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CHEST

VTE in ICU Patients With COVID-19

To the Editor:

Increased VTE reported in patients with coronavirus disease 2019 (COVID-19)[1,2] leads some to recommend routine use of therapeutic anticoagulation.[3] However, the incidence of VTE in patients with COVID-19 ranges widely, depending on a number of variables. We hypothesized that ICU patients experience increased symptomatic VTE compared with ward patients, despite standard prophylactic anticoagulation.

Methods

Patients

Data on patients with COVID-19 admitted to Brigham and Women's Hospital entered into the Research Registry for the Study of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Infection (institutional review board approved) were retrospectively collected from March 7 to April 13, 2020; median follow-up was 7 days (interquartile range [IQR], 4-14 days). Readmissions were not included. SARS-CoV-2 positivity was determined by reverse-transcription polymerase chain reaction on nasopharyngeal samples. Subjects were classified as ICU patients if any time during admission was spent in the ICU.

Treatment protocols and ICU admission criteria for patients with COVID-19 were documented at covidprotocols.org. CBC count was measured daily; prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP), and ferritin were measured at admission and at least every 3 days. Pharmacologic VTE prophylaxis was recommended for all patients, with enoxaparin 40 mg subcutaneously daily, or unfractionated heparin 5,000 International Units subcutaneously twice or three times daily, if not contraindicated. Administered doses were confirmed in the electronic medical record. Direct oral anticoagulants were not used in admitted patients.

Outcomes

The primary outcome was symptomatic VTE caused by lower extremity DVT or pulmonary embolism (PE), determined by CT pulmonary angiography (CTPA) or compression ultrasonography (CUS). In intubated patients, symptomatic VTE was defined as imaging performed because of clinical findings suggestive of VTE. No surveillance imaging was performed. Suspected PE events in mechanically ventilated unstable patients with respiratory decompensation, right heart strain on echocardiogram, and a decision to move to therapeutic anticoagulation for suspected PE, were reviewed and confirmed by three authors. Major bleeding was defined using International Society on Thrombosis and Haemostasis[4] criteria. ARDS was defined by Berlin criteria.[5]

Statistical Analysis

Analyses were performed in R 3.6.1 (The R Project for Statistical Computing). Variables were compared with Student *t* tests, analyses of variance, or rank-sum tests, as appropriate. Kaplan-Meier analyses were performed using the survival R package; we performed Tarone-Ware tests because most events occurred early in the follow-up time, and Fine and Gray[6] competing risks analysis to ensure cumulative incidences were approximately similar to Kaplan-Meier models. Cox regression was used to evaluate the association of inflammatory and coagulation markers with VTE events. Proportional hazard assumptions were evaluated with Schoenfeld residual plots and tests. Association of aPTT with inflammatory markers was assessed with linear regression. Models were adjusted for age, sex, and BMI.

Results

Characteristics of the Study Population

Median follow-up time of the 210 patients (Table 1) was 7 days (IQR, 4-14 days); ICU follow-up time was significantly longer than non-ICU follow-up (12 vs 5 days, respectively). Twenty patients (9.5%) were still admitted at the end of the study. ICU patients exhibited a distinct hyperinflammatory procoagulant phenotype with prolonged aPTT and significantly higher levels of fibrinogen, D-dimer, LDH, ferritin, CRP, and lactic acid (Table 1). In linear regression, aPTT was nominally associated with CRP ($\beta = 1.16$; 95% CI, 0.09-2.2; $P = .035$), but not D-dimer, LDH, erythrocyte sedimentation rate, or ferritin levels.

Of the 210 patients, 190 (90.5%) received anticoagulation at admission, with 169 (80.5%) with prophylactic anticoagulation. Twenty patients received no anticoagulation, for reasons including patient/family refusal (n = 5), contraindication because of bleeding risk (n = 7), transition to comfort care (n = 1), postpartum (n = 3), and unknown (n = 4). There were nine symptomatic radiographically confirmed VTE events. Seven of 17 CUSs showed proximal DVT, and two of 25 CTPA scans were positive, with both PE events involving lobar or segmental pulmonary arteries. Eight VTE events occurred in the ICU; one PE occurred after transfer to the ward after prolonged ICU admission. Eight of nine VTE events occurred while on prophylactic

