On admission hemoglobin and albumin; two novel factors associated with thrombosis in COVID-19 pneumonia

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Abstract

Introduction: The unrelenting storm of coronavirus disease (COVID-19) since late 2019 has turned into a crucial health matter of the globe. There is increasing evidence in terms of a hypercoagulable state by this infection. Therefore, the current study aims to clarify the association between thromboembolic events in COVID-19 and the patient, the infection, and in-hospital related characteristics. Methods: The current case-control study has been conducted on 243 COVID-19 pneumonia patients (83 cases with thrombotic events and 160 controls without thrombosis) in 2020. The thrombotic events included deep venous thrombosis (DVT) (n=9), pulmonary thromboembolism (PTE) (n=48), acute myocardial infarction (AMI) (n=17), cerebrovascular accidents (CVA) (n=4) and arterial thrombosis (n=5). On admission, hemodynamic parameters, on admission laboratory assessments, mobility during hospitalization, type of oxygenation, intensive care unit (ICU) admission requirement, duration of ICU and hospital stay were recorded in the checklist. Results: According to logistic regression assessment, on admission O2 saturation (OR: 0.97, 95%CI: 0.94-0.99), hemoglobin level (OR: 0.87, 95%CI: 0.77-0.97) and albumin level (OR: 0.53, 95%CI: 0.3-0.86) were independently correlated with thrombosis due to COVID-19. Other factors, including demographic, infection severity, laboratory and in-hospital characteristics, were not significantly associated with thrombotic events. Conclusion: Based on this study's findings, hemoglobin and albumin levels were the independent factors associated with the thrombotic events in COVID-19 patients.

Introduction:

The unrelenting storm of coronavirus disease (COVID-19), which has emerged since December 2019, has turned into a crucial health matter of the globe. This infection has involved over 90 million people worldwide and led to death in approximately 2 million cases. This pandemic's exact pathophysiology is unknown yet, and scientists are searching for efficient management approaches to this infection(1, 2).

COVID-19 is an acute complex systemic disorder which presentation varies from mild influenza-like symptoms to catastrophic conditions by interstitial pneumonia progressing to acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure(3).

Increasing evidence is going on regarding hypercoagulable states among those infected with COVID-19, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The epidemiological studies have stated a wide range of 7.7-49% for thrombotic events incidence in COVID-19 infected patients, including deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), ischemic cerebrovascular accident (CVA), acute myocardial infarction (AMI), and arterial thrombosis (4-7). An increase in the inflammatory factors, endothelial dysfunction, and thromboinflammation propagated by angiotensin-converting enzyme-2 are the potential factors presumed to play a role in coagulopathy pathogenesis (8).

Although numerous studies have been conducted to assess the prevalence, etiology, and features of thromboembolic events due to SARS-CoV-2, the knowledge in this regard is limited(9, 10). Therefore, the current study aims to clarify the correlation between thromboembolic events incidence in COVID-19 and the patient, infection, and in-hospital related characteristics.

Methods:

Study population:

The current case-control study has been conducted on 243 patients admitted at Amin and Alzahra Hospitals (affiliated at Isfahan University of Medical Sciences) due to SARS-CoV-2 from May to June 2020. The included patient consisted of 83 cases with thrombotic events and 160 ones as controls with no thrombotic event, matched according to presence of COVID-19 pneumonia.

The study proposal was provided to the Ethics Committee of Isfahan University of Medical Sciences and approved by IR.MUI.MED.REC.1399.692 code number. After that, the study protocol was explained to the patients, if possible, or their legal guardians; they were reassured about the confidentiality of the obtained information and requested to sign written consent for participation in the study.

The case group was 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 and signs of COVID-19 pneumonia was present in the imaging. The inclusion of the patients was done using a convenience sampling.

Also all patients in the control group had positive result for PCR test and radiographic signs of COVID-19 pneumonia, but with no thrombotic event. The control group was matched to the cases with a 2: 1 proportion.

The previous history of coagulopathies and a recent history of thrombotic events (DVT, PTE, CVA, or AMI) within a month prior to the hospital admission were determined as the exclusion criteria.

