incidence of venous thromboembolism in critically ill patients with COVID-19 compared with critically ill non-COVID patients

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Abstract

Background COVID-19 is a novel coronavirus that is currently responsible for the global pandemic. It has been reported that up to 25% [1] of hospitalized patients with COVID-19 develop VTE (venous thromboembolism), and this can be as high as 31% in ICU patients with COVID-19 [2].

Aims To determine VTE rates in ICU patients with COVID compared to those admitted with influenza and a control group.

Methods We performed a retrospective chart review of 113 patients admitted to ICU at our hospital. Patient characteristics, comorbidities, coagulation profile and prevalence of radiologically proven VTE were recorded and compared between groups.

Results More males than females were found in each group. When groups were compared the mean age, BMI and cigarette smoking were similar, as was the incidence of diabetes, chronic obstructive pulmonary disease and chronic kidney disease. aPTT was higher in the COVID-19 (30.9 ± 3.7 SD) vs (12.8 ± 4.1 SD) the influenza group vs (15.2 ± 4.1 SD) in controls $p < 0.001$, but fibrinogen was lower 6.2 ± 1.6 SD vs 34.6 ± 14.0SD vs 30.8 ± 5.0 SD, respectively, $p < 0.001$. VTE rates in the COVID (13.2%) (DVT 5.3%, PE 10.5%) and influenza groups (15.8%) (DVT 13.2%, PE 2.6%) were similar but were higher than the control group (8.1%) (DVT 8.1%, PE 2.7%), but not significantly so ($p = 0.5$).

Conclusions ICU patients with COVID-19 displayed an abnormal coagulation profile and a VTE rate that is similar to ICU patients with influenza. VTE occurred despite thromboprophylaxis and remains a pertinent differential to keep in mind.

Keywords COVID · DVT · Influenza · Invasive ventilation · PE · VTE

Introduction

SARS-CoV2 is a novel coronavirus that is currently responsible for the global pandemic of 2019–2020. The infection is associated with a marked alveolar inflammatory cell infiltrate that progresses to acute respiratory distress syndrome (ARDS) and ultimately to multiorgan failure. Several studies have also reported evidence of a COVID-19-associated coagulopathy [3–7]. The most frequent findings are fibrinogen and D-dimer elevation, both of which correlate with rising inflammatory markers [8]. It has been reported that up to 25% [1] of hospitalized patients with COVID-19 develop venous thromboembolism (VTE), and this figure can be as high as 31% [2] in ICU patients with COVID-19. The aim of this study was to determine if VTE rates are higher in ICU patients with COVID compared to ICU patients admitted with seasonal influenza and to ICU patients admitted for non-respiratory reasons.

Methods

We performed a retrospective chart review of 113 patients that were admitted to ICU at our hospital. We included three distinct groups:

1. The COVID group: This included the first 38 patients admitted to ICU during the first wave of COVID in Ireland between March 31, 2020, and April 13, 2020.

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2. The influenza group: This included the last 38 patients admitted to our ICU with influenza. They were cared for between February 06, 2016, and March 22, 2020.
3. The control group: This included the last 37 patients that required invasive ventilation for a non-respiratory reason for greater than 48 h, and these were admitted between November 02, 2019, and January 29, 2020.

We aimed to establish the incidence rate of VTE in COVID-19 patients admitted to ICU compared to patients admitted with influenza and the control group.

We recorded each patient's background and comorbidities, results of investigations and whether they developed VTE or not. The severity of illness was indicated by SAPSII and SOFA scores. We reviewed the radiological evidence that confirmed VTE or lack thereof. Imaging predominantly included ultrasound and CT pulmonary angiogram, ordered for clinical suspicion of VTE, but some patients were found to have VTE, incidentally on CT TAP, that was ordered for a different reason.

We also looked at each patient's coagulation profile on admission and how they were anticoagulated in ICU both before and after diagnosis of VTE. The majority of patients received prophylactic anticoagulation, subcutaneous enoxaparin. A number of patients were on therapeutic anticoagulation for a different reason, for example, atrial fibrillation.