TABLE 1] Clinical Characteristics of All Patients Included in the Study

Characteristics	Overall (N = 210)	Wards (n = 108)	ICU (n = 102)	*P* Value (ICU vs Wards)
Age, y	62.21 ± 16.23	59.94 ± 17.19	64.61 ± 14.86	.037
Sex, male	101 (48.1)	42 (38.9)	59 (57.8)	.009
Race				.054
Asian	12 (5.7)	10 (9.3)	2 (2.0)	
Black	60 (28.6)	31 (28.7)	29 (28.4)	
Hispanic	33 (15.7)	16 (14.8)	17 (16.7)	
White	67 (31.9)	35 (32.4)	32 (31.4)	
Other	26 (12.4)	14 (13.0)	12 (11.8)	
Unavailable	12 (5.7)	2 (1.9)	10 (9.8)	
Weight, kg	84.65 ± 23.29	81.58 ± 19.11	87.91 ± 26.74	.049
BMI, kg/m^2	29.80 ± 7.04	29.53 ± 6.24	30.08 ± 7.83	.573
Comorbidities				
Hyperlipidemia	80 (38.1)	37 (34.3)	43 (42.2)	.30
Hypertension	125 (59.5)	56 (51.9)	69 (67.6)	.029
Coronary artery disease	18 (8.6)	7 (6.5)	11 (10.8)	.386
Congestive heart failure	18 (8.6)	10 (9.3)	8 (7.8)	.905
Diabetes mellitus	70 (33.3)	31 (28.7)	39 (38.2)	.188
Atrial fibrillation	17 (8.1)	8 (7.4)	9 (8.8)	.902
Asthma	35 (16.7)	20 (18.5)	15 (14.7)	.578
COPD	17 (8.1)	7 (6.5)	10 (9.8)	.529
Idiopathic pulmonary fibrosis	5 (2.4)	2 (1.9)	3 (2.9)	.676
History of solid organ malignancy	40 (19.0)	27 (25.0)	13 (12.7)	.037
History of hematologic malignancy	11 (5.2)	3 (2.8)	8 (7.8)	.126
Bone marrow transplant	4 (1.9)	0 (0.0)	4 (3.9)	.054
Solid organ transplant	5 (2.4)	3 (2.8)	2 (2.0)	> .99
Tobacco history	54 (25.7)	29 (26.9)	25 (24.5)	.818
Prior VTE	9 (4.3)	5 (4.6)	4 (3.9)	> .99
Platelets, k/μL	210.73 ± 92.82	203.19 ± 83.12	218.73 ± 101.89	.226
Fibrinogen, mg/dL	561.32 ± 187.76	462.89 ± 170.01	605.22 ± 179.40	< .001
Prothrombin time, s	13.85 (13.17-14.90)	13.55 (12.90-14.60)	13.95 (13.40-15.10)	.007
Activated partial thromboplastin time, s	34.30 (31.10-38.80)	33.50 (29.98-35.60)	34.80 (31.35-40.05)	.029

(Continued)

TABLE 1] *(Continued)*

Characteristics	Overall (N = 210)	Wards (n = 108)	ICU (n = 102)	*P* Value (ICU vs Wards)
D-dimer, ng/mL at admission	1,064.00 (564.00-2,244.00)	798.00 (408.00-1,446.00)	1,456.50 (732.75-2,660.25)	< .001
D-dimer, ng/mL at peak	2,887.00 (1,122.00-4,000.00)	1,032.50 (502.25-2,437.25)	3,964.00 (2,499.50-4,000.00)	< .001
Lactate dehydrogenase, Units/L	330.00 (247.50-450.50)	278.00 (230.00-346.00)	423.00 (299.50-534.00)	< .001
Ferritin, μg/L	589.50 (269.50-1,251.75)	407.00 (212.00-855.00)	773.00 (359.00-1,574.00)	< .001
C-reactive protein, mg/L	99.30 (43.00-169.90)	65.70 (19.30-117.30)	149.60 (81.60-221.50)	< .001
Lactate, mmol/L	1.50 (1.00-2.10)	1.30 (0.93-1.70)	1.70 (1.15-2.35)	.007
Anticoagulation at start of admission	190 (90.5)	91 (84.3)	99 (97.1)	.003
Prophylactic anticoagulation	169 (80.5)	80 (74.1)	89 (87.3)	.025
Therapeutic anticoagulation	21 (10.0)	11 (10.2)	10 (9.8)	> .99
No. of VTE events				.006
DVT	7	0	7	
PE	2	0	2	
Suspected PE	2	0	2	
On therapeutic anticoagulation at time of VTE event (%)				.001
No	8	0	8	
Yes	1	0	1	
ARDS	86 (41.0)	0 (0.0)	86 (84.3)	< .001
Intubated	88 (41.9)	0 (0.0)	88 (86.3)	< .001
Bacterial pneumonia	9 (4.3)	0 (0.0)	9 (8.8)	.001
CVVH	17 (8.1)	0 (0.0)	17 (16.7)	< .001
CVVH circuit failure	9 (4.3)	0 (0.0)	9 (8.8)	.001
Total length of stay, d	7.00 (4.00-15.00)	5.00 (2.00-7.50)	15.00 (8.00-21.50)	< .001
ISTH major bleeding	2 (1.0)	0 (0.0)	2 (2.0)	.235
Death	35 (16.7)	7 (6.5)	28 (27.5)	< .001
Days followed	7.00 (4.00-14.00)	5.00 (2.00-8.00)	12.00 (7.00-19.00)	< .001
Discharged	190 (90.5)	107 (99.1)	83 (81.4)	< .001

