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On-admission versus in-hospital thromboembolism due to COVID-19 infection. What is the particular characteristic of those with early thrombotic events?

Abstract

Introduction: Increasing evidence has declared a hypercoagulable state in the coronavirus 2019 infection (COVID-19), while the etiology has remained a question. For the first time, the current study has aimed to compare the contributors of thromboembolism among those whose primary manifestations of COVID-19 were thrombosis vs the patients with a thrombotic event during the period of hospitalization.

Material and methods: This case-control study has been conducted on 267 COVID-19 patients, including 59, 48, and 160 ones with an on-admission, in-hospital, and without a thrombotic event, respectively. The events were defined as deep vein thrombosis (DVT), ischemic cerebrovascular accidents (CVA), pulmonary thromboembolism (PTE), or acute myocardial infarction (AMI). The demographic, physical examination, clinical and laboratory assessments of the groups were compared.

Results: The DVT (OR: 5.18; 95% CI: 1.01–26.7), AMI (OR: 11.1; 95% CI: 2.36–52.3), and arterial thrombosis (OR: 5.93; 95% CI: 0.63–55.8) were significantly associated with an on-admission thrombosis compared to those who presented in-hospital events. Lower levels of oxygen saturation were the only significant predictor index inversely associated with on-admission thrombosis compared to those with an event during the hospital admission period.

Conclusion: PTE development was the most common in-hospital thrombotic event, whereas other thromboembolism types were remarkably more often among cases with on-admission events. Oxygen saturation was the only predictor of premature thrombosis that was inversely associated with outpatient events.

Key words: COVID-19, thrombophilia, thromboembolism, SARS-CoV-2, case-control studies

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Introduction

The pandemic of the novel coronavirus infection (COVID-19) is still progressing worldwide and is the underlying etiology of numerous daily deaths since December 2019 [1]. COVID-19 presentation varies from asymptomatic courses in 30–40% of the cases. Of those symptomatic ones, 81% experience a mild disease, 14% are moderate cases, and the remained 5% develop intense endothelial activation with exuberant inflammatory response, a remarkable cytokine release associated with Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure (MOF). The overall fatality of COVID-19 accounts for 2.3% [2, 3].

An increasing body of evidence declares that patients with COVID-19 are predisposed to venous and arterial thrombosis [4]. The mecha-

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nism by which the patients are at a hypercoagulable state is not well-recognized; nevertheless, it may link to overactivation of neutrophil traps and platelets, proinflammatory cytokine release, endothelial dysfunction, and complement activation [5–7].

Due to an increasing trend in the number of confirmed cases with severe COVID-19, numerous reports have been emerged suggesting that the patients with severe courses of COVID-19, requiring hospitalization, intensive care unit (ICU) admission, and in general, critically ill patients are at significantly increased risk of thrombotic events development [8, 9]. Nevertheless, a paucity of knowledge is available regarding thrombosis incidence among mild-to-moderate cases who have developed on-admission thrombosis [10].

Thromboprophylaxis is a debating issue among COVID-19 patients; however, inadequate evidence for anticoagulant agents' routine use is available [11–13]. The current study aims to compare the characteristics of the COVID-19 patients with thrombosis on admission, during the period of hospital admission and with no thrombotic event, to make a thorough vision of thromboprophylaxis necessity in target populations.

Material and methods

Study population

The current case-control study has been conducted on 267 patients in three groups, including 59 ones with an on-admission thrombotic event, 48 ones with thrombosis during hospitalization, and 160 ones without any thromboembolism. This multicentric study has been performed among the patients admitted at Amin and Alzahra Hospitals (affiliated at Isfahan University of Medical Sciences) due to SARS-CoV-2 from May to June 2020.

This study met the Helsinki ethics declaration criteria and was derived from the approved proposal by Isfahan University of Medical Sciences Ethics Committed by code IR.MUI.MED.REC.1399.692. Written consent was obtained from the patients if possible; or by their legal guardians.