Statistical analysis was conducted using one-way ANOVA tests with SPSS and Stata with $p < 0.05$ considered to be significant. The study was approved by the hospital.

Results

SAPSII scores and SOFA scores were similar in the COVID and influenza groups, but significantly higher in the control group (Table 1). The ICU mortality in the COVID-19 group, the influenza group and the control group was 21.1%, 31.6% and 35.1%, respectively. It is important to keep in mind that the control group included a vast range of illnesses that lead these patients to requiring intensive care.

Male patients were more frequently represented than female patients in all groups. Mean age, BMI and cigarette smoking were similar. There was no significant difference in the rates of diabetes, chronic obstructive pulmonary disease, and chronic kidney disease between the groups (Table 1).

In terms of blood results, the COVID group showed a significantly elevated aPTT compared to the other two groups, but PT and platelet counts were similar. Fibrinogen levels were increased above the normal range in the COVID group but were significantly more elevated in the two comparison groups. A significant rise in LDH was seen in the COVID-19 group compared to the other two groups, but no significant difference was identified between the other parameters (Table 2).

The incidence rate of VTE in the COVID group was 13.2% (DVT 5.3%, PE 10.5%) compared to the influenza group 15.8% (DVT 13.2%, PE 2.6%) and the control group, 8.1% (DVT 8.1%, PE 2.7%). Although VTE rates were similar, there was a higher rate of PE in the COVID group, but this did not reach statistical significance (Table 3). All patients that developed VTE had received prophylactic anticoagulation before diagnosis, and all received therapeutic anticoagulation once the diagnosis was made.

Discussion

A large number of observational studies of venous thromboembolism (VTE) in general ICU patients [9–13] have been conducted. Deep vein thrombosis (DVT) is estimated to occur in at least 10% of ICU admissions, but some estimates are as

Table 1 Clinical characteristics

Parameters	COVID-19 $n = 38$	Influenza $n = 38$	Control $n = 37$	p value
Sex (M:F)	28:10	20:18	26:11	0.1
Age (years) (mean, SD)	57.9 [14.8]	61.0 [17.4]	58.4 [18.2]	0.7
Diabetes (n, %)	9 (23.7)	6 (15.8)	4 (10.8)	0.3
Heart disease (n, %)	6 (15.8)	18 (47.4)	12 (32.4)	0.01
COPD (n, %)	5 (13.2)	14(36.8)	8(21.6)	0.04
Smoker (n, %)	2 (5.3)	7(18.4)	9(24.3)	0.06
CKD (n, %)	3 (7.9)	1(2.6)	0	0.1
BMI (kg/m^2) (mean, SD)	25.7 [5.4]	27.5 [9.2]	26.4 [6.4]	0.5
SAPS II (mean, SD)	49 (18.1)	56.8 (17.5)	61.5 (16.4)	0.009
SOFA(mean, SD)	6 (4.1)	8.8(3.9)	9.2(3.3)	0.001

COPD chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *BMI* body mass index, *SAPS* Simplified Acute Physiologic Score, *SOFA* Sequential Organ Failure Assessment

Table 2 Blood results

Parameters	Normal range	COVID-19 $n = 38$	Influenza $n = 38$	Control $n = 37$	p value
PT (seconds) (mean, SD)	9.9–13.1	13.9 [2.7]	12.8 [4.1]	15.2 [4.1]	0.09
aPTT (seconds) (mean, SD)	24.0–36.0	30.9 [3.7]	16.8 [12.9]	15.2 [4.1]	< 0.001
Fibrinogen (g/L) (mean, SD)	1.9–3.5	6.2 [1.6]	34.6 [14.0]	30.8 [5.0]	< 0.001
Platelets (× 109/L) (mean, SD)	140–450	235.9 [97.6]	186.7 [105.7]	233.5 [156.1]	0.5
CRP (mg/L) (mean, SD)	< 10	171.0 [107.5]	186.7 [105.7]	233.5 [156.0]	0.8
LDH (IU/L) (mean, SD)	135–250	431.2 [237.8]	101.5 [84.6]	92.9 [108.6]	< 0.001

