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LETTER TO THE EDITOR

Post-hospitalization venous thromboembolism in COVID-19 patients: Evidence against routine post-hospitalization prophylactic anticoagulation

Dear Editors,

The association between COVID-19 and an increased risk of venous thromboembolic (VTE) events, particularly in the critically ill, has been well reported.[1] While guidelines exist for thromboprophylaxis during hospitalization, the role for thromboprophylaxis post-hospitalization remains uncertain and controversial. Current guidelines recommend against the blanket use of post-hospitalization thromboprophylaxis and suggest that it be considered after individualized assessment of bleeding and thrombotic risk.[1,2] There is however a paucity of data on the post-hospitalization VTE events in COVID-19.[3,4] In the absence of prospective data, the role for prophylactic anticoagulation in COVID-19 patients post-hospitalization remains uncertain.

In our prospective study, we had 2 objectives: (a) to study the incidence of VTE events post-discharge, which was determined by looking at readmissions to our hospital for VTE events or patient-reported symptoms at follow-up that would suggest a VTE event and necessitate admission for further evaluation, (b) to characterize the thrombogenicity of recovered COVID-19 by studying hemostatic assays, specifically activated partial thromboplastin time (aPTT)-based clot waveform analysis (CWA). COVID-19 patients admitted to Singapore General Hospital were enrolled upon written informed consent. This study was approved by SingHealth Centralized Institutional Review board (CIRB no. 2018/3045). All patients were given a six- to eight-week follow-up upon discharge. We calculated the modified IMPROVE-VTE score for our cohort. The International Medical Prevention Registry on Venous thromboembolism (IMPROVE) VTE score is a predictive score designed to assess the risk of VTE in hospitalized medical patients.[5] It has been used as a possible criteria in ongoing trials to decide on the need for post-hospitalization VTE prophylaxis in COVID-19 patients.[6] APTT-based CWA were generated during the analysis of the standard aPTT assay triggered with Dade Actin FSL reagent (Siemens Healthcare) and retrieved from CS2100i automated coagulation analyzers (Sysmex Corporation). CWA parameters of interest were min1, min2, and max2 denoting the maximum velocity, maximum acceleration, and maximum deceleration of the clot formation process, respectively. Higher parameters indicate hypercoagulability.[7] Coagulation samples for recovered COVID-19 patients were taken at 2 settings. In non-ICU patients, this was at follow-up; in ICU patients, when two consecutive COVID-19 testing were negative, indicating recovery. Data analysis was performed using SPSS 25.0 (IBM SPSS statistics) IBM Corporation) software. t Test was used to compare coagulation parameters during illness and at recovery.

Between January 20th and 1st Jul 2020, 115 patients were recruited into this study, of which 63 (54.8%) patients attended their follow-up visit. Baseline characteristics are shown in Table 1. Sixteen (13.9%) patients required oxygen supplementation, a marker of severity of illness, among which seven (6.1%) patients required intensive care unit (ICU) care. Non-ICU COVID-19 patients did not receive prophylactic anticoagulation during hospitalization. Four ICU COVID-19 patients received prophylactic anticoagulation only during their ICU stay, in accordance with our ICU protocol for VTE prophylaxis. The modified IMPROVE-VTE score in both non-ICU and ICU COVID-19 patients was <4. Taking into account d-dimer, only one patient in the non-ICU group and three patients in the ICU group fulfilled the high-risk criteria based on the modified IMPROVE-VTE score. No patients received prophylactic anticoagulation post-hospitalization. We observed no VTE events during hospitalizations nor readmissions for VTE events post-hospitalization as of 1st December 2020. At follow-up, no patient presented with symptoms that would suggest a VTE event.