Diagnosis of thrombotic events:

DVT diagnosis was made according to the patients' clinical manifestations (11) and confirmed through Doppler ultrasonography. To make a PTE diagnosis, computed tomographic pulmonary angiography (CTPA) was done for those referred with the symptoms compatible with PTE(12). Acute MI was determined as ST-segment elevation myocardial infarction (STEMI) or non-STEMI. Typical chest pain for cardiac ischemia plus an elevation in highly-sensitive troponin levels as a sensitive and specific cardiac biomarker was defined

as acute MI. ST-segment elevation myocardial infarction (STEMI) in two or more echocardiogram leads indicating the involvement of a particular epicardial territory or new-onset left bundle branch block (LBBB); otherwise, non-STEMI. Hemiplegia, facial hemiparesis, or dysarthria with a CT scan compatible with an ischemic CVA was the CVA determinants.

All patients received the required COVID-19 treatment and anticoagulant according to Iran's national guidelines.

Data collection:

The demographic information, including age, gender and smoking, and full medical history, were entered into the study checklist.

The patients' examinations in the period of hospitalization were recorded, as well. The assessments included the admission levels of hemodynamic parameters (oxygen saturation (O2 sat), pulse rate (PR), systolic (SBP) and diastolic blood pressure (DBP)) and the on admission laboratory assessments (polymorphonuclear cells absolute count (PMN), absolute lymphocyte count (lymph count), hemoglobin (Hb), platelet count (PLT), troponin level, fibrin degradation product (FDP), fibrinogen, d-dimer, ferritin, C-reactive protein (CRP), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), albumin (Alb) and lactate dehydrogenase (LDH)).

Anticoagulation in the studied group was classified as no anticoagulation, prophylactic, intermediate and therapeutic dose. Type of anticoagulation prior to thrombotic event was studied in the case group. Prophylactic doses were 5000 IU of subcutaneous unfractionated heparin (UFH) (twice daily), or 40 mg of subcutaneous low molecular weight heparin (LMWH) (once daily) or 10 mg of oral rivaroxaban (daily). Intermediate doses included 7500 IU of subcutaneous UFH (twice daily), or 60 mg of subcutaneous LMWH (daily), or 40 mg of subcutaneous LMWH (twice daily). The therapeutic doses were determined as 80 IU/kg of IV UFH followed by infusion of 18 IU/kg/h or 1 mg/kg of subcutaneous LMWH (twice daily) or 15 mg of oral rivaroxaban (twice daily).

The hospitalization-related characteristics were gathered as well. These data were mobility during the hospitalization (complete bed rest (CBR) or relative bed rest (RBR)), type of ventilation (non-invasive ventilation/ intubation), ICU admission requirement, length of hospitalization, the time between hospitalization to ICU admission, and death incidence.

Data analysis:

The obtained data were entered into the Statistical Package for Social Sciences (SPSS; version 14.0, SPSS Inc., Chicago, IL, USA). The descriptive data were presented in mean, standard deviation, median, Range for the continuous variable, as well as absolute numbers and percentages for categorical variables. 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 a t-test. Binary logistic regression analysis was applied to estimate the odds ratio and find the association between the assessed factors and thrombotic events in the crude model and adjusted model for age and gender. A P-value of less than 0.05 was considered as a significant level.

Results:

This study has been conducted on patients with COVID-19 pneumonia, including two groups of cases (N=83) with and controls (N=160) without thrombotic events. The cases consisted of 48 (57.8%), 9 (10.8%), 17 (20.5%), 4 (4.8%), and 5 (6.0%) with PTE, DVT, AMI, CVA, and arterial thrombosis, respectively.

The thrombotic events occurred in fifty-one patients (61.5%) on admission or within the first two days of hospitalization. The mean period between COVID-19 symptoms onset and a thrombotic event incidence was 8.2±8.6 (median: 7). Forty-three (51.8%) of the cases required ICU admission, among which thrombosis occurred in 26 ones (60.5%). Further information is presented in Table 1.