The case groups were selected from the patients with any thrombotic event, including deep vein thrombosis (DVT), ischemic cerebrovascular accidents (CVA), pulmonary thromboembolism (PTE), or myocardial infarction (MI) whose COVID-19 infection was approved by a positive polymerase chain reaction (PCR) test. The participants who met the inclusion criteria entered into the study using convenience sampling. The cases were divided into two groups, including on-admission thromboembolism, defined as admission due to any of the above events or thrombosis incidence by the first two days of hospitalization; otherwise, assigned as those with thromboembolism during the period of hospital admission.

Similar criteria were adopted for the control group.

Pregnancy, immune deficiency, history of coagulopathies, and a thromboembolic event within a month before the hospitalization regardless of its type (DVT, PTE, CVA, or MI) were determined as the exclusion criteria.

Diagnosis of thrombotic events

Presentations compatible with Well's criteria with a confirmatory Doppler ultrasonography were administered to make a DVT diagnosis [14]. Suspicion of PTE due to clinical manifestation was confirmed using computed tomographic pulmonary angiography (CTPA) [15]. Acute MI was defined as ST-segment elevation myocardial infarction (STEMI) or non-STEMI according to a typical chest pain plus a significant increase in highly-sensitive troponin as a sensitive and specific cardiac biomarker. ST-segment elevation in two or more electrocardiogram leads indicating the involvement of a particular epicardial territory or new-onset left bundle branch block (LBBB) was defined as STEMI; otherwise, non-STEMI. Hemiplegia, facial hemiparesis, or dysarthria with a CT scan compatible with an ischemic CVA were the CVA determinants.

The included patients received anti-COVID-19 infection and anticoagulation therapies according to Iran's national guidelines.

Data collection

The demographic characteristics, including age, gender, smoking, comorbidities (diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), any malignancy, cerebrovascular accidents (CVA), ischemic heart disease (IHD), and history of PTE), smoking and medical history, were entered into the study checklist.

On admission, hemodynamic information (oxygen saturation, pulse rate, systolic and diastolic blood pressure, respiratory rate, and mobility) and laboratory assessments (complete blood count, albumin, ferritin, C-reactive protein (CRP), d-dimer, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), fibrinogen, troponin, and lactate dehydrogenase (LDH)) were recorded in the study

checklist as well. A reference laboratory did all the assessments to minimize the potential bias.

The course of disease severity was defined according to an on-admission level of oxygen saturation; therefore, oxygen saturation > 93%, 90–93%, and < 90% were determined as mild, moderate, and severe diseases.

Anticoagulation in the studied group was classified as no anticoagulant therapy, prophylactic, intermediate dose, and therapeutic dose. The remedies were initiated before thrombosis incidence. Prophylactic doses included 5000 IU subcutaneous unfractionated heparin (UFH) (3 times a day) [for BMI > 40 kg/m^2:7500 IU subcutaneous UFH (three times a day)] or 40 mg subcutaneous enoxaparin (once daily) (for BMI > 40 kg/m^2:40 mg subcutaneous enoxaparin (twice daily)) was administered. Intermediate doses included 7500 IU subcutaneous UFH (three times a day) or 60 mg subcutaneous enoxaparin (daily). The therapeutic doses were determined as 80 IU/kg UFH bolus infusion followed by 18 IU/kg/h UFH infusion or 1 mg/kg subcutaneous enoxaparin (twice daily). The doses were defined according to national protocols. The anticoagulant-related adverse effects, including gastrointestinal (GI) bleeding, hemoptysis, hematuria, were recorded. The other probable side effects such as easy bruising, petechiae, or purpura were categorized as other.

The latter outcomes were ICU admission requirement, discharge/death, and non-invasive ventilation (NIV)/ intubation.