The coagulation profiles and CWA parameters were analyzed. Table 2 shows an independent comparison of coagulation profiles and CWA parameters of non-ICU COVID-19 patients during hospitalization and at follow-up. There was a significant decrease in median CWA parameters (min1 and min2) at follow-up (min1: 5.37%/s vs 4.37%/s, $P = .013$; min2: 0.79%/s^2 vs 0.69%/s^2, $P = .034$) although their aPTT were not significantly different. At follow-up, all patients had CWA parameters and coagulation parameters within normal ranges. Among our study population, five patients had paired CWA results—during acute illness and at recovery. Of these, three patients exhibited elevated min1 during the acute phase of COVID-19, median (IQR) 7.31%/s (7.10,8.00), and the subsequent normalization of this parameter during recovery, median (IQR) 5.39%/s (5.06,5.68). Two of the three patients were ICU COVID-19 patients and were the only ICU patients in our study that had paired CWA parameters.

We observed no VTE event during and post-hospitalization in our cohort. Studies reporting post-discharge VTE events in COVID-19 patients are few. In a retrospective study by Roberts et al, post-discharge VTE rate was 4.8 per 1000 discharges.[4] The authors concluded that the event rate was low and suggested against the use of post-discharge thromboprophylaxis. The majority of our patients

TABLE 1 Clinical characteristics, venous thromboembolic events, and follow-ups of COVID-19 patients (n = 115)

	Non-ICU (n = 108)	ICU (n = 7)
Demographics		
Age, Median (IQR)	38 (30,50)	65 (64,69)
Gender no.(%)		
Male	81 (75)	5 (71.4)
Female	27 (25)	2 (28.6)
Race—no.(%)		
Chinese	37 (34.3)	4 (57.1)
Malay	3 (2.8)	0 (0)
Indian	60 (55.6)	2 (28.6)
Others	8 (7.4)	1 (14.3)
Comorbidities no.(%)		
Hypertension	22 (20.4)	5 (71.4)
Hyperlipidemia	7 (6.5)	1 (14.3)
Diabetes Mellitus	4 (3.7)	1 (14.3)
Ischemic Heart Disease	4 (3.7)	1 (14.3)
Prior stroke	1 (0.9)	0 (0)
Renal disease	2 (1.9)	0 (0)
Chronic lung disease	10 (9.3)	1 (14.3)
Liver disease	0 (0)	0 (0)
Active malignancy	0 (0)	0 (0)
Anti-thrombotic agents no.(%)		
Anti-platelet	4 (3.7)	2 (28.6)
Anti-coagulation	0 (0)	1 (14.3)
Clinical course		
Required oxygen supplementation—(n/%)	9 (8.3)	7 (100)
Length of stay in ICU, Median (IQR)	-	11 (8,11)
Length of stay in hospital, Median (IQR)	7 (5,13)	49 (31,72)
D-dimer, Median (IQR)	0.44 (0.30,3.16)[a]	1.05 (0.81,13.44)[b]
D-dimer level more than 2x ULN (n/%)	4 (3.7)	3 (42.8)
Modified IMPROVE-VTE score (n/%)		
≤1	105 (97.2)	0 (0)
2	3 (2.8)	0 (0)
3	0 (0)	7 (100)
≥4	0 (0)	0 (0)
Venous thrombotic events—(n/%)	0 (0)	0 (0)
Follow-up		
Single follow-up—(n/%)	50 (46.3)	1 (14.3)
Multiple follow-up—(n/%)	6 (1.0)	6 (85.7)
Median length to first follow-up, d (IQR)	37 (30,48)	44 (35,47)
Mean length to first follow-up, d (SD)	42 (19)	43 (9)
Median length to last follow-up, d (IQR)	90 (69 128)	172 (89 186)
Mean length to last follow-up, d (SD)	94 (31)	152 (51)
Venous thrombotic events	0 (0)	0 (0)

[a]12 patients had d-dimer values.

