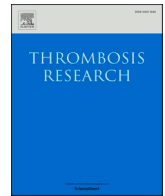




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Full Length Article

Lower limb deep vein thrombosis in COVID-19 patients admitted to intermediate care respiratory units

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ABSTRACT

COVID-19 has been associated with an increased risk of thrombotic events; however, the reported incidence of deep vein thrombosis varies depending, at least in part, on the severity of the disease. Aim of this prospective, multicenter, observational study was to investigate the incidence of lower limb deep vein thrombosis as assessed by compression ultrasound in consecutive patients admitted to three pulmonary medicine wards designated to care for patients with COVID-19 related pneumonia, with or without respiratory failure but not requiring admission to an intensive care unit.

Consecutive patients admitted between March 27 and May 6, 2020 were enrolled. Patients were excluded if they were less than 18-year-old or if compression ultrasound could not be performed for any reason. Patients were assessed at admission (t0) and after 7 days (t1). Major and non-major clinically relevant bleedings were recorded.

Sixty-eight patients were enrolled. Two were excluded due to anatomical abnormalities that prevented compression ultrasound; sixty patients were retested at (t1). All patients were started on antithrombotic prophylaxis, unless therapeutic anticoagulation was required.

Deep vein thrombosis as assessed by compression ultrasound was observed in 2 patients (3%); one of them was later deemed to represent a previous episode. No new episodes were detected at t1. One major and 2 non-major clinically relevant bleedings were observed.

In the setting of patients with COVID-related pneumonia not requiring admission to an intensive care unit, the incidence of deep vein thrombosis is low and our data support not screening asymptomatic patients.

1. Introduction

Infection with the novel coronavirus SARS-CoV-2 is responsible for a disease called COVID-19 [1]. Since its description at the end of 2019, the disease has spread throughout the world and has been designated a pandemic by the World Health Organization on March 12, 2020 [2]. The

severity of the disease varies widely; while some infected patients are asymptomatic or show symptoms of a mild upper airway infection, in some cases the disease progresses to a severe, potentially fatal pneumonia complicated with respiratory failure [1].

Activation of blood coagulation has rapidly emerged as a distinctive clinical feature in patients with the most severe forms of the disease [3]

Abbreviations: CUS, compression ultrasound; DVT, deep vein thrombosis; P/F, PaO₂/FiO₂; LMWH, low molecular weight heparin; CPAP, continuous positive airway pressure; SD, standard deviation.

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and high levels of coagulation-related biomarkers are associated with a poor prognosis [4]. Furthermore, numerous reports have shown a high incidence of venous thromboembolic events in COVID-19 patients [5–7]. However, the reported incidence of thrombotic events varies depending on the severity of disease and thromboprophylaxis strategies. Based primarily on anecdotal observations, the use of low molecular weight heparin (LMWH) at therapeutic doses has been initially suggested in specific subsets of patients [8], although caution has been recommended in view of the inevitable hemorrhagic risk associated with such practice [9].

Aim of this study was to investigate the incidence of symptomatic and asymptomatic lower limb deep vein thrombosis (DVT), that represent the most relevant origin of pulmonary embolism [10], as assessed by compression ultrasound (CUS) systematically performed in consecutive patients admitted to three intermediate care respiratory units with COVID-19-related pneumonia not requiring endotracheal intubation.

2. Patients and methods

2.1. Patient population and study design

This was a prospective, observational, multicentric study conducted from March 27 to May 6, 2020 in three pulmonary units in Italy. The study protocol was approved by the local ethical review board. All patients fulfilling the inclusion criteria gave their consent to the study. The study was conducted in accordance with the STROBE statement for prospective observational studies [11].

All three units were designated intermediate care units for patients with COVID-19-related pneumonia not requiring endotracheal intubation. Consecutive patients admitted within the study period with a diagnosis of COVID-19-related pneumonia were included. SARS-CoV-2 infection was confirmed by a reverse transcription polymerase chain reaction test on a nasopharyngeal swab, while the presence of consolidation(s) or ground-glass areas detected by chest computer tomography scans defined the diagnosis of pneumonia [12]. Exclusion criteria were age < 18 years and any reason that prevented the performance of CUS.

Demographic data, comorbidities, previous history of DVT or pulmonary thromboembolism and ongoing anticoagulant and/or antiplatelet therapies were recorded. Routine blood data, blood coagulation parameters and arterial blood gas analysis were also collected at admission (t0). D-dimer was tested after 7 ± 1 (range) days (t1) as well.

All major and non-major clinically relevant bleeding events during the observation period were also recorded.

All patients were started on prophylactic LMWH or fondaparinux except in the presence of specific contraindications per international guidelines [13] or unless higher doses were justified by other medical reasons. Patients on direct oral anticoagulants were switched to prophylactic LMWH to avoid interactions with antiviral therapy; home antiplatelet therapy was maintained.