Data analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 22.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, median, range for the continuous variable, and frequency and percentages for categorical variables. Regarding the three separate primary case-control studies, we aimed to compare the groups in pairs (without thrombotic event group with thrombose on admission group; without thrombotic event group with thrombosis during hospital group, thrombosis during hospital with thrombose on admission group). As the sample size in the two groups was less than 100, the normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the distribution of some variables was not normal, nonparametric tests were used. The chi-square test or Fisher's exact test was utilized to compare the categorical variables between the groups. The continuous variables were compared using the Mann-Whitney U test. Binary logistic regression analysis was applied to estimate the odds ratio and determine the association between the assessed factors and thrombotic events in the crude and adjusted model. Logistic regression was separately constructed for each of the factors in the crude model, while all variables were entered together in the adjusted model. In addition, logistic regression models were verified in terms of goodness of fit by –2 log-likelihood. A p-value of less than 0.05 was considered as a significant level.

Results

The current study has been conducted on 267 COVID-19 patients. In-hospital thromboembolism was significantly more frequent in males than in controls ($p = 0.006$). Among the hemodynamic parameters, oxygen saturation ($p = 0.020$) and respiratory rate ($p = 0.021$) were statistically different between those with thrombosis during the hospitalization period and the controls, but not the other groups. Mobility status was another significant difference among the studied groups. The laboratory parameters assessments revealed a remarkable difference in neutrophil, lymphocyte, and platelet counts, albumin, ferritin, d-dimer, INR, fibrinogen, troponin, and LDH levels. PTE incidence ($p < 0.0001$) was the primary type of event in those who experienced thromboembolism during hospitalization, whereas AMI was statistically more frequent among those with on-admission thrombosis ($p = 0.003$). The severity of COVID-19, anticoagulation and respiratory aid type were remarkably associated with thrombosis incidence ($p < 0.05$) (Table 1).

The time assessments revealed significant correlations between symptom initiation to admission and thrombosis incidence, the period between hospitalization to ICU admission, and the period between hospitalization to discharge or death ($p < 0.05$) (Table 2).

DVT, MI, and arterial thrombosis were significantly associated with on-admission thrombosis compared to those who presented any thrombotic event during hospitalization. Lower levels of oxygen saturation were the only significant predictor index inversely associated with on-admission thrombosis compared to those with an event during the hospital admission period.

Discussion

Patients with COVID-19 infection are typically admitted to the hospital because of respi-

