



Deep vein thrombosis in COVID-19 patients in general wards: prevalence and association with clinical and laboratory variables

Anna Maria Ierardi¹ · Nicola Gaibazzi² · Domenico Tuttolomondo² · Stefano Fusco³ · Vincenzo La Mura⁴ · Flora Peyvandi⁴ · Stefano Aliberti^{5,6} · Francesco Blasi^{5,6} · Diletta Cozzi⁷ · Gianpaolo Carrafiello^{2,8} · Massimo De Filippo⁹

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Abstract

Background Preliminary reports suggest a hypercoagulable state in COVID-19. Deep vein thrombosis (DVT) is perceived as a frequent finding in hospitalized COVID-19 patients, but data describing the prevalence of DVT are lacking.

Objectives We aimed to report the prevalence of DVT in COVID-19 patients in general wards, blinded to symptoms/signs of disease, using lower extremities duplex ultrasound (LEDUS) in random patients. We tested the association of DVT with clinical, laboratory and inflammatory markers and also reported on the secondary endpoint of in-hospital mortality.

Patients/Methods $n = 263$ COVID-19 patients were screened with LEDUS between March 01, 2020 and April 05, 2020 out of the overall $n = 1012$ admitted with COVID-19.

Results DVT was detected in $n = 67$ screened patients (25.5%), $n = 41$ patients (15.6%) died during the index hospitalization. Multiple logistic regression demonstrated that only C-reactive protein (odds ratio 1.009, 95% CI 1.004–1.013, $p < 0.001$) was independently associated with the presence of DVT at LEDUS. Both age (odds ratio 1.101, 95% CI 1.054–1.150, $p < 0.001$) and C-reactive protein (odds ratio 1.012, 95% CI 1.006–1.018, $p < 0.001$) were instead significantly independently associated with in-hospital mortality.

Conclusions The main study finding is that DVT prevalence in COVID-19 patients admitted to general wards is 25.5%, suggesting it may be reasonable to screen COVID-19 patients for this potentially severe but treatable complication, and that inflammation, measured with serum C-reactive protein, is the main variable associated with the presence of DVT, where all other clinical or laboratory variables, age or D-dimer included, are instead not independently associated with DVT.

Keywords Deep vein thrombosis · Screening · COVID-19 · Duplex ultrasound · C-reactive protein

✉ Anna Maria Ierardi
amierardi@yahoo.it

¹ Radiology Department, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

² Cardiology Department, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

³ School of Radiology, University of Milan, Milan, Italy

⁴ Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, U.O.C. Medicina Generale Emostasi e Trombosi, University of Milan, Milan, Italy

⁵ UOC Pneumologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

⁶ Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

⁷ Department of Radiology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

⁸ Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

⁹ Department of Medicine and Surgery (DiMeC), Unit of Radiology, University of Parma, Parma, Italy

Introduction

Acute respiratory disease from SARS-CoV-2 (COVID-19) or coronavirus disease 2019, is an infectious, mainly respiratory disease caused by a virus named SARS-CoV-2 and it is the cause of the ongoing worldwide pandemic in 2020.

One of the reasons that explains the rapid and uncontrolled spread of the virus is due to the relatively long incubation period, in which the infected subjects typically show no, mild or non-respiratory symptoms and whose duration can vary between 2 and 14 days during which the host can be contagious. Inter-human transmission occurs by contact with infected secretions or by air (coughing or sneezing) droplets [1, 2].

A key step in the diagnostic process of patients suspected for COVID-19 is the use of chest computed tomography. The HRCT (high-resolution computed tomography) without the use of contrast rapidly allows the radiographic diagnosis of interstitial pneumonia and provide helpful prognostic information [3–5]. Chest X-ray has also proved useful in the emergency setting as a quantitative method of the extent of SARS-CoV-2 pneumonia, correlating with an increased risk of intensive care unit admission [6].

There are several reasons why a patient affected by COVID-19 may be predisposed to concomitant thrombotic and thromboembolic disease.

Preliminary reports suggest the presence of a hypercoagulable state in COVID-19, with several (and partly conflicting) haemostatic abnormalities being documented, such as high D-dimer and other fibrin degradation products, high fibrinogen, prolonged activated partial thromboplastin time, positivity for lupus anticoagulant and other abnormalities, suggesting some forms of undetermined coagulopathy [7–9]. It is unknown whether these haemostatic changes are directly caused by SARS-CoV-2 or rather a consequence of the cytokine storm following the systemic inflammatory response syndrome, as observed in other viral disease [10–13].