Table 1- The characteristics of the thrombotic cases(n=83)

Time from admission to thrombosis incidence-day	
Mean(SD)	4.9(10.4)
Median(Range)	1(0-72)
Thrombotic event incidence on admission-n (%)	51(61.5)*
Time from onset of COVID-19 symptoms to thrombosis incidence-day	
Mean(SD)	8.2(8.6)
Median(Range)	7(0-40)
ICU admission	43(51.8)
Thrombosis incidence in ICU-n (%)	26/43(60.
The interval between ICU admission to thrombosis incidence-day(n=26)	
Mean(SD)	5.8(8.8)
Median(Range)	3(0-37)
Time interval between thrombosis incidence to ICU admission-day(n=17)	
Mean(SD)	3.6(5.7)
Median(Range)	2(1-25)
Thrombosis type-n (%)	
PTE	48(57.8)
DVT	9(10.8)
AMI	17(20.5)
CVA	4(4.8)
Arterial thrombosis	5(6.0)
D-dimmer at time of thrombosis diagnosis	
Mean(SD)	4858(3377
Median(Range)	3885(654-
Thrombosis diagnosis within less than two days after admission (n=5) was defined as on admission thrombosis.	*Thrombo

The gender distribution of thrombotic events revealed insignificant differences according to the type of the events, but the comparison of the cases with controls revealed a significantly higher prevalence of females among the case group (P-value=0.025). None of the comorbid conditions were associated with thrombotic events (P-value>0.05). The patients' mobility and anticoagulation status were remarkably different between the cases and control (P-value<0.0001). It is also worth noting that all the cases with CVA and arterial thrombosis had not received any form of anticoagulation (P-value<0.001). Detailed information in terms of the comparison between cases and controls is demonstrated in Table 2.

Table 2- The comparison of demographic and medical characteristics between cases and controls

	Thrombosis form PTE (n=48)	**Thrombosis form DVT (n=9)**	**Thrombosis form AMI (n=17)**	**Thrombosis form CVA (n=4)**	**Thrombosis form Arterial thrombosis (n=5)**	**Thrombosis form P-Value**	**Total Case (n=83)**	**Control (n=160)**	**P-**
Gender-male-n (%)	15(31.3)	4(44.4)	3(17.7)	3(75.0)	2(40.0)	0.219	27(32.5)	76(47.5)	0.0
Age-year-Mean(SD)	59.7(17.9)	62.8(22.3)	64.8(15.1)	695(18.3)	64(34.8)	0.172	61.8(18.9)	59.0(17.6)	0.2

Age group-n (%)	Age group-n (%)	Age group-n (%)	Age group-n (%)	Age group-n (%)	Age group-n (%)	Age group-n (%)	Age group-n (%)	Age group-n (%)	Ag gro n (%
<18	0(0)	0(0)	0(0)	0(0)	0(0)	0.606	0(0)	1(0.63)	0.8
18-29	2(4.2)	1(11.1)	0(0)	0(0)	1(20.0)		4(4.82)	7(4.38)	
30-59	22(45.8)	3(33.3)	9(52.9)	1(25.0)	1(20.0)		36(43.4)	65(40.6)	
60[?]	24(50.0)	5(55.5)	8(47.1)	3(75.0)	3(60.0)		43(51.8)	87(54.3)	
ESRD-n (%)	1(2.1)	0(0)	2(11.8)	0(0)	0(0)	0.520	3(3.6)	13(8.1)	0.1
COPD-n (%)	1(2.1)	0(0)	0(0)	0(0)	0(0)	0.904	1(1.2)	6(3.8)	0.2
Malignancy-n (%)	0(0)	0(0)	1(5.9)	0(0)	0(0)	0.507	1(1.2)	10(6.3)	0.0
CVA-n (%)	3(6.3)	0(0)	1(5.9)	1(25.0)	1(20.0)	0.376	6(7.2)	8(5.0)	0.4
DM-n (%)	9(18.8)	0(0)	6(35.3)	2(50.0)	3(60.0)	0.045*	20(24.1)	37(23.1)	0.8
IHD-n (%)	10(20.8)	2(22.2)	6(35.3)	1(25.0)	2(40.0)	0.324	21(25.3)	25(15.6)	0.0
PTE-n (%)	1(2.1)	0(0)	0(0)	0(0)	0(0)	0.935	1(1.2)	1(0.63)	0.6
Smoking-n (%)	5(10.4)	2(22.2)	2(11.8)	1(25.0)	0(0)	0.761	10(12.1)	17(10.6)	0.7
CBR-n (%)	39(81.3)	7(77.8)	15(88.2)	0(0)	0(0)	0.643	70(84.3)	101(63.1)	0.0
RBR-n (%)	21(43.7)	5(55.6)	4(23.5)	0(0)	5(20.0)	0.056	31(37.4)	83(51.9)	0.0
Anticoagulation-n (%)									
No anticoagulation	23(47.9)	7(77.8)	16(94.1)	4(100)	5(100)	0.001*	55(66.3)	32(20.0)	<0
Prophylactic dose	18(37.5)	2(22.2)	0(0)	0(0)	0(0)	0.011*	20(24.1)	97(60.3)	<0
Intermediate dose	1(2.1)	0(0)	0(0)	0(0)	0(0)	0.947	1(1.2)	11(6.9)	0.0
Therapeutic dose	6(12.5)	0(0)	1(5.9)	0(0)	0(0)	0.587	7(8.4)	20(12.5)	0.3

Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Ch tes cat gor var abl and dep der t-t for cor uo var abl we sig car P- val 0.0

The anticoagulant-related side effects have been demonstrated in Table 3.

Table 3. Anticoagulant-related adverse effects

Side effects of Anticoagulants-n (%)	**PTE (n=48)**	**DVT (n=9)**	**AMI (n=17)**	**CVA (n=4)**	**Arterial thrombosis (n=5)**	**P-Value**	**Total Case (n=83)**	**Control (n=160)**	P-v
GI-bleeding	4(8.3)	1(5.9)	0(0)	1(0.25)	0(0)	0.540	6(7.2)	8(5.0)	0.4
Hemoptysis	4(8.3)	1(11.1)	0(0)	0(0)	0(0)	0.639	5(6.0)	6(3.7)	0.4
Hematuria	3(6.3)	0(0)	0(0)	0(0)	0(0)	0.668	3(3.6)	3(1.9)	0.4
Others	2(4.2)	1(11.1)	1(25.0)	0(0)	0(0)	0.453	6(7.2)	2(1.3)	0.0

Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Chi2 test for categorical variable and independent t-test for a continuous variable were significant if P-value< 0.05	Ch tes cat gor var abl and dep den t-t for con uo var abl we sig car P- val 0.0

The intubation requirement rate was significantly more in CVA cases than the other groups of patients with thrombotic events (P-value=0.048). The most prolonged period of hospitalization belonged to the cases with arterial thrombosis, whereas the shortest period between hospitalization to ICU admission was found in CVA cases (P-value=0.044).

Table 4- The comparison of hospitalization characteristics between cases and controls

	Thrombosis form	**Thrombosis form**	**Thrombosis form**	**Thrombosis form**	**Thrombosis form**	**Thrombosis form**	**Total Case (n=83)**	**Control (n=160)**	**P-**
	PTE (n=48)	**DVT (n=9)**	**AMI (n=17)**	**CVA (n=4)**	**Arterial thrombosis (n=5)**	**P-Value**			
NIV-n (%)	8(16.7)	2(22.2)	0(0)	0(0)	1(20.0)	0.340	11(13.3)	19(11.9)	0.7
Intubation-n (%)	7(14.6)	2(22.2)	3(17.6)	3(75.0)	2(40.0)	0.048*	17(20.5)	83(23.7)	0.5
ICU-n (%)	23(47.9)	3(33.3)	10(58.8)	0(0)	3(60.0)	0.222	43(51.8)	84(52.5)	0.9
Death-n (%)	7(14.6)	1(11.1)	6(35.3)	2(50.0)	1(20.0)	0.204	17(21.5)	31(19.4)	0.8

