



Early detection of deep vein thrombosis in patients with coronavirus disease 2019: who to screen and who not to with Doppler ultrasound?

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Received: 20 June 2020 / Accepted: 21 July 2020 / Published online: 18 August 2020
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Abstract

Purpose Aim of the study is to evaluate the incidence of DVT in COVID-19 patients and its correlation with the severity of the disease and with clinical and laboratory findings.

Methods 234 symptomatic patients with COVID-19, diagnosed according to the World Health Organization guidelines, were included in the study. The severity of the disease was classified as moderate, severe and critical. Doppler ultrasound (DUS) was performed in all patients. DUS findings, clinical, laboratory's and therapeutic variables were investigated by contingency tables, Pearson chi square test and by Student *t* test and Fisher's exact test. ROC curve analysis was applied to study significant continuous variables.

Results Overall incidence of DVT was 10.7% (25/234): 1.6% (1/60) among moderate cases, 13.8% (24/174) in severely and critically ill patients. Prolonged bedrest and intensive care unit admission were significantly associated with the presence of DVT (19.7%). Fraction of inspired oxygen, *P/F* ratio, respiratory rate, heparin administration, D-dimer, IL-6, ferritin and CRP showed correlation with DVT.

Conclusion DUS may be considered a useful and valid tool for early identification of DVT. In less severely affected patients, DUS as screening of DVT might be unnecessary. High rate of DVT found in severe patients and its correlation with respiratory parameters and some significant laboratory findings suggests that these can be used as a screening tool for patients who should be getting DUS.

Keywords Venous thrombosis · Ultrasonography · Doppler; diagnosis · COVID-19 · Pandemics

Abbreviations

ICU Intensive care unit
DVT Deep vein thrombosis

CRP C-reactive protein
AUC Area under the curve
WHO World Health Organization

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O ₂	Oxygen
COVID 19	Coronavirus disease 2019
CXR	Chest X-ray
CT	Computed tomography
rRT-PCR	Reverse transcriptase polymerase chain reaction
LICU	Low-intensity care unit
MICU	Mid-intensive care unit
PE	Pulmonary embolism

Introduction

Deep vein thrombosis (DVT) occurred in 3.5% of intensive care unit (ICU) patients and 1.3% in hospitalized patient in medicine wards [1, 2].

A hallmark of patients affected by coronavirus disease 2019 (COVID-19) is coagulopathy.

Mechanism and pathogenesis is still not clear, although excessive inflammation, hypoxia, immobilization and diffuse intravascular coagulation could be possible factors associated with high incidence of thromboembolism [3, 4].

Clinical observations stemming from patients admitted to intensive care units (ICU) showed that several patients have signs of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) [5, 6].

The purpose of this study was to explore the incidence of DVT in COVID-19 patients and correlate it with the severity of the disease as well as with clinical and laboratory findings.

Materials and methods

A total number of 234 patients, with the mean age of 61.63 years, including 164 females (70%) and 70 males (30%), diagnosed with coronavirus disease 2019 admitted in our Hospital from March 15th and April 7th 2020 were included in our study (Table 1).

All the patients were diagnosed according to the World Health Organization (WHO) guidelines [7]. These patients underwent a series of investigations, including clinical examinations, laboratory tests, chest X-ray (CXR), sometimes computed tomography (CT), and real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for SARS-CoV-2. The severity of the disease of the hospitalized patients was judged according to the Seventh Revised Edition of the “The diagnosis and treatment plan for the novel coronavirus disease” [8] in moderate, severe and critical disease, and patients were sorted in Low intensity care units (LICU), Mid-intensive Care Units (MICU) and Intensive Care Units (ICU), respectively.

All patients were asymptomatic and were underwent to Doppler ultrasound (DUS) examination. Two skilled operators performed the bedside examinations, with portable US machines available in each ward and using the linear probe (Fig. 1). DUS findings were classified as positive or negative; femoral and/or popliteal thrombosis was considered as positive DVT (Figs. 2a, b, 3a, b, c).

All the continuous and categorical variables analyzed are summarized in Table 1 and include clinical, laboratory’s and therapeutic factors. Each patient needed oxygen (O₂) therapy and was treated at least with prophylactic heparin administration (Table 1).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No informed consent was required.

The study was approved by our Institutional Review Board (Radcovid03/2020).

SPSS v25.0 (IBM, Chicago, IL) was used for all statistical analyses; *p* values were considered significant when < 0.05.