In this context, deep vein thrombosis (DVT) is perceived by clinicians on the field as a frequent finding in hospitalized COVID-19 patients, although data describing the true prevalence of DVT in COVID-19 are completely lacking. The few existing published reports on DVT in hospitalized patients with COVID-19 are either specifically collected only in intensive care units or they describe overall thromboembolic events. Existing reports either enrolled patients based on clinical signs or symptoms of DVT or of thromboembolic events in general, performing duplex ultrasound because of this very high index of clinical suspicion, or addressed only patients admitted to intensive care units [14–18]; by so doing such studies select highest-risk, symptomatic patients, in particular

excluding the ones with mild or no symptoms or signs of DVT, finally reporting biased data on DVT prevalence.

We aim to (a) describe the prevalence of DVT by screening COVID-19 patients independently from their symptomatic status for DVT, using lower extremities duplex ultrasound (LEDUS) scan in random patients admitted to general wards (low or mid intensity care units), where the vast majority of COVID-19 patients are initially admitted, (b) test the potential association of DVT with clinical, laboratory and inflammatory markers, (c) report on the secondary end point of in-hospital mortality.

Methods

This cross-sectional, single-centre study used a complete radiologist-performed LEDUS scan to assess the prevalence of DVT of the lower extremities in laboratory-confirmed COVID-19 patients between March 01, 2020 and April 05, 2020. In-hospital mortality was also collected as a secondary end point.

Patients selection

We screened with LEDUS a random sample of patients with laboratory-confirmed COVID-19, admitted and treated in non-intensive care units (low-intensity and mid-intensity care units) dedicated to COVID-19; such patients were initially admitted because of clinically-suspected COVID-19, but only the ones in whom the diagnosis was then confirmed by SARS-CoV-2 viral nucleic acid assay in nasopharyngeal swabs were selected for screening. We did not include patients who were diagnosed with COVID-19 during hospital stay, but were admitted for other medical conditions.

Index screening test

Patients were selected for LEDUS screening in a quasi-random fashion. In fact LEDUS random screening was clinically felt appropriate and spontaneously implemented by the radiology department, after the notion spread that COVID-19 could be a systemic pro-thrombotic disease. Based on the voluntary availability of one of the radiologists in charge on each day of the week, he/she was randomly assigned one of the designated COVID-19 units of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, rotating on a daily basis, to perform bedside LEDUS in a minimum of 10 random patients for each working day. Patients to be scanned were chosen starting alternatively from the first or last room in the ward depending on the day.

Clinical variables

The demographics, traditional cardiovascular risk factors and the available laboratory blood tests (C-reactive protein, D-dimer and Fibrinogen) were the independent variables to be tested for an association with the primary endpoint (DVT) or with the secondary endpoint (in-hospital death).

Endpoints

The presence of DVT at the full LEDUS scan was the primary endpoint; in-hospital death, collected at least 30 days after admission was the secondary endpoint.

This study complied with the edicts of the 1975 Declaration of Helsinki and was approved by our Institutional Review Board.

Statistical methods

No statistical sample size calculation was performed a priori, and sample size was equal to the number of patients enrolled during the study period. Categorical variables are expressed as number of patients (percentage) with 95% CIs, and continuous variables as mean (SD) or median (interquartile range [IQR]) as appropriate. The means for continuous variables were compared using independent group *t* tests when the data were normally distributed, otherwise, the Mann-Whitney test was used. Proportions for categorical variables

were compared using the χ^2 test, although the Fisher exact test was used when data were limited. Stepwise multiple logistic regression was used to assess the relationship between, first the demographic and clinical variables and then adding laboratory variables, and the end point of the detection of DVT at LEDUS; secondarily we tested the end point of in-hospital mortality. All variables with $p < 0.1$ on univariable analysis were considered for the inclusion into multivariable logistic regression models. A 2-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed with Stata statistical software, version 15.0 (StataCorp LLC, USA).

Results

Two hundred and sixty three patients laboratory-confirmed COVID-19 patients were randomly screened with LEDUS, out of the overall 1012 admitted to the hospital with confirmed COVID-19 in the same period of time. Mean age was 63 ± 15 , $n = 175$ patients were male (66.5%) and $n = 41$ patients (15.6%) died during their index hospitalization, $n = 222$ (84.4%) were discharged home alive. DVT was detected in 67 of the 263 screened patients (25.5%), among which 22 DVT were bilateral (32.8%). In 21 patients DVT was found in the femoral veins (31.3%), 18 in the popliteal veins (26.9%) and 28 in the calf veins (41.8%) (Table 1 reports baseline characteristics and frequencies of

Table 1. Demographics, clinical, laboratory tests, LEDUS results and frequency of end points.