Values are mean ± SD, No. (%), median (interquartile range), or as otherwise indicated. CVVH = continuous venovenous hemofiltration; ISTH = International Society on Thrombosis and Haemostasis; PE = pulmonary embolism.

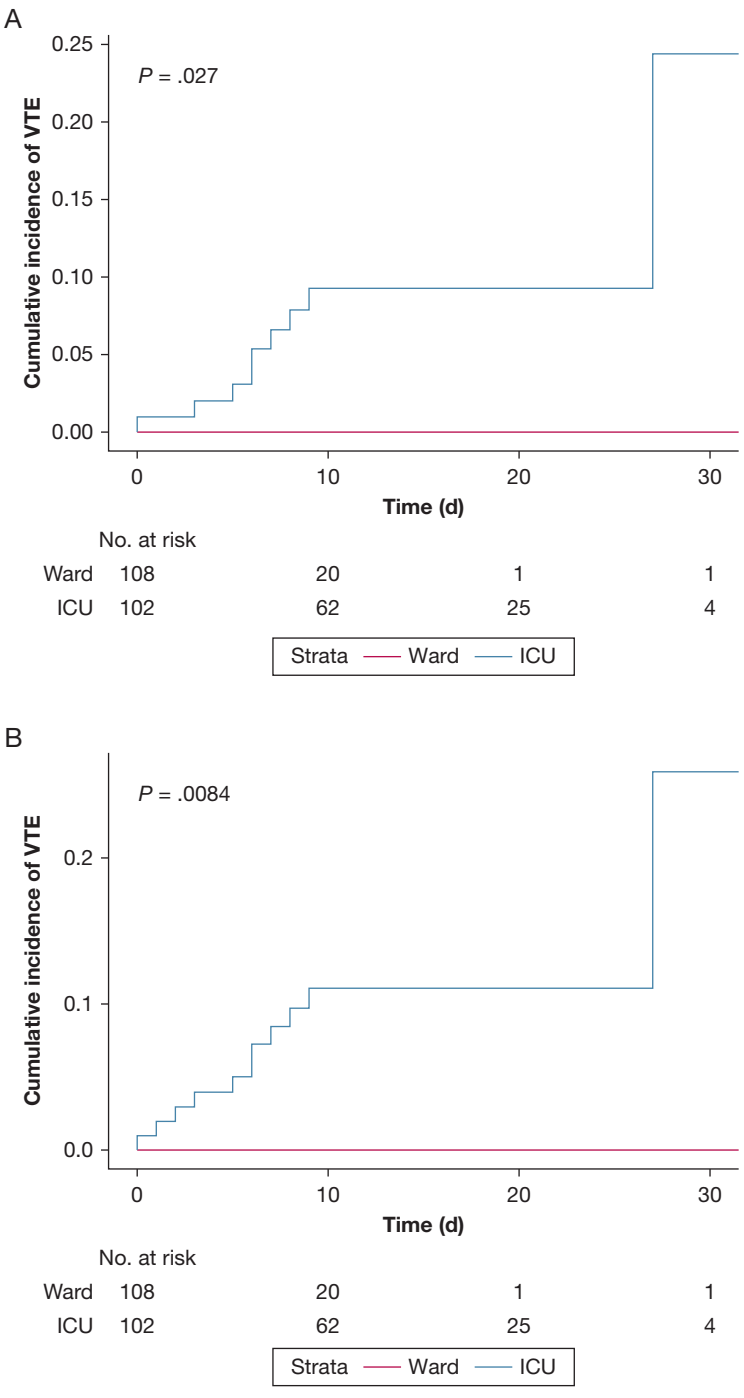

Figure 1 – *A-B, Cumulative incidence plots based on Kaplan-Meier analyses, stratified by whether patients required ICU admission. Risk sets are shown below the graphs. P values are derived from Tarone-Ware tests. A, Cumulative incidences using radiographically confirmed VTE events. B, Cumulative incidences based on VTE definitions in part A and strongly suspected pulmonary embolism with right ventricular strain on echocardiography and a clinical change to therapeutic anticoagulation.*

anticoagulation. The median time from ICU admission to VTE diagnosis was 6 days (IQR, 5-7 days), suggesting that patients were not admitted to the ICU because of VTE. An additional two ICU patients had suspected PE with increase to therapeutic anticoagulation.

For ICU patients on anticoagulation, the 14-day cumulative incidence of radiographically confirmed VTE was 9.3% (95% CI, 4.7-17.8). No events occurred in ward patients. Including strongly suspected PEs leading to initiation of therapeutic anticoagulation, the 14-day

cumulative incidence of VTE was 11.1% (95% CI, 6.1-19.7). Cumulative incidences of VTE stratified by ward and ICU patients are shown in Figure 1. Competing risk models yielded similar results. In Cox regression, LDH, CRP, ferritin, D-dimer, and aPTT were not significantly associated with an increased hazard for VTE events.

Two major bleeding events occurred: one hemodynamically significant bleed with a drop in hemoglobin $\geq$ 2 g/dL in $<$ 24 h, and one intracranial hemorrhage. Both patients were receiving therapeutic anticoagulation at the time: one patient with DVT, and one admitted on therapeutic anticoagulation for prior VTE.

Discussion

Patients in the ICU had a higher incidence of symptomatic VTE events compared with ward patients, with a 14-day cumulative incidence of 9.3% despite the use of at least standard dose VTE prophylaxis in all patients experiencing an event. Our findings suggest that standard dose VTE prophylaxis is effective for ward patients, but may be insufficient to prevent VTE in ICU patients with COVID-19.