2.2. CUS

Proximal CUS was performed at t0 and t1. The CUS study included the evaluation of the collapse of the common and deep femoral veins (from the level just distal to the inguinal ligament to the junction of the common femoral vein and the great saphenous vein) and the popliteal vein (at the level of the popliteal fossa) bilaterally [14]. During the ultrasound evaluation, direct pressure was applied with the use of the transducer to completely compress the vein; if the vein was completely compressed, DVT at that site was excluded. Lack of ability to fully compress the vein was considered a positive test result.

2.3. Outcomes

The primary outcome was the rate of objectively confirmed diagnoses of symptomatic or asymptomatic proximal DVT detected by

CUS. The secondary outcome was the rate of major and non-major clinically relevant bleeding.

2.4. Statistical analysis

Continuous data are reported as mean and standard deviations (SD). Categorical variables, whenever dichotomous or nominal, are reported as absolute frequencies and percentages. Data were analysed by Prism v.6.2 software (GraphPad, San Diego, Ca, USA).

3. Results

Between March 27 and May 6, 2020 68 patients who met the inclusion criteria were admitted to the 3 participating units. Two patients were excluded because orthopedic deformities prevented the performance of CUS. Of the remaining 66 patients who underwent CUS at t0, 2 patients died, 3 patients were discharged, and 1 patient was transferred to an intensive care unit due to worsening of the respiratory failure within the first week and therefore 60 (91%) underwent the second CUS at t1.

3.1. Patients' characteristics

The mean age was 74 ± 14 years; 38 patients (57.6%) were male. The most frequent comorbidities were hypertension (63.6%), cardiovascular diseases (39.4%), respiratory diseases (16.6%) and malignancies (16.6%). All patients' characteristics are shown in Table 1. At t0, respiratory failure was present in 43 patients (65.2%). The ratio between the arterial oxygen partial pressure (PaO₂) and the inspired oxygen fraction (FiO₂) (P/F) was 252 ± 98 mm Hg (mean \pm DS) while arterial lactate values, available for 46 patients, were within normal limits (Table 2). During hospitalization, 19 patients (28.8%) required non-invasive ventilation in continuous positive airway pressure (CPAP) mode. At the end of the data collection (May 6, 2020) 9 patients (13.6%) had died, 16 patients (24.2%) were still hospitalized, while 41 patients (62.1%) had been discharged. D-dimer levels at t0 were 3.7 times the local laboratory cut-off for the exclusion of venous thromboembolism and at t1 greater than 11 times. Routine blood chemistry data of coagulation were on average within normal limits, as well as platelet count values; the number of lymphocytes was slightly below the normal range (Table 2).

3.2. Anticoagulants and antiplatelet agents

At admission, 15 patients (22.7%) were on antiplatelet home therapy, 10 (15.1%) were on anticoagulants at therapeutic dose, 55 patients (83.3%) were prescribed LMWH or fondaparinux at prophylactic dose, while thromboprophylaxis was withheld in one patient (1.5%) due to a recent major gastric bleeding (Table 3).

Table 1
Baseline characteristics.

Mean age, years (DS)	74 (14)
Male sex, n (%)	38 (57.6)
Medical history	
Hypertension n (%)	42 (63.6)
Respiratory diseases n (%)	11 (16.6)
Malignancies n (%)	11 (16.6)
Obesity n (%)	5 (7.6)
Diabetes n (%)	8 (12.1)
Cardiovascular diseases n (%)	26 (39.4)
Past thromboembolic events	
Pulmonary embolism n (%)	2 (3.0)
Deep vein thrombosis n (%)	1 (1.5)
Chronic kidney diseases n (%)	5 (7.6)
Chronic liver diseases n (%)	3 (4.5)

Table 2
Blood chemistry and respiratory functional data.

Parameter	Mean (DS)
D dimer at the admission, % of cut-off	372 (512)
D dimer at 7 days, % of cut-off	1146 (458)
White blood cells/mm ³	9004 (5039)
Platelets/mm ³	247,053 (137,799)
Lymphocytes/mm ³	1178 (1307)
C-reactive protein (mg/dl)	7.54 (5.74)
Creatinine (mg/dl)	1.08 (1.35)
International normalized ratio	1.24 (0.20)
Activated partial thromboplastin time (s)	33.6 (7.6)
Fibrinogen (mg/dl)	543.8 (199.0)
Ferritin (ng/dl)	580.5 (424.6)
Respiratory failure at admission n (%)	43 (65.2)
PaO ₂ /FiO ₂ (mm Hg)	252 (97.6)
Arterial lactates (mmol/l) ^a	1.21 (0.71)

Parameter	Number (%)
Patients with D-dimer levels above the threshold for the exclusion of venous thromboembolism	
t0	47 (71.2)
t1	56 (93.3)

^a Available in 46 patients.