Table 1. Demographic and clinical characteristic of the studied population

	Group 1. COVID-19 with thrombotic events on admission (n = 59)	Group 2. COVID-19 with thrombotic events during hospitalization (n = 48)	Group 3. COVID-19 without thrombotic events (n = 160)	P-value		
				1.2	1.3	2.3
Demographic						
Age-year mean (SD)	61.8 (17.8)	63.2 (18.8)	58.8 (17.8)	0.690	0.261	0.134
Gender-male, n (%)	37 (62.2)	36 (75.0)	84 (52.5)	0.175	0.178	0.006*
Comorbidities, n (%)						
Diabetes	15 (25.4)	8 (18.2)	37 (23.1)	0.383	0.723	0.484
COPD	1 (1.7)	0 (0)	6 (3.8)	0.381	0.453	0.192
ESRD	2 (3.4)	1 (2.3)	13 (8.1)	0.739	0.218	0.174
Malignancy	1 (1.7)	1 (2.3)	10 (6.3)	0.833	0.171	0.301
CVA	4 (6.8)	3 (6.8)	8 (5.0)	0.994	0.608	0.636
IHD	15 (25.4)	13 (29.6)	25 (15.6)	0.642	0.096	0.036*
PTE history	1 (1.7)	0 (0)	1 (0.63)	0.386	0.460	0.599
Smoking, n (%)	8 (13.6)	3 (6.8)	1 (10.6)	0.273	0.545	0.452
Pre-hospitalization medication — n (%)						
None	35 (59.3)	31 (64.6)	118 (73.8)	0.578	0.039*	0.217
Aspirin	19 (32.2)	10 (20.8)	28 (17.5)	0.188	0.019*	0.600
Clopidogrel	4 (6.8)	1 (2.1)	0 (0)	0.252	0.001*	0.067
Prophylaxis anticoagulant	2 (3.4)	3 (6.3)	3 (1.9)	0.486	0.506	0.112
Anticoagulant therapy	1 (1.7)	0 (0)	3 (1.9)	0.365	0.930	0.339
On-admission clinical presentations						
O2 saturation, mean (SD)	84.2 (10.8)	80.9 (10.8)	86.3 (8.1)	0.620	0.800	0.020*
Pulse rate, mean (SD)	95.3 (21.2)	90.1 (15.2)	92.6 (19.8)	0.376	0.147	0.950
Pulse rate > 100, n (%)	19 (32.2)	12 (25.0)	35 (21.9)	0.414	0.116	0.650
Systolic blood pressure mean (SD)	121.4 (18.1)	125 (19.2)	124 (20.6)	0.851	0.570	0.622
Systolic blood pressure < 90 mm Hg, n (%)	2 (3.4)	0 (0)	4 (2.5)	0.198	0.720	0.269
Diastolic blood pressure, mean (SD)	76.4 (12.7)	78.3 (14.3)	75.6 (14.4)	0.985	0.464	0.249
Diastolic blood pressure < 60 mm Hg, n (%)	4(6.8)	0 (0)	5 (3.1)	0.066	0.227	0.215
Respiratory rate, n (%)	23.3 (7.3)	25.7 (5.4)	23.7 (6.2)	0.078	0.856	0.021*
RBR	17 (28.8)	23 (47.9)	83 (51.9)	0.042*	0.002*	0.630
CBR	48 (81.4)	37 (77.1)	101 (63.1)	0.587	0.010*	0.073
On admission, laboratory characteristics						
Neutrophil count, median (IQR)	8160 (5753–12288)	5760 (5005–9120)	5430 (3289–8562)	0.006*	< 0.0001*	0.656
Lymphocyte count, median (IQR)	1117 (787–1428)	700 (607– 832)	963 (700–1385)	< 0.0001*	0.03 *	< 0.0001*
LNR, median (IQR)	7.3 (4.2–13.3)	8.5 (6.2–13.9)	5.3 (3.17–8.9)	0.434	0.062	0.001*
Hemoglobin (g/dL), median (IQR)	12.4 (10–13.6)	13.1 (11.2–14.8)	13.1 (11.6-14.3)	0.232	0.174	0.984
Platelet× 10 ^ -3, median (IQR)	211 (147–272)	174 (135–240)	171 (137–227)	0.096	0.030*	0.929
Albumin [g/dL], median (IQR)	3.4 (3.0–3.5)	3.1 (2.9–3.6)	3.5 (3.1–3.9)	0.151	0.002*	0.008*