No.(%, if not otherwise specified)	Total
Demographics	
Number of patients	263
Age, median [lower–upper quartile], y	63 [54–76]
Female sex	88 (33)
Risk factors and patient history	
Hypertension	128 (49)
Dyslipidaemia	27 (10)
Current Smoker	17 (6)
Diabetes mellitus	53 (20)
Obesity	45 (17)
History of prior DVT ¹	7 (3)
Laboratory blood tests	
C-reactive protein, median [lower–upper quartile] (mg/l)	52 [13–115]
D-dimer, median [lower–upper quartile] ng/ml	1332 [809–3779]
Fibrinogen, [lower–upper quartile] ng/dl	536 [390–691]
End points	
Patients with DVT at LEDUS	67 (25.5)
Bilateral DVT	22 (33)
Femoral veins DVT	21 (31)
Patients who died in-hospital	41 (16)

DVT deep vein thrombosis, LEDUS lower extremities duplex ultrasound

end points). LEDUS was performed at a mean 9 ± 6 day after hospital admission. All patients, from admission and at least until the day LEDUS was performed, were per hospital protocol treated with prophylactic doses of weight-adjusted enoxaparin (100 international units per kilogram, once per day, the dose being halved in severe chronic kidney disease).

Primary end point

Figure 1 shows the box and whisker plots graphically demonstrating the distribution of continuous independent variables—age, C-reactive protein, D-dimer and fibrinogen—in patients with and without the finding of DVT at LEDUS.

When testing univariable association of the demographic or clinical variables (Table 2, left column) only the presence of hypertension (odds ratio 1.858, 95% CI 1.021–3.380, $p = 0.042$) was significantly associated with DVT; among laboratory variables, C-reactive protein (odds ratio 1.009, 95% CI 1.005–1.012, $p < 0.001$), D-dimer (odds ratio 1.000, 95% CI 1.000–1.000, $p = 0.021$) and fibrinogen

(odds ratio 1.003, 95% CI 1.002–1.004, $p < 0.001$) were also significantly associated with DVT. Since C-reactive protein and fibrinogen were strongly and significantly correlated ($r = 0.610$, $p < 0.001$) only C-reactive protein and not fibrinogen (mainly because C-reactive protein use is more widespread) were inserted in the multiple logistic regression analysis. Stepwise multiple logistic regression demonstrated that only C-reactive protein (odds ratio 1.009, 95% CI 1.004–1.013, $p < 0.001$) was finally independently associated with the presence of DVT at LEDUS (Table 2, right columns).

Secondary end point

Regarding the secondary end point of in-hospital mortality, age (odds ratio 1.089, 95% CI 1.056–1.12, $p < 0.001$), dyslipidaemia (odds ratio 3.286, 95% CI 1.216–8.877, $p = 0.019$) and C-reactive protein (odds ratio 1.006, 95% CI 1.005–1.013, $p < 0.001$) were significantly associated in univariable assessment, while in multivariable stepwise logistic