PT prothrombin time, *aPTT* activated partial thromboplastin time, *CRP* C-reactive protein, *LDH* lactate dehydrogenase

high as 37%. The incidence of pulmonary embolism (PE), however, is considerably lower. Studies report that COVID-19 is associated with increased rates of VTE that have been reported to be as high as 25% [1] of hospitalized patients with the infection. Even higher rates (31%) have been reported in COVID-19 patients who are admitted to ICU [2]. In this study, we found a much lower rate of 13.2%. This may reflect population differences, admission criteria to ICU, difference in thromboprophylaxis regimens or small study numbers. In a large study, Klok et al. [2] evaluated the incidence of DVT, PE, ischaemic stroke, myocardial infarction and systemic arterial embolism in COVID-positive ICU patients. Thirty-one out of 184 cases (16.8%) had a thromboembolic event (arterial 3 and CT pulmonary angiogram/ultrasound-confirmed DVT/PE in 28). Compared to non-COVID patients, the incidence of VTE (28/184 [15.2%]) does not seem particularly high. However, a recent study suggests that patients with COVID who received prophylactic LMWH have a better prognosis [14]. In this study, Tang et al. retrospectively reported the outcomes for 449 COVID-19 patients, of which 99 had received some form of prophylactic anticoagulation (enoxaparin 40–60 u/day or unfractionated heparin (UFH) 10,000–15,000 u/day).

We compared our cohort of COVID-19 patients with a cohort of patients admitted to ICU with influenza, a viral illness associated with respiratory morbidity and systemic inflammatory response. The VTE rates were similar in both. Of note, the group with influenza was cared for from 2016 to date, and there was no change in thromboprophylaxis policies in the ICU over this time. We also selected a second control group of patients admitted to ICU with non-respiratory pathology. VTE rates were lower in this group but not significantly so. Of interest, PE was more frequent than DVT in the COVID-19 group, but the numbers are small.

In our study, we noted that aPTT levels were significantly elevated in the COVID group, compared to the other groups, who were within normal range. Fibrinogen levels were elevated above the normal range throughout all groups, but there was a significant elevation in the non-COVID groups. These findings are consistent with those reported in another study of coagulation profiles in COVID-19 patients admitted to ICU and the ward [15]. Of interest, fibrinogen levels were even more elevated in patients admitted to ICU with influenza and other reasons, highlighting the importance of thromboprophylaxis in critical care [16]. Zuo et al. described eight types of antiphospholipid antibodies in COVID-19 patients that may account for the prolonged aPTT. They also found that 50% of their cohort were positive for at least one autoantibody. We do not have this data in our group, but it would be an interesting study going forward and may shed more light on the coagulation profile demonstrated.

The limitation of the study is that it is retrospective, and imaging to detect VTE was only conducted in patients if clinically indicated.

In conclusion, patients admitted to ICU with COVID-19 did have a VTE rate of 13.2%, but this was not significantly different from ICU admissions with seasonal influenza and non-respiratory conditions. VTE still occurred in the COVID and influenza groups despite prophylactic anticoagulation and emphasizes the importance of vigilance for thrombosis in these patients.

Table 3 Rate of VTE, DVT and PE*

Parameters	COVID-19 $n = 38$	Influenza $n = 38$	Control $n = 37$	p value
VTE (n, %)	5 (13.2)	6 (15.8)	3 (8.1)	0.5
PE (n, %)	4 (10.5)	1 (2.6)	1 (2.7)	0.2
DVT (n, %)	2 (5.3)	5 (13.2)	3 (8.1)	0.4

VTE venous thrombotic event, *PE* pulmonary embolism, *DVT* deep vein thrombosis

*Some patients had both DVT and PE

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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