→

Table 1. cont. Demographic and clinical characteristic of the studied population

	Group 1. COVID-19 with thrombotic events on admission (n = 59)	Group 2. COVID-19 with thrombotic events during hospitalization (n = 48)	Group 3. COVID-19 without thrombotic events (n = 160)	P-value		
				1.2	1.3	2.3
On admission, laboratory characteristics						
CRP, n (%)	82 (47–111)	96 (40–127)	63 (21–104)	0.768	0.112	0.198
D-dimer [ng/mL], median (IQR)	3307 (2238– 6766)	3500 (1076–6824)	1491 (859–3175)	0.849	< 0.0001*	0.010*
INR, median (IQR)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	0.95 (1.1–1.3)	0.655	< 0.0001*	0.012*
PT [s], median (IQR)	13.5 (11.8–15.3)	13.1 (11.6–15.6)	12.7 (11.4–14.1)	0.928	0.437	0.128
PTT [s], median (IQR)	29 (28–33)	30 (28–35)	31 (28–34)	0.407	0.032*	0.442
FDP [μg/mL], median (IQR)	25 (25–28)	25 (22–27)	25 (18–36)	0.677	0.588	0.549
Fibrinogen [mg/dL], median (IQR)	339 (224–421)	249 (210–285)	339 (243–415)	0.117	0.923	0.003*
Troponin [ng/mL], median (IQR)	36 (7–942)	9 (1–108)	8 (2–20)	0.147	0.007*	1.000
LDH [IU/L], median (IQR)	897 (622–1331)	951 (668–1208)	725 (576–1024)	0.476	0.105	0.009*
Thrombosis type, n (%)						
PTE	29 (49.2)	43 (89.6)	–	< 0.0001*	–	–
DVT	7 (11.8)	2 (4.2)	–	0.182	–	–
MI	15 (25.4)	2 (4.2)	–	0.003*	–	–
CVA	4 (6.8)	0 (0)	–	0.126	–	–
Arterial	4 (6.8)	1 (2.1)	–	0.377	–	–
Disease severity, n (%)						
Severe	37 (62.7)	41 (85.4)	99 (61.9)	0.022*	0.810	0.009*
Moderate	14 (23.7)	3 (6.3)	34 (21.3)			
Mild	7 (13.6)	4 (8.3)	27 (16.9)			
Anticoagulation before thrombosis incidence, n (%)						
None	53 (89.8)	9 (18.8)	30 (18.8)	< 0.0001*	< 0.0001*	0.427
Prophylactic doses	4 (6.8)	24 (50.0)	97 (60.6)			
Intermediate doses	0 (0)	4 (8.3)	11 (6.9)			
Therapeutic doses	2 (3.4)	11 (22.9)	22 (13.8)			
Side effects of Anticoagulants, n (%)						
GI-bleeding	2 (3.4)	6 (12.5)	8 (5.0)	0.075	0.613	0.069
Hemoptysis	2 (3.4)	4 (8.3)	6 (3.4)	0.269	0.900	0.193
Hematuria	0 (0)	3 (6.3)	3 (1.9)	0.051	0.290	0.112
Others	2 (3.4)	4 (8.3)	2 (1.3)	0.269	0.294	0.010*
Hospitalization outcome, n (%)						
ICU admission	28 (47.5)	30 (62.5)	84 (52.5)	0.120	0.508	0.222
NIV	7 (11.9)	17 (35.4)	19 (11.9)	0.004*	0.998	<0.0001*
Intubation	13 (22.0)	12 (25.0)	38 (23.8)	0.718	0.790	0.859
Discharge	43 (72.9)	36 (75.0)	129 (80.6)	0.804	0.216	0.399
Death	16 (27.1)	12 (25.0)	31 (19.4)			

Chi^2/exact test for categorical variable and Mann-Whitney U for a continuous variable were significant if $p < 0.05$

Table 2. Time intervals [day]

	Day median (IQR)			P-value		
	Group 1. COVID-19 with thrombotic events on admission (n = 59)	**Group 2. COVID-19 with thrombotic events during hospitalization (n = 48)**	**Group 3. COVID-19 without thrombotic events (n = 160)**	**1.2**	**2.3**	**1.3**
Symptom initiation to admission	7 (2–14)	7.5 (7–14)	7 (3–10)	0.312	0.012*	0.527
Symptom initiation to thrombosis incidence	7 (2–14)	18.5 (12–24.5)	—	< 0.0001*	—	—
Admission to thrombosis incidence	0	7 (4–11.5)	—	< 0.0001*	—	—
Hospital-to-ICU admission	1 (0–2.5)	2.5 (1–6)	2 (1–5)	0.007*	0.051	0.179
Admission to discharge	8 (5–10)	17 (12.5–21)	10 (6–17)	< 0.0001*	0.0001*	0.027*
Admission to death	6.5 (2–14)	13 (8.5–20.5)	16 (9–21)	0.022*	0.115	0.011*

Chi^2/exact test for categorical variable and Mann-Whitney U for a continuous variable were significant if $p < 0.05$

ratory distress, coughing, shortness of breath, and fever. Nevertheless, an increased risk of thrombosis in numerous cases has been noted [16], particularly among critically ill patients [17]. Although numerous studies have notified the significance of anticoagulant prophylaxis or therapy for ill ICU-admitted and even, to lower extents, for hospital admitted patients with COVID-19 pneumonia, risk of thrombosis development due to COVID-19 infection among unadmitted, hospitalized due to thrombosis and the SARS-CoV-2-infected patients without pneumonia had been underestimated.