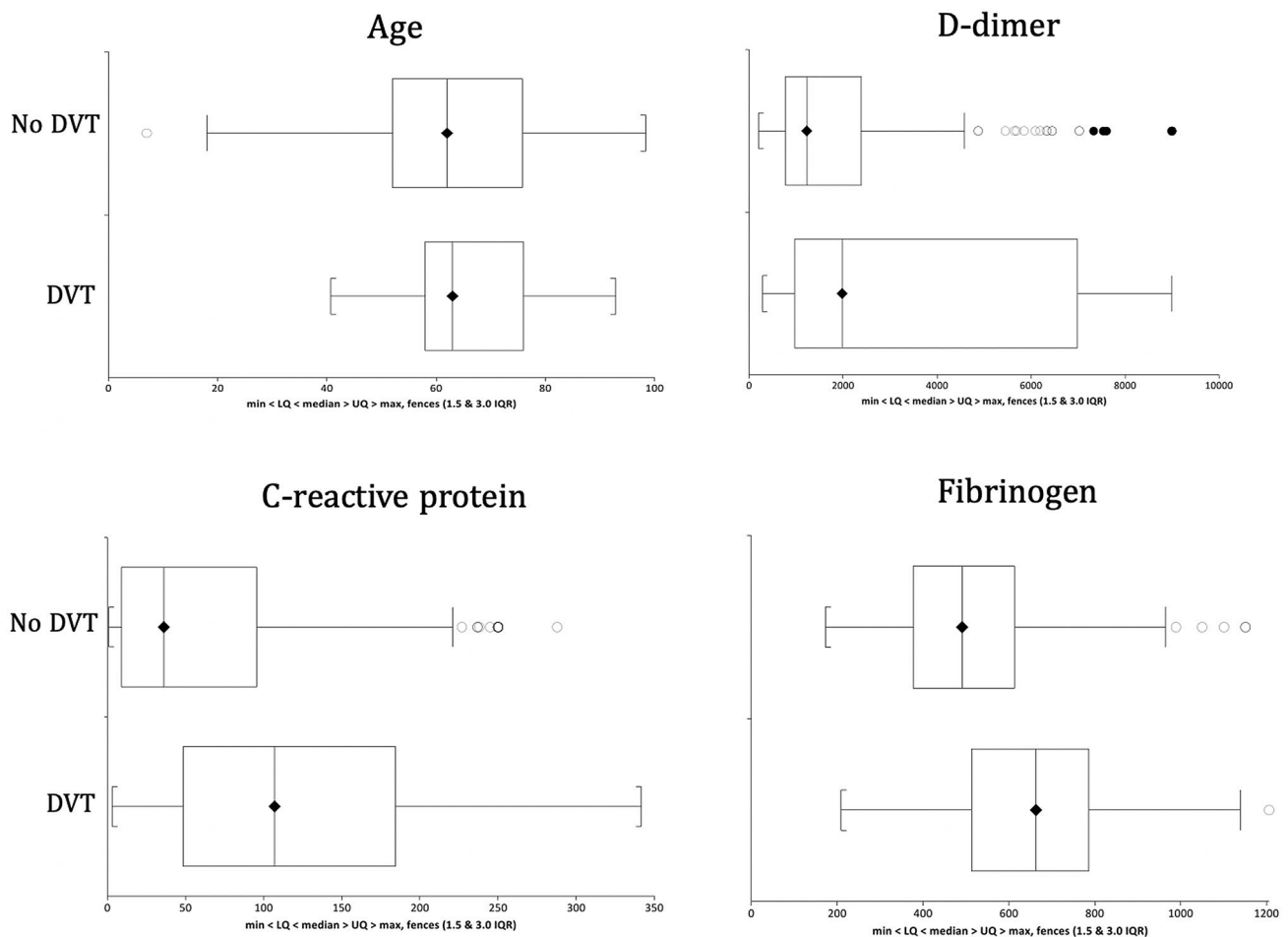


Fig. 1 Distribution of main continuous independent variables in the groups with and without deep vein thrombosis (DVT) at lower extremities duplex ultrasound. DVT: deep vein thrombosis

Table 2 Relationship of demographics, clinical factors, and serum biomarkers, with deep vein thrombosis at LEDUS

Deep Vein thrombosis of the Lower Extremities			
Univariable analysis		Multivariable analysis	
OR (95% CI)	p value	Model 1: clinical OR (95% CI)	p value
		Model2: Clinical + serum laboratory markers OR (95% CI)	p value
Age	1.014 (0.996–1.034)	—	—
Female sex	1.858 (0.770–2.439)	—	—
Hypertension	1.25 (1.021–3.380)	0.781 (0.366–1.666)	0.523
Dyslipidemia	2.439 (0.919–6.472)	2.801 (1.007–7.787)	0.048
Current Smoker	0.399(0.088–1.807)	—	—
Diabetes mellitus	1.476 (0.676–3.220)	—	—
Obesity	0.682 (0.247–1.882)	—	—
History of prior DVT	4.085 (0.890–18.746)	3.692 (0.589–23.160)	0.163
D-dimer	1.00006 (1.00001–1.00011)	—	—
C-reactive protein	1.009 (1.005–1.012)	—	0.093
Fibrinogen	1.003(1.002–1.004)	—	1.009 (1.004–1.013)
			*

Bold values indicate the statistical significance of some of them; fibrinogen was not inserted in model 2 because of collinearity with C-reactive protein

DVT Deep vein thrombosis

*Fibrinogen has not been inserted in Model 2 because of collinearity with C-Reactive protein

regression, only age (odds ratio 1.101, 95% CI 1.054–1.150, $p < 0.001$) and C-reactive protein (odds ratio 1.012, 95% CI 1.006–1.018, $p < 0.001$) were significantly and independently associated with in-hospital mortality.