Time from hospitalization to ICU admission-day Mean(SD) Median(Range)	Time from hospitalization to ICU admission-day 7.5(13.6) 2(0-58)	Time from hospitalization to ICU admission-day 2.0(2.0) 2(0-4)	Time from hospitalization to ICU admission-day 1.2(1.6) 0.5(0-4)	Time from hospitalization to ICU admission-day 0.7(0.9) 0.5(0-2)	Time from hospitalization to ICU admission-day 2.0(1.7) 1(1-4)	Time from hospitalization to ICU admission-day <0.0001* 0.538	Time from hospitalization to ICU admission-day 4.6(10.4) 2(0-58)	Time from hospitalization to ICU admission-day 3.9(5.5) 2(0-33)	Ti fro hos tal tio IC ad da 0.6 0.2
Hospitalization length-day Mean(SD) Median(Range)	Hospitalization length-day 14.5(13.7) 10(2-67)	Hospitalization length-day 12.8(8.0) 10(5-30)	Hospitalization length-day 8.5(7.8) 5(0-25)	Hospitalization length-day 9.8(6.5) 8(4-19)	Hospitalization length-day 19.4(15.3) 16(9-46)	Hospitalization length-day 0.044* 0.541	Hospitalization length-day 13.1(12.1) 9(0-67)	Hospitalization length-day 13.8(10.5) 11(1-83)	Ho len da 0.6 0.2
Time to Discharge-day Mean(SD) Median(Range)	Time to Discharge-day 14.7(13.9) 10(2-67)	Time to Discharge-day 13.7(7.9) 10(7-30)	Time to Discharge-day 11.1(8.1) 8(0-25)	Time to Discharge-day 6.5(3.5) 6(4-9)	Time to Discharge-day 12.8(4.3) 12(9-17)	Time to Discharge-day 0.041* 0.760	Time to Discharge-day 13.7(11.9) 10(0-67)	Time to Discharge-day 13.3(11.0) 10(1-83)	Ti to Dis da 0.8 0.9
Time to death-day Mean(SD) Median(Range)	Time to death-day 12.9(12.4) 6(2-31)	Time to death-day 5(0) 5(5-5)	Time to death-day 3.8(4.8) 1.5(1-13)	Time to death-day 13.0(8.5) 13(7-19)	Time to death-day 46(0) 46(46-46)	Time to death-day 0.021* 0.148	Time to death-day 11.2(13.0) 5(1-46)	Time to death-day 15.8(7.9) 16(2-34)	Ti to dea da 0.1 0.1

Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Chi2 test for cate- gorical vari- able and in- depen- dent t-test for a contin- uous vari- able were signifi- cant if P- value< 0.05	Ch tes cat gor var abl an dep den t-t for cor uo var abl we sig car P- val 0.0

Table 5 demonstrates the hemodynamic and laboratory characteristics of the cases versus controls. The mean oxygen saturation in the case group was remarkably lower than controls (P-value=0.031); however, the groups' comparison based on the categorized oxygen saturation revealed an insignificant difference (P-value=0.768).

The laboratory evaluations revealed significant differences between the groups in terms of PMN count, hemoglobin level, platelet count, d-dimer, albumin, and lactate dehydrogenase levels (P-value<0.05). The comparison of troponin level regardless of the thrombotic event type was accompanied by significantly higher levels in the case group (P-value=0.027), but by eliminating those with AMI, the two groups were similar (P-value=0.607).

Table 5- The comparison of on admission maximum-values of hemodynamic and laboratory parameters between the cases and controls

	Case (n=83)	Control (n=160)	P-Value
O2sat-Mean(SD)	83.6(11.4)	86.3(8.1)	0.031*
O2sat group-n (%)	O2sat group-n (%)	O2sat group-n (%)	O2sat group-n (%)
[?]90	60(72.3)	116(72.5)	0.768
>90 to [?]93	11(13.3)	17(10.6)	
[?]94	12(14.5)	27(16.9)	
PR-n (%)	93.6(18.8)	92.6(19.8)	0.707
RR-n (%)	23.9(6.8)	23.7(6.2)	0.773
Systolic BP-n (%)	124.8(19.1)	124(20.6)	0.850
Diastolic BP-n (%)	77.9(13.9)	75.6(14.4)	0.241
PMN count-n (%)	8311(4253)	6737(4872)	0.013*
Hb-n (%)	12.3(2.6)	13.0(2.1)	0.021*
Lymph count-n (%)	1344(905)	1236(887)	0.372
PLT×10ˆ3-n (%)	220.5(96.9)	193.5(94.4)	0.037*
Troponin-Mean(SD)	1721(6723)	51.4(172.9)	$0.027^{*\&}$
Troponin-Mean(SD)ˆ	238.8(492.5)	51.4(172.9)	$0.607^{\&}$

