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Venous thromboembolism associates with SARS-CoV-2 more than seasonal influenza☆

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To the Editors-in-Chief,

SARS-CoV-2 is a novel respiratory virus associated with increased venous thromboembolism (VTE) risk with estimates of 21% [1]. This observation prompted empiric anticoagulation at the time of hospitalization [2]. Preliminary reporting from randomized trials suggests full dose anticoagulation was beneficial in moderately ill patients [3] but may actually cause harm in the critically ill SARS-CoV-2 infected patients [4]. We previously reported that hospitalized patients on chronic anticoagulation at the time of SARS-CoV-2 diagnosis did not develop thrombotic complications [5]. We hypothesized that anticoagulation at the outset of infection would be uniquely beneficial in SARS-CoV-2 because of the high risk for thrombotic complications; influenza provided a comparison group as a respiratory virus with substantial rates of hospitalization, respiratory failure, and death. We used influenza hospitalizations at our institution as a control group to ask the question: is chronic anticoagulation at the time of infection beneficial in hospitalized SARS-CoV-2 patients, and if so, is there an apparent benefit for hospitalized influenza? We compared 1) baseline characteristics (including chronic anticoagulation use) and 2) outcomes (venous thromboembolism [VTE], bleeding, respiratory failure, mortality) between hospitalized patients with SARS-CoV-2 and seasonal influenza 2019–2020 at our institution.

This was a retrospective, single-institution study with institutional review board approval. Our search identified all patients with a hospital admission and either positive SARS-CoV-2 PCR testing from March 13, 2020, through September 30, 2020, or positive Influenza A or B PCR testing from September 1, 2019, through May 1, 2020, at the University of Rochester Medical Center's (URMC) three hospitals. We used electronic medical record (EMR) interrogation confirmed by manual chart review to identify all those using therapeutic anticoagulation (warfarin, enoxaparin, direct oral anticoagulants [DOAC]) regardless of indication for at least 1 month before positive PCR testing. Use was verified by clinic or hospital notes, medication order dates, and/or blood work. We collected demographics, laboratory values, the rate of imaging-confirmed or clinically apparent thrombosis or complications; temporal relationship of the thrombotic event; hospitalization/intensive care unit (ICU) admission rate; type of anticoagulation used at home and in the hospital; bleeding complications; and mortality. We used the same criteria previously reported in identifying thrombosis or bleeding complications [5]. Vital status at discharge and at 90 days were recorded from the electronic medical record.

Categorical variables are reported as counts and percentages and compared with Chi-Square testing. Continuous variables are reported as median with interquartile ratio. Student's paired *t*-test, Mann-Whitney test, or Chi-square were performed as appropriate for group comparisons. Statistical analysis was performed with SAS 9.4.

☆ All authors have made substantial contributions: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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There were 495 patients with SARS-CoV-2 and 429 patients with influenza admitted to the URMC. There was no difference in the rate of chronic anticoagulation use at baseline between the two viruses (Table 1). In the SARS-CoV-2 patients, therapeutic anticoagulation was continued for all but 8 (1 had anticoagulation held because of a subdural, 7 received standard or intermediate venous thromboembolic prophylactic dosing). The chronically anti-coagulated SARS-CoV-2 and influenza patients were older with increased co-morbidities compared to those not anticoagulated (Table 1). There were no clinically relevant laboratory differences between the groups (data not shown).

Coronavirus patients developed more severe disease and had higher inpatient mortality compared to influenza patients. VTE was significantly more likely among those with SARS-CoV-2 than those with influenza (chi-square = 10.39, $p = 0.001$). It appears chronically anticoagulated patients may have had less severe respiratory failure with numerically fewer patients proned, fewer intubations, and lower maximum PEEP than those who were not anti-coagulated at the time of SARS-CoV-2 diagnosis (Table 2). There were 22 SARS-CoV-2 patients (4.4%) with a VTE during their hospitalization (16 DVT only, 2 pulmonary embolism (PE) only, 4 both). The median age was 66 years old (45, 73), most were men (16, 73%), and the average BMI was 27.3 (24.8, 39.1). The median baseline D-Dimer for SARS-CoV-2 patients subsequently diagnosed with VTE was 1.63 (0.94, 4.42) μg/mL (median baseline D-Dimer in SARS-CoV-2 without subsequent VTE =1.11 (0.59, 1.92) ug/ml); median time to diagnosis was 10 days (2,11). Four VTE were diagnosed at admission and required non-ICU level care. VTE was seen more commonly in the ICU setting, 15 (8.9% of all ICU admissions in the SARS-CoV-2 cohort) vs 7 (2.1% of non-ICU patients, chi-square = 11.98, $p = 0.0005$). All but one of the VTE diagnoses occurred in those not taking chronic anticoagulation, all of whom had been treated with prophylactic anticoagulation. The one deep vein thrombosis (DVT) (upper extremity – mid brachial vein) in the chronically anticoagulated group occurred in a non-ICU setting 3 weeks after diagnosis. There were more bleeding events in the chronic anticoagulation group (Table 2). Among SARS-CoV-2 patients that died, patients or surrogates defined goals of hospital care and elected less aggressive interventions because of severe underlying co-morbidities in 11 patients (61%) on chronic anticoagulation and 22 patients (31%) not on chronic anticoagulation (chi-square = 5.58, $p = 0.02$). For those with respiratory failure requiring intubation, there was no difference in mortality between the chronically and not chronically anticoagulated groups, 4 (44%) vs 29 (32%), $p = 0.43$.