Discussion

The main finding of this screening study is the description that DVT in random, laboratory-confirmed COVID-19 patients admitted to general wards is 25.5%. The prevalence of DVT in patients admitted because of COVID-19 is here reported for the first time, to the best of our knowledge, using a LEDUS screening strategy in a random sample of subjects with COVID-19. We did not assess patients pre-selected based either on their extreme clinical severity (as done when assessing only patients in intensive care units) or based on the presence of symptoms and signs of DVT. We think the current study supports the concept that approximately one quarter of COVID-19 patients admitted to general wards in fact have DVT, by so doing suggesting it may be reasonable to screen COVID-19 patients for this potentially severe but treatable complication.

The second finding is that the grade of inflammation, in this case measured with serum C-reactive protein, is the main (and only independent) variable associated with the presence of DVT, where all other clinical or laboratory variables, age or D-dimer included, are instead not independently associated with DVT.

Interestingly, the commonly used threshold of a D-dimer >500 ng/ml to suspect DVT (or other thromboembolic events) in general patients did not fit in the specific COVID-19 setting, in which D-dimer is in fact known to be generally increased [19]. For example, in the current study the median D-dimer value was 1332 ng/ml (lower-upper quartile 809–3779 ng/ml) and the use of the <500 ng/ml cut-off would classify only 28 patients (11%) as low-risk for DVT; unfortunately, this 500 ng/ml D-dimer cut-off also demonstrated suboptimal sensitivity in our cohort, “missing” the DVT diagnosis in 3 patients out of the 28 with a D-dimer value lower than 500 ng/ml. The 3 patients with DVT and D-dimer <500 ng/ml, however, had very high C-reactive protein values, which highlights the role of inflammation. In fact, if we alternatively approached COVID-19 patients starting from C-reactive protein values, it is of interest that in the 36 patients (14%) with normal C-reactive protein at admission (normal range is 0.5–5 mg/l), no one had DVT at LEDUS, in spite of a frequently high D-dimer (>500 ng/ml in 26 out of 36 patients). On the other side of the tail of C-reactive protein distribution, if we consider the 18 patients with high inflammatory status, according to a C-reactive protein >150 mg/l, 11 out of

18 patients (61%) had DVT at LEDUS. These observations lead to speculate that the grade of systemic inflammation may be the key determinant facilitating DVT in COVID-19 and this is confirmed by the results of the multiple logistic regression analysis reported in Table 2, showing that only C-reactive protein (not D-dimer or other clinical variables) is independently associated with DVT. According to our study, the finding of an extremely high or extremely low C-reactive protein value can certainly better inform the clinician reinforcing the decision to indicate LEDUS or not as a screening tool for DVT in a given COVID-19 patient.

C-reactive protein, but also age in this case, were independently significantly associated with the secondary end point of in-hospital mortality. In this regard, our study confirms the association between C-reactive protein and mortality suggested at this time only in few pre-print reports (not yet published in peer-reviewed journals), in which age and inflammation severity were among the main key variables associated with mortality [19–22].

Limitations

The current study is a cross-sectional screening study, with the addition of the collection of short-term, in-hospital death follow-up, in which the available clinical and laboratory data were only the ones available from the chart or other electronic records. Cross-sectional studies cannot prove causation but only inform on associations detected.

The LEDUS was performed by voluntary trained radiologists operating at the bedside in the complex clinical contagious scenario of COVID-19 wards, so that the LEDUS images are not available for review, but only the written official report was stored, available from the electronic chart and radiology reporting system. Randomization of patients to be screened with LEDUS was directly performed by the radiologist in charge on the field, simply starting to scan patients either from the first room of the unit and on, or reverse from the last room, depending on the day, so that while this is theoretically not an ideal randomization process, it was the best that could be achieved during an infective outbreak and it should have avoided most types of selection bias. Several laboratory variables were available only in a percentage of the study population and consequently they could not be used in the current analysis, and among them, granular body mass index was not available in all patients, only the binary variable “obesity” found in the charts, defined by a body mass index >29 kg/m² being available for all patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

Informed consent The informed consent has been obtained from all patients.

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