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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Abstract

BACKGROUND. 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.

CONCLUSIONS. 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.

Key Points:

- *DVT occurs even in patients treated with therapeutic anticoagulation from admission, highlighting the high thromboembolic potential of COVID-19.*
- *Bedrest and ICU admission resulted significantly associated with the presence of DVT.*
- *In severe COVID-19 patients with specific respiratory parameters and laboratory findings, DUS may be considered a valid tool for early identification of DVT.*

Background

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.

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).

Table 1
Variables list and descriptive statistics

Continuous variables	**N**	**Min**	**Max**	**Mean**	**Standard Dev.**
Age *(years)*	234	7	98	61,63	14,21
BMI *(kg /m²)*	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/mm3)*	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				**N**	**%**
Sex					
	Male			70	29,90
	Female			164	70,10
Smoke					

Continuous variables	N	Min	Max	Mean	Standard Dev.
	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
Asthenia					
	Yes			29	12,39
	No			205	87,61
Myalgia					100,00
	Yes			12	5,13

Continuous variables	N	Min	Max	Mean	Standard Dev.
	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

Continuous variables	N	Min	Max	Mean	Standard Dev.
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
	Mid intensity of care			128	54,70
	Low intensity of care			60	25,64
O2 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

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. DUS findings were classified as positive or negative; femoral and/or popliteal thrombosis was considered as positive DVT.

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 the 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-intensity 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, therapeutical 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: 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. 1. ROC curve (Table 3 and Fig. 2) showed the highest AUC for IL-6 (0.820) with a sensitivity of 83.3% and a specificity of 80.6% for a cut-off of 64.95 pg/mL, with an accuracy (AUC) of 82,0%.

Table 2
Student T-test results

T-Test	*p-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

Table 3
ROC curve analysis for significant continuous variables at Student T-test.

Variable	AUC	Cut-off	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

Discussion

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

Klok FA et al [3] reported an 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 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]. 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 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 reterospective 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.

Conclusion

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. In these patients, DUS may be considered a useful and valid tool for early identification of DVT.

List Of Abbreviations

ICU: intensive care unit

DVT: deep vein thrombosis

CRP: C-reactive protein

AUC: area under the curve

WHO: World Health Organization

O2: 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

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Boards of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Study Code: Radcovid03/2020 - Opinion n: 374_2020). The informed consent was waived by the Institutional Review Boards of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study conception, design and supervision: AMI, GC. Clinical data collection: AA, SF, ES. Statistical analysis: AC. Manuscript editing: AMI. Manuscript preparation and critical revision: SA, MCA, VV, MP, VM,

GG, MV, BR, FP, AP, FB.

All authors read and approved the final manuscript.