To the best of our knowledge, no effort has been made to compare the patients with an event before hospital admission versus those who developed it in the hospital. Our study's main scope was to make a thorough vision of thromboprophylaxis necessity in outpatients with mild-to-moderate COVID-19 infections.

In the current 3-armed parallel case-control study, we observed that the patients with on-admission thrombosis were similar to the second group who developed thrombosis in the course of hospitalization, and to the control group who did not experience any event, in terms of demographic, past medical history, smoking and pre-admission medications. These findings were consistent with most of the previous studies in the literature [18–20].

An ineffective role of antiplatelet therapy to prevent thrombosis, either by aspirin or clopidogrel, was a noteworthy finding of our study. Accordingly, we do not recommend antiplatelet treatment initiation for outpatients to minimize the risk of thrombotic events; however, by risk assessment, those on the treatment with these agents should continue [21]. Nevertheless, the insights about the routine administration of antiplatelet agents to prevent COVID-19-related complications are different. On the one hand, some of the researchers favored antiplatelet agents, aspirin in particular, as they present early antiplatelet therapy may be beneficial due to their inhibitory effects on platelet activation and neutrophil-to-platelet aggregation generation; the critical mechanisms for thrombosis formation [22, 23]. It should be noted that most of the studies recommending aspirin administration have targeted patients with cardiovascular disorders, not all types of thrombotic events. On the other hand, growing evidence suggests antiplatelet therapy's inefficacy for the primary prevention of thrombosis. According to the guideline, these agents are recommended regardless of being infected with SARS-CoV-2 to secondarily prevent the events such as AMI, stroke, and peripheral artery disease in intervened cases [21].

Among the on-admission hemodynamic parameters, oxygen saturation and mobility status were the only significant differences among the three studied groups. Oxygen saturation is a determinant of disease severity. Thus those with a more severe course of COVID-19 had worse

Table 3. Factors associated with premature thrombosis

	Odds ratio for premature thrombosis (95% CI)	
	Thrombotic events during hospitalization	
	Crude	Adjusted
Age	0.99 (0.97–1.02)	1.01 (0.97–1.04)
Comorbidity		
0	1	1
1	1.10 (0.46–2.61)	0.46 (0.12–1.47)
2	2.03 (0.36–11.3)	1.79 (0.18–17.80)
3	0.81 (0.10–6.16)	0.37 (0.019–5.35)
4	No data	No data
Thrombosis type		
PTE	1	1
DVT	5.18 (1.01–26.7)*	3.59 (0.21–59.73)
MI	11.1 (2.36–52.3)*	7.04 (0.95–52.04)
CVA	No data	No data
Arterial	5.93 (0.63–55.8)*	1.42 (0.88–23.2)
On admission clinical or laboratory presentations		
O_2 sat < 90	0.28 (0.10–0.74)*	0.13 (0.017–1.04)
Respiratory rate	0.94 (0.88–1.01)	0.94 (0.83–1.04)
Lymphocyte count	1.00 (0.99–1.00)	0.99 (0.99–1.01)
D-dimer [ng/mL]	1.00 (0.99–1.00)	1.00 (1.00–1.00)*
CRP [mg/L]	0.99 (0.98–1.01)	1.00 (0.98–1.01)
LDH [IU/L]	1.00 (0.99–1.00)	1.00 (0.99–1.01)

Comorbidity: 0 = none, 1, 2, 3 = have at least one, two, or three of underlying disease (DM, COPD, CVA, IHD). Logistic regression was used to estimate the Crude and Adjusted (all variables entered in the model) odds ratio. In the crude model, the goodness fit was good so that the -2 log Likelihood was above 62 for each variable separately. However, in the adjusted model, it was about 44.57; *$p < 0.05$

oxygenation status that leads to immobility, non-invasive or mechanical ventilation requirement, ICU admission, and therefore, were prone to venous thromboembolic events [24, 25].