A correlation between the DUS result (positive/negative) and many clinical, laboratory’s and therapeutic variables (see Table 1 for variables list) was investigated by contingency tables and Pearson chi square test for categorical variables and by Student *t* test and Fisher’s exact test for continuous variables. Continuous variables that showed a significant correlation were studied also with ROC curve analysis.

Results

The 234 patients included in the study were hospitalized as follows: 46 in ICU, 128 in MICU and 60 in LICU (Table 1).

At DUS, asymptomatic DVT finding was reported in 25/234 cases (10.7%). Contingency tables and Pearson chi square test showed a good association for prolonged bedrest and ward type. Only 2 out of 82 were self-mobilizing versus 23 out of 152 bedrest patients showed DVT on DUS (sensitivity: 92.0%; specificity: 38.3%; *p* value: 0.003). Moreover, only 1 out of 60 low-intensity care wards patients (1.6%) versus 15 out of 128 mid-intensive care wards (11.7%) and 9 out of 46 high-intensity care wards patients (19.6%) showed DVT on DUS (chi square 9.05; *p* value: 0.01).

Student *t* test and Fisher’s exact test showed good associations for ventilation, therapeutic and laboratory’s variables. More in detail, deep vein thrombosis was found in patients with an higher fraction of inspired oxygen (*p* value: 0.002), a lower P/F ratio (*p* value: 0.0007) and an higher respiratory rate (*p* value: 0.049); moreover, in these patients heparin dosage was higher, despite number of administration per day (q24 h / q12 h / q8 h). Higher values of d-dimer (*p* value:

Table 1 Variables list and descriptive statistics

Continuous variables	<i>N</i>	Min	Max	Mean	standard dev
Age (years)	234	7	98	61.63	14.21
BMI (kg /m ²)	56	23.15	42.9	29.08	5.14
Time from symptoms onset (days)	228	0	36	7.21	4.63
Admission to DUS time (days)	233	0	34	10.14	8.29
Systolic blood pressure (mmHg)	233	90	180	130.03	17.43
Diastolic blood pressure (mmHg)	233	45	100	73.57	11.06
Heart rate (beats per minute)	234	40	130	80.19	15.05
FiO ₂	165	0.3	1	0.49	0.14
SpO ₂	231	0.95	100	95.55	6.97
PF ratio	195	57	472	225.45	97.51
Respiratory rate (breaths per minute)	232	12	40	21.69	4.88
Platelet (cells/mm ³)	233	45	812	328.28	145.40
INR	229	0.044	4.3	1.18	0.33
Partial thromboplastin time	231	1.01	77.9	34.01	7.49
D-dimer (µg/mL)	229	200	90681	4006.0	8900.1
Fibrinogen (mg/dl)	209	120	1139	509.14	190.62
IL-6 (pg/mL)	68	1.5	543	59.09	90.95
Ferritin (ng/mL)	228	69.4	15033	1278.38	1627.82
C reactive protein (mg/L)	232	0	34.15	5.74	6.50
Procalcitonin (ng/mL)	153	0.02	40.8	0.61	3.37
Heparin dosage (UI)	202	2850	12500	5653.22	1799.23
Categorical variables		<i>N</i>		<i>%</i>	
Sex					
Male		70		29.90	
Female		164		70.10	
Smoke					
Yes		203		86.75	
No		26		11.11	
COPD					
Yes		18		7.69	
No		211		90.17	
Asthma					
Yes		10		4.27	
No		219		93.59	
Fever					
Yes		207		88.46	
No		25		10.68	
Cough					
Yes		141		60.26	
No		89		38.03	
Dyspnea					
Yes		156		66.67	
No		76		32.48	
Chest pain					
Yes		6		2.56	
No		224		95.73	
Other symptoms					
Yes		100		42.74	
No		134		57.26	

Table 1 (continued)

Categorical variables	<i>N</i>	%
Asthenia		
Yes	29	12.39
No	205	87.61
Myalgia		100.00
Yes	12	5.13
No	222	94.87
Gastroenteric symptoms		
Yes	32	13.68
No	202	86.32
Alteration of consciousness		
Yes	16	6.84
No	218	93.16
Upper airways symptoms		
Yes	10	4.27
No	224	95.73
Deep vein thrombosis risk factors		
Yes	42	17.95
No	192	82.05
Cancer		
Yes	26	11.11
No	208	88.89
Cardiovascular risk factors		
Yes	138	58.97
No	96	41.03
Obesity		
Yes	37	15.81
No	197	84.19
Hypertension		
Yes	93	39.74
No	141	60.26
Ischemic heart disease		
Yes	17	7.26
No	217	92.74
Myocardial infarction		
Yes	8	3.42
No	226	96.58
Diabetes		
Yes	40	17.09
No	194	82.91
Dyslipidemia		
Yes	23	9.83
No	211	90.17
Prolonged bed rest		
Yes	152	64.96
No	82	35.04
Venous catheter		
Yes	15	6.41
No	219	93.59
Ward type		
High intensity of care	46	19.66