FDP-Mean(SD)	26.2(6.1)	24.60(12.1)	0.639
Fibrinogen-Mean(SD)	276.6(115.1)	326.9(116.3)	0.034
D-dimer-Mean(SD)	4803(3735)	2830(2997)	<0.0001*
Ferritin-Mean(SD)	765(596)	715(580)	0.598
CRP-Mean(SD)	75.5(43.3)	66.1(46.4)	0.166
PT-Mean(SD)	15.2(6.9)	13.7(5.5)	0.089
PTT-Mean(SD)	33.1(9.3)	34.1(12.5)	0.544
INR-Mean(SD)	1.37(0.67)	1.22(0.55)	0.060
ALB-Mean(SD)	3.3(0.52)	3.5(0.61)	0.009*
LDH-Mean(SD)	1349(1802)	861(456)	0.046*&
*Chi^2 test for categorical variable and independent t-test (or median test &) for a continuous variable were significant if P-value< 0.05 # Adjusted for Gender and Anticoagulation ^ Cases without MI (n=66) was compared with Control	*Chi^2 test for categorical variable and independent t-test (or median test &) for a continuous variable were significant if P-value< 0.05 # Adjusted for Gender and Anticoagulation ^ Cases without MI (n=66) was compared with Control	*Chi^2 test for categorical variable and independent t-test (or median test &) for a continuous variable were significant if P-value< 0.05 # Adjusted for Gender and Anticoagulation ^ Cases without MI (n=66) was compared with Control	*Chi^2 test for categorical variable and independent t-test (or median test &) for a continuous variable were significant if P-value< 0.05 # Adjusted for Gender and Anticoagulation ^ Cases without MI (n=66) was compared with Control

According to Table 6, oxygen saturation, hemoglobin, and albumin levels were the only markers inversely associated with thrombotic events.

Table 6- Logistic regression assessments of related factor to thrombosis incidence

Oxygen saturation	
PMN absolute count	
Hemoglobin	
Lymphocyte absolute count	
Platelet count	
Troponin	
D-dimer	
Albumin	
Lactate dehydrogenase	

adjusted for Gender and Anticoagulation dose * Odds Ratio was considered significant in 0.05 level, using logistic regress

Discussion:

In the current case-control study, we tried to assess the clinical, laboratory, and in-hospital characteristics of the patients with thrombotic events following a SARS-CoV-2 infection and find the predisposing factors that make a person prone to thrombotic events. Over 60% of the cases admitted in ICU, experienced the thrombotic event after ICU admission. There are several studies representing the high incidence of these events in critically ill patients, as well (4, 6, 7, 13). Nevertheless, 61.5% of the COVID-19 infected patients had a thrombotic event on-admission or presented it within the first two days. A paucity of knowledge is available regarding the characteristics of COVID-19 for increasingly developing these events.

The studies on general populations insisted on the role of medical conditions including hypertension, diabetes mellitus, chronic pulmonary disorders, chronic renal disorders, and active malignancy on thrombotic events incidence (14), which has been notified in patients with SARS-CoV-2(7). However, none of the comorbid conditions was remarkably different between cases and controls in this study. We assume that better insight may be provided in larger populations.

Among the hemodynamic parameters, oxygen saturation was found the only independent factor associated with the thrombotic events. SARS-CoV-2 pneumonia can lead to improper oxygenation due to acute respiratory distress itself. In addition, inappropriate respiration disables a person from exertion and is causative for immobilization, as well (15-17). It should be noted that approximately 63% of the cases were admitted due to PTE, a condition accompanying by a decrease in oxygen saturation, and CVA, which required intubation due to a similar condition. Therefore, a two-sided association should be considered between the oxygen saturation and thrombotic events.

We found on-admission hemoglobin level as an inverse factor associated with thrombotic events, which has not been noted previously. Furthermore, most of the studies represented an insignificant difference between those with thromboembolic events and the control groups(13, 18).