Higher levels of absolute neutrophil count among those with on-admission thrombosis in comparison to the two other groups not only reinforced the theory about the rule of neutrophil hyperactivity and neutrophil traps in COVID-19-related hypercoagulability pathogenesis [26] but also ignites a hypothesis in terms of neutrophil count administration to make a decision for thromboprophylaxis administration in outpatient cases [27]. Because of the significance of neutrophil count, Petito *et al*. have even marked it as a more vital predictor of thrombosis than platelet in COVID-19 [28]. Albumin, d-dimer, platelet, and FDP were the other on-admission laboratory parameters that differed between the patients with on-admission events and the controls but not with the second group. However, we have no appropriate scale to decide for thromboprophylaxis in COVID-19. The similarity of these on-admission parameters regardless of the time of event among the cases with thrombosis versus the control group can help provide a comprehensive view in this term.

On the other hand, a hypothesis is ignited that an appropriate cumulative cut-off value for these parameters may appropriately stratify thrombosis risk. It is worth noting that d-dimer and FDP are well-known representatives of coagulopathy and thrombosis [29], and albumin is an acute phase reactant relating to the severity of an inflammatory process [30]. PTE was the most common type of in-hospital thrombotic event, while the other types were more prominent in the latter group. Forty-three cases developed PTE, while only 24 and 11 were under prophylactic and therapeutic doses of anticoagulants, respectively. In addition, most of the cases with in-hospital events had severe courses of the disease. Throm-

boembolism in critically ill patients has been reported in numerous studies [31–33], while Mestre-Gómez *et al*. represented a considerable rate of venous thromboembolic events among non-critical cases [19]. Moreover, the incidence of thromboembolism under anticoagulation has been notified as well; findings that promote the theory about the routine therapeutic anticoagulant therapy among hospital admitted patients in general and severe COVID-19 cases in particular [19, 34].

The evaluation of predictors for premature thromboembolism incidence versus in-hospital events revealed that DVT, AMI, and arterial thrombosis incidence were considerably more probable to occur than PTE. None of the demographic, laboratory and hemodynamic parameters other than oxygen saturation was associated with on-admission events. Decreased oxygen saturation was a predicting factor for in-hospital thromboembolism, which is discussed above as a factor associated with disease severity, mobility, and ICU admission; accounted as risks of thrombosis, particularly PTE.

We observed a significant interval between the day of symptom initiation and thrombosis incidence among those with on-admission versus in-hospital events, reinforcing the logic for routine use of anticoagulant agents in outpatients to prevent further events. Most of the studies regarding anticoagulation in outpatient cases have been conducted on hospital discharged subjects who continued their treatment rather than outpatients [35, 36]. However, promising outcomes have been achieved for those outpatients treated with anticoagulant agents; the etiology has not been well investigated yet. According to IMPROVEDD [37] or other validated scoring systems, some of the researchers believe that thromboembolism risk assessment is required, and only moderate-to-high risk cases should be administered the agents [13]. In contrast, the others claimed that anticoagulation is required for inpatients only [38]. However, according to growing data about the increased risk of thrombotic events, the incidence thereof in mild-to-moderate COVID-19 patients have weighed the theory over the routine use of anticoagulants for outpatients [39].

Conclusion

Based on this study, significant differences were observed in clinical and laboratory parameters between the cases with and without thrombotic events, while the patients with on-admission or in-hospital events were not notably different. PTE development was the most common in hospital, whereas other thromboembolism types were remarkably more frequent among cases with on-admission events. Oxygen saturation was the only predictor of premature thrombosis that was inversely associated with outpatient events. To make a decision for routine anticoagulation for patients with mild-to-moderate COVID-19 infection, further studies are required.

Conflict of interests

None declared.

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