Table 1 (continued)

Categorical variables	N	%
Mid-intensity of care	128	54.70
Low intensity of care	60	25.64
O ₂ therapy		
Nasal cannula	29	12.39
Venturi/reservoir	42	17.95
C-PAP	85	36.32
Orotracheal intubation	78	33.33
Heparin administration		
q24 h	101	43.16
q12 h	125	53.42
q8 h	8	3.42

**Fig. 1** Thrombosis of the common femoral vein

0.000004) and IL-6 levels (p value: 0.002), higher ferritin (p value: 0.01), and higher C reactive protein (p value: 0.004) were found in patients with DVT compared with those without DVT. Moreover, time between hospital admission and DUS was lower in DVT patients (p value: 0.03). Details are shown in Table 2 and Fig. 4. ROC curve (Table 3 and Fig. 5)

showed the highest AUC for IL-6 (0.820) with a sensitivity of 83.3% and a specificity of 80.6% for a cutoff of 64.95 pg/mL, with an accuracy (AUC) of 82.0%.

Discussion

Apart from respiratory failure, coagulopathy is a common abnormality in patients with COVID-19.

Klok FA et al. [3] reported a high incidence of thrombotic complications (acute pulmonary embolism (PE), deep vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism) in patients with COVID-19 infections (31%) admitted at ICU. All patients received at least standard doses thromboprophylaxis.

Data about the incidence of DVT is scarce. A recent published study has shown an incidence of 25% of DVT in ICU COVID-19 patients; the significant increase of D-dimer resulted as a good index for identifying high-risk patients [5].

Llitjos JF et al. reported 69% incidence rate of DVT in severe mechanically ventilated COVID-19 patients; all patients were treated with therapeutic anticoagulation from admission [6].

Even in our Hospital, from the beginning of the outbreak, an unusually high mortality rate due to pulmonary embolism occurred among hospitalized COVID-19 patients who were under prophylactic dose of low molecular weight heparin. Therefore, we decided to implement a screening program for DVT in COVID-19 patients hospitalized.

We found that DVT even occurs in patients treated with therapeutic anticoagulation from admission, highlighting the high thromboembolic potential of COVID19. Bedrest and ICU admission resulted significantly associated with the presence of DVT.

Our results have shown an incidence for DVT of 10.7%, lower than in other mentioned publications. The reason is to