The cumulative incidence of 9.3% for VTE in ICU patients with COVID-19 is somewhat lower than recently reported cumulative incidences of VTE in ICU patients with COVID-19 ranging from 11% to 70%.[1,2,7,8] In two studies,[1,2] the dose of prophylactic anticoagulation was 25% lower, possibly explaining their higher VTE rates. One study using screening CUS found DVTs in 100% of those on prophylactic and 56% of those on therapeutic anticoagulation[8]; however, our study focuses on symptomatic VTE events leading to a change in anticoagulation. The threshold to obtain CTPA or CUS in patients with COVID-19 at our institution is extremely high given infection control concerns and difficulty moving mechanically ventilated patients; VTE rates are likely underestimated. Patients in the ICU had significantly higher fibrinogen, LDH, CRP, and D-dimer levels. Because of recent reports of the presence of lupus anticoagulants resulting in elevated aPTT, we found that although the aPTT was associated with CRP levels, elevated aPTT levels did not predict VTE events.[9]

In summary, ICU patients exhibited a distinct phenotype characterized by elevated inflammatory markers, ARDS, and a significant increase in the cumulative incidence of symptomatic VTE compared with those not requiring ICU care, suggesting that standard VTE prophylaxis is insufficient in these patients. Heparins were used for VTE prophylaxis, not direct oral anticoagulants; therefore, failure was not caused by drug-drug interactions. Although individual inflammatory markers did not predict VTE events, it is likely that the development of a thromboinflammatory phenotype is a harbinger of critical illness, need for ICU care, and risk of VTE. Most VTE events occurred early in hospital admission, with a second set of events later in the course for ICU patients. These findings suggest that patients requiring ICU care experience events early in the setting of profound host inflammatory responses to SARS-CoV-2, but later VTE risk may be caused by factors associated with prolonged ICU care. Further investigation into the appropriate dose of prophylactic anticoagulation and associated risks and benefits in ICU patients with COVID-19 is urgently needed.

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