There was no difference in outcomes between chronically anticoagulated and non-anticoagulated influenza patients (Table 2), despite the anticoagulated patients being older with more comorbid illness at baseline. The only influenza DVT among those chronically anticoagulated was identified at the time of admission in a patient with a history of DVT (Protein S deficiency), and the INR was subtherapeutic.

Our retrospective, single-center cohort study confirms that hospitalized SARS-CoV-2 has a higher risk for VTE compared to a control group of influenza. Our report suggests that chronic anticoagulation decreases VTE risk at the time of SARS CoV-2 and may be associated with decreased severity of respiratory dysfunction. Our health care system was never overwhelmed during the pandemic, and our data were manually reviewed and confirmed.

We found that patients in both cohorts who were taking chronic therapeutic anticoagulation were significantly older than those not taking chronic anticoagulation. This large age discrepancy likely muted any benefit associated with anticoagulation at the time of infection; the anti-coagulated SARS-CoV-2 group had a much higher burden of co-morbid illness and more often chose to limit potentially life-saving interventions. Our data suggest that respiratory failure was less severe in

Table 1
Baseline demographics.

	Coronavirus			Influenza			*p*-value		
	Total* ($n = 495$)	AC** ($n = 65$)	No AC** ($n = 430$)	Total* ($n = 429$)	AC*** ($n = 56$)	No AC*** ($n = 373$)	*	**	***
Age (years)	67 (52, 77)	75 (67, 84)	65 (50, 76)	62 (44, 73)	73 (60, 78)	60 (40, 71)	<0.001	<0.001	<0.001
Sex									
Female	256 (52%)	33 (51%)	223 (52%)	236 (55%)	29 (52%)	207 (56%)	0.31	0.87	0.60
Ethnicity									
Caucasian	291 (59%)	43 (66%)	248 (58%)	289 (67%)	45 (80%)	244 (65%)	0.01	0.10	0.04
African American	164 (33%)	20 (31)	144 (34%)	115 (27%)	9 (16%)	106 (28%)			
Other	40 (8%)	2 (3%)	38 (9%)	25 (6%)	2 (4%)	23 (6%)			
BMI (kg/m^2)	29 (23.9, 35.4)	27.5 (21.5, 34.4)	29.2 (24.2, 35.4)	29.1 (24.2, 34.9)	28.5 (24.3, 36.5)	29.3 (24.2, 34.9)	0.48	0.27	0.91
Smoking									
Active	40 (8%)	5 (8%)	37 (8%)	89 (21%)	7 (13%)	82 (22%)			
Former	191 (39%)	31 (48%)	160 (37%)	175 (41%)	31 (55%)	144 (39%)	<0.001	0.48	0.84
Never	264 (53%)	29 (45%)	233 (54%)	165 (39%)	18 (32%)	147 (39%)			
COPD	83 (17%)	16 (25%)	67 (16%)	120 (28%)	16 (29%)	104 (28%)	<0.001	0.07	0.91
Dementia	71 (14%)	16 (25%)	55 (13%)	19 (4%)	4 (7%)	15 (4%)	<0.001	0.01	0.29
OSA	71 (14%)	16 (25%)	55 (13%)	77 (18%)	14(25%)	63 (17%)	0.14	0.01	0.14
DM	188 (38%)	28 (43%)	160 (37%)	143 (33%)	24 (43%)	119 (32%)	0.14	0.36	0.10
VTE history	42 (9%)	26 (40%)	16 (4%)	36 (8%)	17 (30%)	19 (5%)	0.96	<0.001	<0.001
Atrial Fib	93 (19%)	41 (63%)	52 (12%)	92 (21%)	42 (75%)	50 (13%)	0.31	<0.001	<0.001
HFpEF/HFrEF	78 (16%)	25 (39%)	53 (12%)	71 (17%)	21 (38%)	50 (13%)	0.88	<0.001	<0.001
CAD	91 (18%)	20 (31%)	71 (17%)	77 (18%)	19 (34%)	58 (16%)	0.86	0.006	<0.001
HTN	329 (67%)	55 (85%)	274 (64%)	276 (64%)	50 (89%)	226 (61%)	0.49	0.007	<0.001
CKD	117 (24%)	34 (34%)	95 (22%)	97 (23%)	16 (29%)	81 (22%)	0.71	0.03	0.25
Immunosuppression	39 (8%)	6 (9%)	33 (8%)	33 (8%)	4 (7%)	29 (8%)	0.31	0.67	0.87
Anticoagulation	65 (13%)			56 (13%)					
Oral Xa inhibitor	38	38		31	31				
VKA	24	24		20	20		0.46		
DTI	1	1		2	2				
LMWH	2	2		3	3				