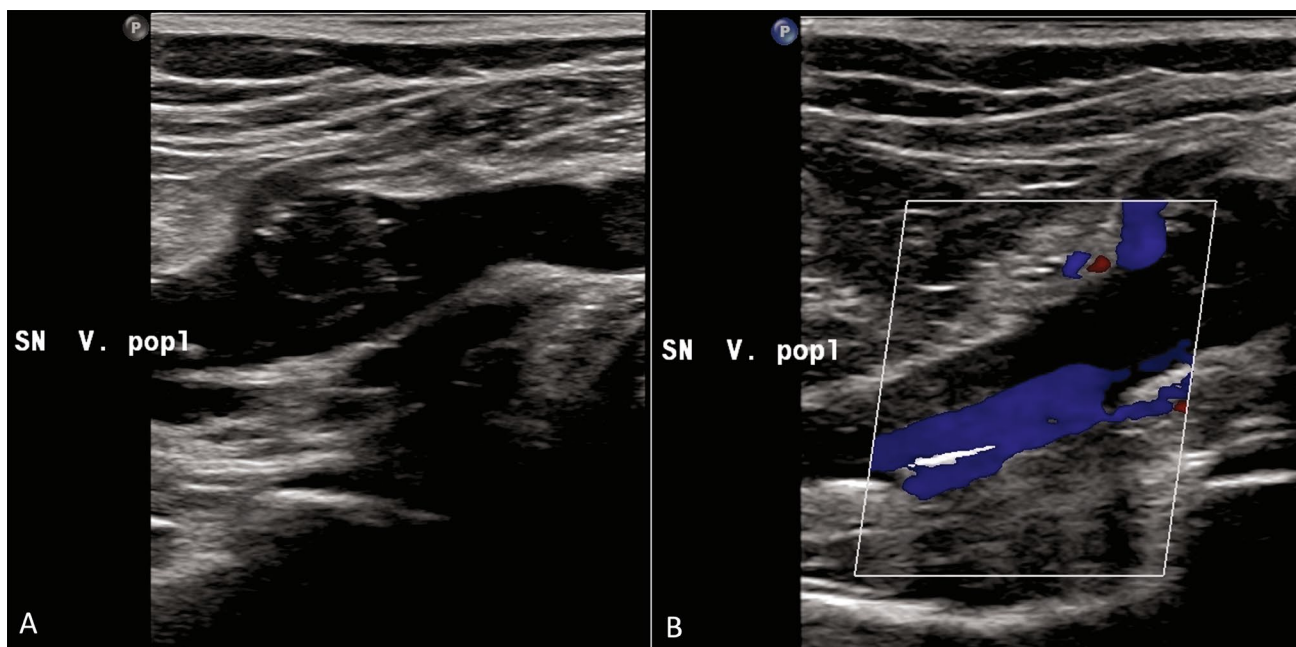


Fig. 2 A, B: Partial thrombosis of the popliteal vein

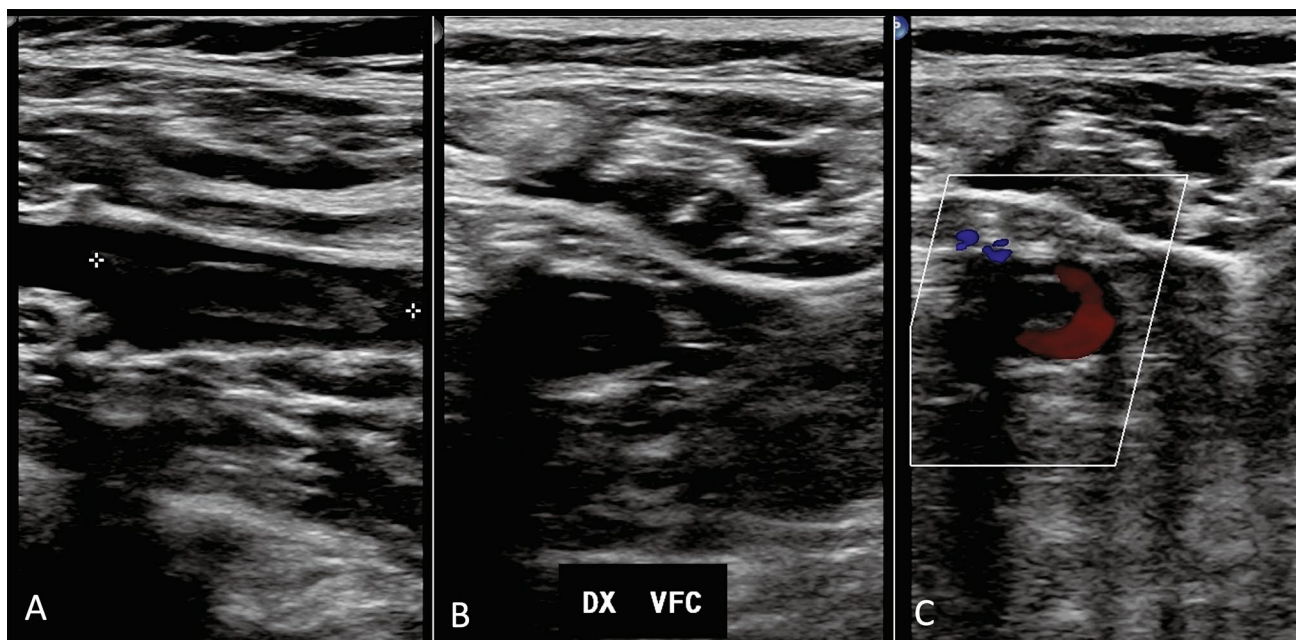


Fig. 3 a, b, c Floating thrombus of the common femoral vein

be found in the fact that our study is the only one in which even patients less severely affected from low intensity wards were included. In medicine wards we found only 1 out of 60 hospitalized patients, with an incidence of 1.6%, similar to that reported in the same wards in non-COVID-19 patients (1.3%) [1, 9, 10]. This observation led us to suppose that in less severely affected patients in low-intensity Covid-19

wards, execution of DUS as screening of DVT might be unnecessary. Our overall incidence of DVT increases to 13.8% considering mid-and high-intensity Covid-19 units (24/174).