It is hypothesized that low hemoglobin level, which represents low blood viscosity, reduces stress formation on the endothelial bed of the vessels and, in turn, inhibits the function of the anti-thrombotic mechanism(19). Therefore, patients with lower hemoglobin levels are prone to thrombotic events due to impaired endothelial function as one of the Virchow triad(20). Recent investigations on COVID-19 have notified increased risk of thromboembolism development due to diverse factors such as the imbalance between oxidative and anti-oxidative processes, accumulation of pro-inflammatory and pro-thrombotic factors, and endothelial dysfunction (21-23). It seems that mentioned factors accompanying low levels of hemoglobin reinforce the cascade of thrombosis formation.

Contrary to most of the investigations insisting on the standalone role of low hemoglobin levels on thrombosis in-hospital and long-term adverse events(24-27), studies in the literature have rarely evaluated the predictive value of hemoglobin level for thrombotic events developing. Yamashita et al. reported exceptional lower levels of hemoglobin among the patients with VTE and, in accordance with other presentations, found a predictive role for this index for in-hospital outcomes, long-term adverse events, and all-cause mortality(28). A similar reverse association was presented by Can and colleagues (19). On the other hand, Kalra hesitates to confirm whether low hemoglobin has a role in cardiovascular events and/or is a marker of comorbidities(25). This poor correlation was noted for thromboembolism, as well(29). Therefore, the attitude about hemoglobin's role in the development of thrombotic events is not unanimous and requires further investigations.

D-dimer was shown to be directly correlated with thrombotic events in our study. It is traditionally known as a marker of inflammation, coagulation activation, and hyperfibrinolysis. The studies assessing these events in COVID-19 patients insisted on the elevated levels of this marker among those who experience a thrombotic event during a course of COVID-19 infection(13, 30). In addition, Lodigiani et al. represented a rapid increase in D-dimer levels among non-survivors of thrombosis in COVID-19 patients(5). Helms and colleagues noted that a rapid rising D-dimer level despite anticoagulation is a reflection of clot formation and a probable thrombotic event. They even recommended imaging assessments for patients with a sudden increase in d-dimer along with the deterioration of the clinical course of the disease (31). The significance of D-dimer is to the extent that guidelines for anticoagulant therapy in this infection have mentioned elevated D-dimer as a factor for high dose anticoagulant treatment (32).

Albumin is the other factor found inversely associated with thrombosis in COVID-19 infection. To the best of our knowledge, despite all the notifications regarding the hypercoagulable state in SARS-CoV-2 infection, albumin level has not been well-studied. Zhang and colleagues determined the proportion of fibrinogen-to-albumin as a determinant for the risk of thrombosis development (33).

The increased probability of thrombosis in hypoalbuminemia has been well-established in chronic conditions such as nephrotic syndrome or cirrhosis(34); however, most of our patients were gathered from the general

population infected by COVID-19. Nevertheless, studies on the general population have stated a significant association between albumin levels with VTE incidence (35) and its severity(36). Further studies on other thrombotic events presented similar correlations (37-39).

To evaluate the role of low albumin levels as a risk factor for thrombosis formation, some believe it as a representative of inflammation status(40). This theory has been confirmed by presenting an inverse correlation between serum albumin level with C-reactive protein and estimated erythrocyte sedimentation(36, 38). In other studies, an antagonistic role of oxidation, stagnant, thrombosis, and leukocyte adhesion has been considered for albumin(41). Further investigations, particularly in the critical group of COVID-19 patients, are required.

The clinical outcomes and hospitalization characteristics were not remarkably different between cases and controls that may have occurred because of early anticoagulation administration in both groups. According to the findings of this study in terms of a significant association between anticoagulant prophylaxis and thrombosis formation, and due to the recommendations of the other investigations of SARS-CoV-2 infected patients, prophylactic anticoagulation is strongly recommended, particularly in critical patients (21, 42, 43). It should also be noted that high number of cases in "no anticoagulation" group may be due to this fact that thrombotic events occurred on admission and no anticoagulation was received by them prior to admission. The significance of prophylaxis is clarified, knowing the high incidence of thrombosis even among those under anticoagulation(22). Therefore, detailed investigations are recommended to determine the ultimate anticoagulant dosage in the target populations.

Conclusion:

Based on this study's findings, hemoglobin and albumin levels were the independent factors associated with thrombotic events in COVID-19 patients.

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