Anticoagulation (AC), Body Mass Index (BMI), Chronic Obstructive Pulmonary Disease (COPD), Obstructive Sleep Apnea (OSA), Diabetes Mellitus (DM), Venous Thromboembolism (VTE), Heart Failure Preserved Ejection Fraction (HFpEF), Heart Failure Reduced Ejection Fraction (HFrEF), Coronary Artery Disease (CAD), Hypertension HTN), Chronic Kidney Disease (CKD), Vitamin K Antagonist (VKA), Direct Thrombin Inhibitor (DTI), Low Molecular Weight Heparin (LMWH).

Table 2
Outcomes.

	Coronavirus			Influenza (n = 429)			p-value		
	Total* (n = 495)	AC** (n = 65)	No AC** (n = 430)	Total* (n = 429)	AC*** (n = 56)	No AC*** (n = 373)	*	**	***
Oxygen requiring (%)	264 (53.3%)	34 (52.3%)	230 (53.6%)	192 (44.7%)	26 (46.4%)	166 (44.2%)	0.0068	0.85	0.76
ICU (%)	171 (34.5%)	20 (30.1%)	151 (35.2%)	58 (13.5%)	5 (8.9%)	53 (14.2%)	0.0001	0.49	0.72
Intubation (%)	96 (19.4%)	8 (12.3%)	88 (20.5%)	21 (4.9%)	3 (5.4%)	18 (4.8%)	0.14	0.12	0.28
PEEP (cm H20) (maximum)	14 (10, 14)	10 (8, 13)	14 (10,15)	8 (8, 12)	8 (8, 16)	9 (7,12)	0.0009	0.01	0.86
Prone positioning (ever)	50 (52.1%)	2 (3.1%)	48 (11.2%)	2 (8.3%)	1 (1.8%)	1 (0.3%)	0.0001	0.04	0.24
Shock requiring vasopressors (%)	82 (16.6%)	9 (13.8%)	73 (17%)	15 (3.5%)	4 (7.1%)	11 (2.9%)	0.0001	0.13	0.11
Bleeding (%)	11 (2.2%)	4 (6.1%)	7 (1.6%)	2 (0.5%)	0	2 (0.5%)	0.02	0.02	0.99
Brain bleed (%)	5 (1%)	1 (1.5%)	4 (0.9%)	2 (0.5%)	0	2 (0.5%)	0.34	0.65	0.99
Total VTE (%)	22 (4.4%)	1 (1.5%)	21 (4.9%)	4 (0.9%)	1 (1.8%)	3 (0.8%)	0.001	0.22	0.99
Pulmonary embolism(%)	6 (1.2%)	0	6 (1.9%)	2 (0.5%)	0	2 (0.3%)	0.22	0.30	0.99
Deep vein thrombosis	20 (4%)	1 (1.5%)	19 (4.4%)	4 (0.9%)	1 (1.8%)	3 (0.8%)	0.003	0.27	0.99
Other arterial Clot	0	0	0	0	0	0	0.99	0.99	0.99
Stroke	4 (0.8%)	1 (1.5%)	3 (0.6%)	1 (0.2%)	0	1 (0.3%)	0.99	0.48	0.99
MI/New cardiomyopathy	6 (1.2%)	1 (1.5%)	5 (1.2%)	5 (1.2%)	1 (1.8%)	4 (1.1%)	0.87	0.79	0.99
Acute kidney injury	215 (43.4%)	31 (47.7%)	184 (42.9%)	126 (29.4%)	17 (30.4%)	109 (29.2%)	0.0001	0.46	0.86
Continuous renal replacement therapy	15 (3%)	3 (4.6%)	12 (2.8%)	5 (1.2%)	1 (1.8%)	4 (1.1%)	0.16	0.43	0.99
ICU length of stay (days)	8 (3,18)	4.5 (2, 14)	9 (3, 19)	6 (3,11)	16 (2, 39)	4 (3,10)	0.48	0.3	0.28
Hospital length of stay (days)	8 (3,21)	16 (7, 38)	8 (3, 19)	4 (2,7)	5 (3, 8)	4 (2,7)	0.0001	0.007	0.34
Death hospital	79 (15.9%)	17 (27.7%)	62 (14.5%)	22 (5.1%)	4 (7.1%)	18 (16.8%)	0.0001	0.02	0.46
Death within 90 days	88 (17.8%)	18 (29.2%)	70 (16.3%)	31 (7.2%)	5 (8.9%)	26 (7%)	0.0001	0.02	0.59