Strengths of the present study is represented by the large analyzed series, which to date, is the largest in literature. Moreover, an association with clinical, laboratory's

Table 2 Student *t* test results

<i>T</i> test	<i>p</i> value	Mean ± SD DVT	Mean ± SD DVT negative
Age	> 0.05	65 ± 10.28	61.22 ± 14.57
BMI	> 0.05	27.23 ± 5.24	29.59 ± 5.05
Time from symptoms onset	> 0.05	7.92 ± 4.62	7.12 ± 4.63
Admission to DUS time	0.029	6.6 ± 8.13	10.56 ± 8.22
Systolic blood pressure	> 0.05	130.64 ± 15.9	129.96 ± 17.64
Diastolic blood pressure	> 0.05	70.84 ± 11.28	73.9 ± 11.02
Heart rate	> 0.05	80.36 ± 17.85	80.17 ± 14.73
FiO ₂	0.0019	0.58 ± 0.2	0.48 ± 0.13
SpO ₂	> 0.05	94.71 ± 2.87	95.64 ± 7.3
PF ratio	0.00072	168.54 ± 77.4	233.44 ± 97.56
Respiratory rate	0.049	23.48 ± 4.6	21.48 ± 4.88
Platelet	> 0.05	288.8 ± 180.97	333.03 ± 140.31
INR	> 0.05	1.2 ± 0.24	1.18 ± 0.34
Partial thromboplastin time	> 0.05	34 ± 6.34	34.01 ± 7.63
D-dimer	0.000004	11571.92 ± 20404.55	3078.75 ± 5641.83
Fibrinogen	> 0.05	527.88 ± 250.82	506.59 ± 181.64
IL-6	0.0021	165.48 ± 121.76	48.79 ± 81.55
Ferritin	0.010	2080.04 ± 2988.36	1184.07 ± 1366.14
C reactive protein	0.0042	9.23 ± 8.42	5.32 ± 6.12
Procalcitonin	> 0.05	0.43 ± 0.41	0.63 ± 3.56
Heparin dosage	0.035	6433.33 ± 2256.84	5562.71 ± 1723.29

SD Standard Deviation; *BMI* Body Mass Index; *FiO₂* Fraction of inspired oxygen; *SPO₂* peripheral capillary oxygen saturation; *PF ratio* PaO₂/FiO₂ ratio; *INR* international normalized ratio