[b]4 patients had d-dimer values.

were young to middle-aged with few comorbidities and had predominantly mild disease. In addition, the modified IMPROVE-VTE score was <4 in all our patients. The cutoffs used to select medically ill patients at high risk for VTE events and for the use of extended thromboprophylaxis were ≥4 or 2 or 3 with an elevated D-dimer.[5] While majority of patients did not have a D-dimer, in the non-ICU group, almost all had a score of 0 or 1. This could account for our observation of no VTE event during hospitalization and at follow-up. Our additional use of APTT-based CWA parameters, though small in sample size, provides further evidence that there is no increased hypercoagulability in COVID-19 patients post-hospitalization. In fact, patients with elevated min1 during acute phase of illness all showed normalization at recovery, signifying a return to normal hemostatic functions. Elevated Min1 above upper limit of normal has been shown to be a predictor for acute VTE.[7] These findings are consistent with published data demonstrating hypercoagulability in acute COVID-19 detected by various global hemostatic assays and normalization of plasmatic factors at convalescence[8,9]

The highest incidence of thrombotic events occurs in ICU COVID-19 patients.[1] However, few studies have reported the incidence of post-hospitalization VTE events in this cohort of patients. Theoretically, ICU COVID-19 patients are likely at higher risk of VTE events post-hospitalization. In our cohort, all seven patients who required ICU care were followed up. Three patients fulfilled the high-risk criteria based on the modified IMPROVE-VTE score. There were no observed VTE events and no reported symptoms suggestive of VTE events at each follow-up visit.

The strength of our study is its prospective nature. The limitations include a small sample size for both clinical and coagulation profile data and a relatively high lost-to-follow-up rate. Thus, caution is warranted in interpretation of our results. Regardless, our study represents one of the few to look at coagulation assays in COVID-19 patients at follow-up or recovery and despite the small numbers has merit in demonstrating the normalization of coagulation profile and CWA parameters. Our cohort was also younger with few comorbidities and predominantly mild disease and thus may not accurately reflect the true burden of post-hospitalization VTE events in COVID-19 patients who required ICU care. Lastly, not all patients in our cohort had a post-discharge medical evaluation and we assumed

TABLE 2 Unpaired comparison of coagulation/CWA parameters during hospitalization and at discharge in non-ICU COVID-19 patients

Coagulation Tests	Normal ranges	During hospitalization[a] (n = 37) Median (IQR)	At follow-up (n = 7) Median (IQR)	*P*-value
APTT, s	25.7-32.9	31.65 (30.70,33.94)	29.50 (28.10,32.13)	.080
Min1, %/s	3.12- .87	5.37 (4.73,7.07)	4.37 (3.33,4.81)	.013
Min2, %/s^2	0.51-1.05	0.79 (0.70,1.01)	0.69 (0.50,0.76)	.034
Max2, %/s^2	0.40-0.91	0.61 (0.52,0.78)	0.57 (0.40,0.63)	.07
PT, s	9.9-11.4	10.30 (9.98,10.8)	10.4 (10.31,11.33)	.385
D-dimer, mg/L FEU	0.19-0.55	0.44 (0.30,3.16)[b]	0.24 (0.21,0.44)	.234
Fibrinogen, g/L	1.80-4.80	3.28 (2.50,3.40)[c]	2.85 (2.45,3.00)	.633
Days since discharge		-	45 (34,55)	-

[a]In patients with multiple coagulation parameters during hospitalization, the highest CWA parameter was taken.

[b]12 patients had d-dimer.

[c]3 patients had fibrinogen.

that those with no record of follow-up or hospital re-admission had no VTE event.

The role for post-hospitalization prophylactic anticoagulation for COVID-19 patients continues to be an area that requires further research. Our study highlights that in otherwise young and relatively healthy patients with mild COVID-19, risk of VTE event post-hospitalization is very low, and in this group of patients, there is likely no role for routine post-discharge prophylactic anticoagulation. Further studies will be needed to ascertain the post-hospitalization VTE event rate in COVID-19 ICU patients.

KEYWORDS

COVID-19, post-hospitalization, prophylactic anticoagulation, venous thrombotic events

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

CWT and JYT had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of data analysis. CWT and JYT contributed to statistical analysis, data interpretation, and drafting of manuscript. CWT, JYT, LHL, HJN, S.K, JGHL conceived the study. CWT, JYT, WHW, and MAC contributed to acquisition data. LHL, S.K, JGHL, and HJN contributed to critical revision of manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL

This study was approved by SingHealth Centralized Institutional Review board (CIRB no. 2018/3045).

DATA AVAILABILITY STATEMENT

The data used and analyzed in this study are available from the corresponding author on reasonable request.

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