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Figures

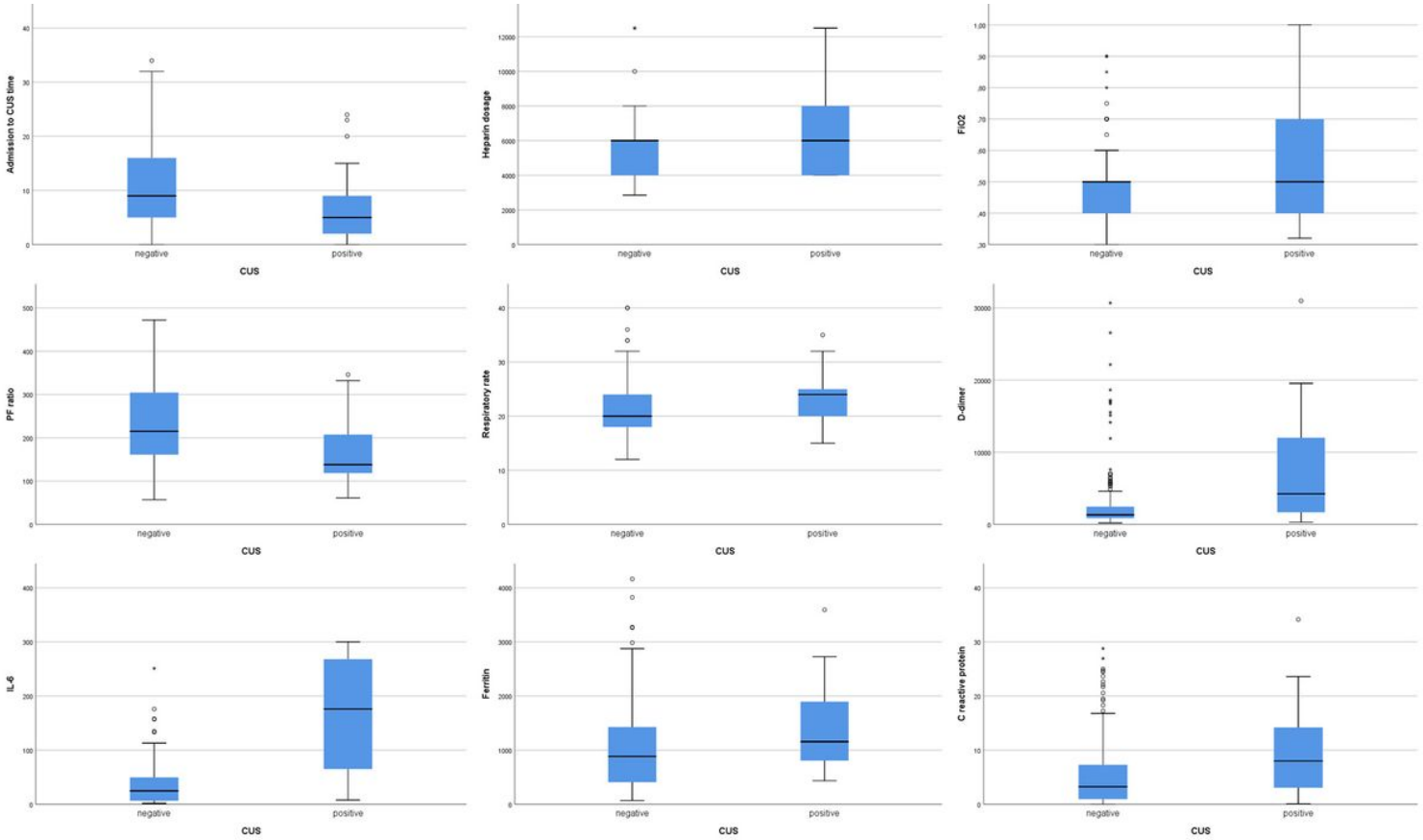

Figure 1

Boxplot for significant continuous variables.

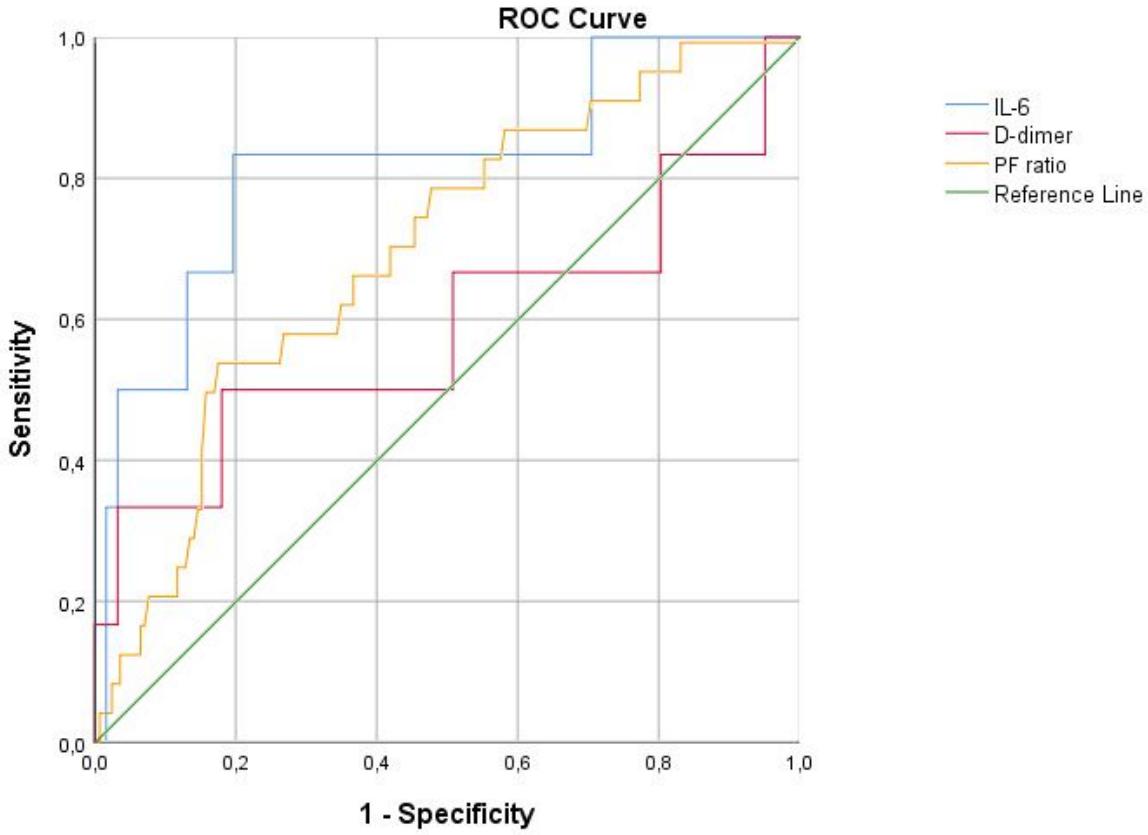

Figure 2

ROC curve for significant continuous variables with AUC > 0,7.

Supplementary Files

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