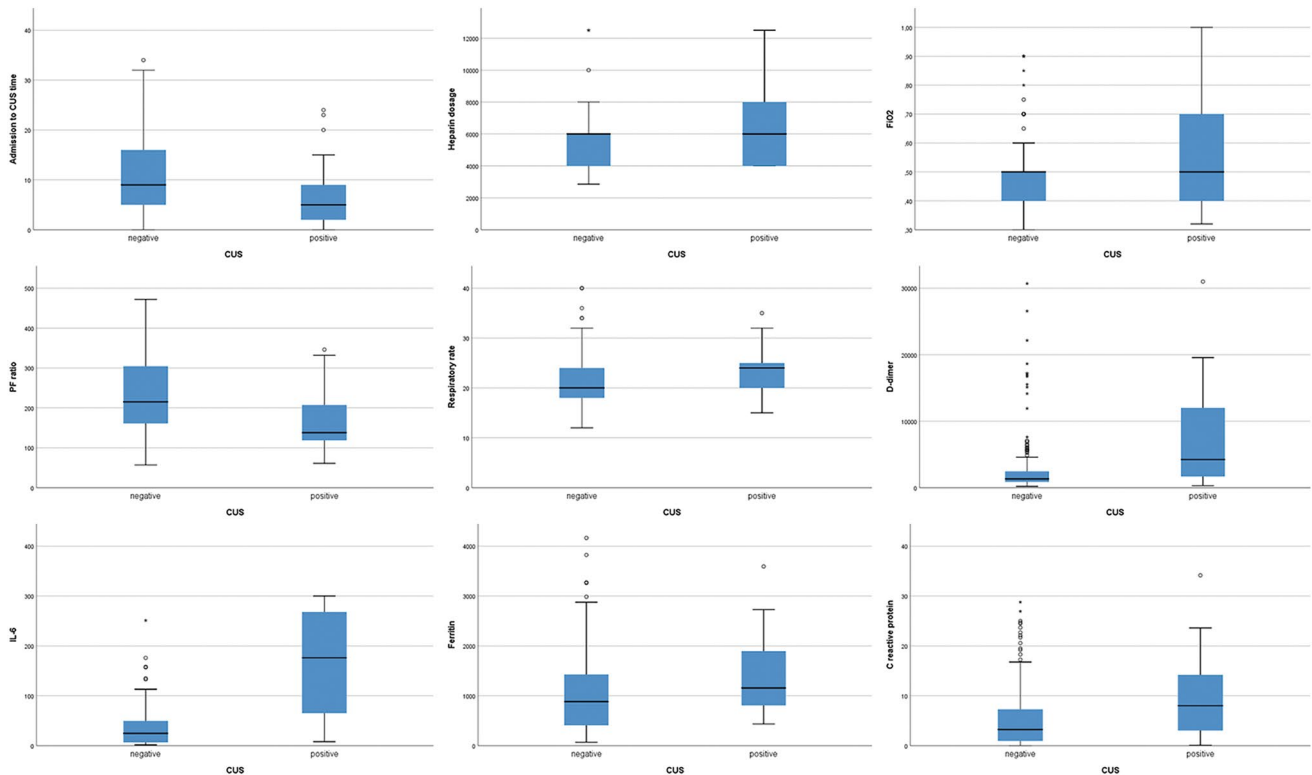
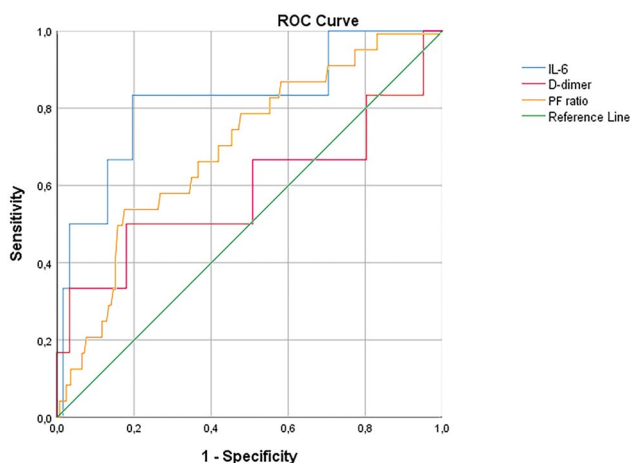


Fig. 4 Boxplot for significant continuous variables

Table 3 ROC curve analysis for significant continuous variables at student *t* test

Variable	AUC	Cutoff	Sensitivity	Specificity
Admission to DUS time (days)	0.661	9.5	0.760	0.490
Heparin dosage (UI)	0.611	5350	0.619	0.470
FiO ₂	0.638	0.525	0.478	0.768
PF ratio	0.701	292.5	0.917	0.292
Respiratory rate (breaths per minute)	0.637	19	0.880	0.314
D-dimer (µg/mL)	0.707	2128	0.680	0.706
IL-6 (pg/mL)	0.820	64.95	0.833	0.806
Ferritin (ng/mL)	0.663	907.5	0.708	0.515
C reactive protein (mg/L)	0.659	4.1	0.720	0.570

**Fig. 5** ROC curve for significant continuous variables with AUC > 0.7

and therapeutic parameters was investigated and confirmed for the first time. Indeed, both the fraction of inspired oxygen, P/F ratio and the respiratory rate and heparin administration, d-dimer, IL-6, ferritin and CRP resulted correlated with the presence of DVT.

However, the study presents some limitations, especially in its retrospective design. Moreover, DUS was performed earlier in DVT patients and DVT patients had an higher dose of heparin, so an underestimation of DVT may be suspected in some cases. This suggests that clinical and laboratory suspicion before investigation is always mandatory.

The high rate of DVT found in our severe COVID-19 patients who were under prophylactic treatment and correlation with respiratory parameters and some significant laboratory findings suggests that these can be used as a screening tool for patients who should be getting DUS [11]. In these patients, DUS may be considered a useful and valid tool for early identification of DVT.

Funding This research received no external funding.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical standards This study was conducted in accordance with the Helsinki Declaration of 1964 and its late amendments. The study protocol was approved by the institutional Ethics Committee.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was waived for this retrospective study.

Consent for publication All authors expressed explicit consent for the publication of this manuscript.

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