Acute kidney injury was defined based on the Kidney Disease Improving Global Outcomes Clinical Practice Guidelines. Myocardial infarction was diagnosed when ST-elevation was present on electrocardiogram. Cardiomyopathy was diagnosed when an echocardiogram identified left ventricular ejection fraction <50%. Anticoagulation (AC),Positive End-Expiratory Pressure (PEEP), Venous Thromboembolism (VTE), Myocardial Infarction (MI).

our anti-coagulated SARS-CoV-2 cohort. Our ICU followed well-coordinated protocols in managing respiratory failure, making this more likely an effect of anticoagulation than chance observation. Stals et al. reported a similar rate of SARS-CoV-2 infected patients on chronic anticoagulation requiring hospitalization at 13% [6]. They did not comment on whether there was a difference in disease severity. Our observations support the hypothesis that pathologic thrombin and/or Xa signaling plays a greater role in SARS-CoV-2 than for seasonal influenza.

Anticoagulation at the time of hospitalization for SARS-CoV-2 has been studied in an effort to improve outcomes [2,7]. Our earlier report showed that the majority of patients on chronic anticoagulation infected with SARS-CoV-2 remained at home and did not develop VTE despite being an older population [5], and thus therapeutic anticoagulation may provide the best protection at the time of infection. Support for the idea that early anticoagulation is most beneficial was the recent ACTIV trial in non-critically-ill hospitalized patients [3]. It is intriguing that most of our VTE events occurred in the ICU patients but the randomized ICU study did not show benefit for more intense prophylaxis; perhaps the disease-associated prothrombotic processes in critically ill patients are so far advanced that only earlier, therapeutic anticoagulation is beneficial.

Similar to other reports [8–10], we found more severe illness among hospitalized SARS-CoV-2 patients than those with seasonal influenza. The two prior studies comparing influenza to SARS-CoV-2 had similarly aged cohorts and still found more severe disease with SARS-CoV-2 [8,9]; those studies did not evaluate the incidence of VTE or the impact of anticoagulation. Using a large database in the Netherlands, investigators observed more VTE in both seasonal influenza (3.6%) and SARS-CoV-2 (23%) than our present report [6]. They did not study what impact chronic anticoagulation had on thrombotic events; the discrepancy between reports raises questions about the role of genetics, environment, and care practices in VTE development for these serious viral infections. Other work has highlighted the impact of respiratory infections increasing the risk of thrombotic complications [11]. The severity seems to be less severe than what is seen with SARS-CoV-2.

There are limitations to this study. Ours was an observational retrospective study, and it is difficult to determine from a retrospective chart review why interventions were pursued or not. The older age and higher incidence of dementia likely influenced treatment decisions and outcomes in the SARS-CoV-2 group as compared to the influenza patients. A more definitive statement about the incidence of VTE would have required a prospective screening approach in both influenza and SARS-CoV-2 patients.

In summary, this retrospective cohort study observed that hospitalized SARS-CoV-2 patients were more likely to have a clinically apparent VTE than those admitted with influenza. Chronic anticoagulation use for SARS-CoV-2 patients was associated with less severe respiratory failure and numerically fewer VTE. Our real world findings complement the

recent ACTIV study demonstrating that anticoagulation at the earliest time point may be more beneficial in preventing severe illness. Further studies are necessary to determine whether the apparent increased rate of VTE is directly related to a unique aspect of the SARS-CoV-2 infection or more generally to the apparently increased severity of illness.

CRediT authorship contribution statement

Daniel Lachant: Conceptualization, Methodology, Formal analysis, Roles/Writing – original draft.

Dominick Roto: Data Curation, Formal analysis, Formal analysis, Roles/Writing – original draft.

Stephen Rappaport: Methodology, Formal analysis, Roles/Writing – original draft.

Paritosh Prasad: Methodology, Formal analysis, Roles/Writing – original draft.

Neil Lachant: Conceptualization, Formal analysis, Roles/Writing – original draft.

R. James White: Conceptualization, Formal analysis, Roles/Writing – original draft.

The work described has not been published, it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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