Table 3
Anticoagulants therapies at baseline.

Therapy	Patients n (%)
Therapeutic anticoagulant	10 (15.1)
Enoxaparin 100 UI/kg body weight bid	7 (10.6)
Fondaparinux (based on body weight)	1 (1.5)
Warfarin (based on INR)	1 (1.5)
Rivaroxaban 20 mg	1 (1.5)
Prophylactic anticoagulant	55 (83.4)
Enoxaparin 4000 UI/die	31 (47.0)
Enoxaparin 6000 UI/die	4 (6.1)
Fondaparinux 2.5 mg	18 (27.3)
Fondaparinux 1.5 mg (based on creatinine level)	2 (3.0)
No anticoagulants	1 (1.5)

3.3. Lower limb thrombosis

At t0, CUS detected two positive test results (3.0%), one of which was reassessed by one author (FB) with a solid expertise in vascular medicine and deemed to represent a previous DVT, based on the central pattern or recanalization. At t1 both positive tests were confirmed, while no new positive tests were detected.

Table 4 reports the most significant characteristics of the two positive patients.

3.4. Pulmonary embolism

Eight angio-computer tomography scans were performed based on the clinical suspicion of pulmonary embolism and one was found positive. The patient did not show signs of thrombosis at CUS.

3.5. Bleeding

We observed one episode of major bleeding (epistaxis with reduction of hemoglobin level > 2 g/dl) in a patient receiving a therapeutic dose of LMWH. Two non-major clinically relevant bleedings were observed: one (hematuria) in a patient receiving therapeutic dose of fondaparinux and the other (hematochezia) in a patient treated with prophylactic dose of fondaparinux in addition to home treatment with clopidogrel. No major or non-major clinically relevant bleedings were reported in patients treated with prophylactic dose of fondaparinux or LMWH without

Table 4
Clinical details of the two patients with positive CUS.

Patient 1	
Male, 72 years old	
Comorbidities	None
CUS results at	
Left femoral veins	Positive
Right femoral veins	Negative
Left popliteal vein	Negative
Right popliteal vein	Negative
D dimer at admission, ng/ml	4731
D dimer at admission, % of cut-off	1947
PaO ₂ /FiO ₂ (mm Hg)	218
Need for CPAP	Yes
Home antiplatelets or anticoagulants treatments	None
Bleedings	None

Patient 2 (probable chronic thrombosis)	
Male, 83 years old	
Comorbidities	COPD
CUS results at	
Left femoral veins	Positive
Right femoral veins	Negative
Left popliteal vein	Negative
Right popliteal vein	Negative
D dimer at admission, ng/ml	390
D dimer at admission, % of cut-off	130
PaO ₂ /FiO ₂ (mm Hg)	133
Need for CPAP	Yes
Home antiplatelets or anticoagulants treatments	None
Bleedings	None

concomitant antiplatelet therapy.

4. Discussion

Due to its sudden outbreak, COVID-19 has imposed a great burden on the medical community worldwide. As a consequence, therapeutic strategies have sometimes been implemented based on anecdotal clinical impressions [15]. Several groups have observed an increase in blood coagulation parameters, particularly D-dimer, and a correlation between their level and disease severity [4]. In parallel, an increase in the incidence of thromboembolic events has also been reported [5–7,16,17]. This has prompted the use of LMWH beyond the indications currently reported in international guidelines [13]. Since the reported incidence of thromboembolic events varies among different studies at least in part based on the clinical setting (e.g. intensive care units vs. respiratory wards), we investigated the incidence of DVT in the specific setting of three pulmonary wards specifically designated to care for COVID-patients with pneumonia without respiratory failure or with respiratory failure of different severities but not requiring admission to an intensive care unit (i.e., as a general rule, with a P/F ratio ≥ 150 mm Hg). We observed 2 positive CUS (3%), one of which likely related to a previous episode. The data indicate a low incidence of DVT in the specific context described. In keeping with our results, Cattaneo et al. reported no cases of DVT in a group of 64 COVID-19 patients with similar clinical characteristics [18].

The pathogenesis of COVID-19 remains to be elucidated. A role for thromboinflammation, characterized by the disruption of the usual antithrombotic state of the endothelium as well as the increased prothrombotic activity of leukocytes has been postulated [9,19]. These mechanisms might be responsible for local microthrombosis of the pulmonary vessels [20] that might in turn contribute to the severity of the disease, for example through the induction of a ventilation/perfusion mismatch [21]. It is not clear whether these local phenomena are amenable to standard anticoagulant therapy; however, they are likely unrelated to the development of peripheral DVT.

The main limitation of our study is the relatively small sample size.

However, as the incidence and the severity of COVID-19 are lowering at least in Italy, we decided to share the available data, that we believe might be of interest. Furthermore, a sample of 68 patients should have been sufficient to detect a sizable number of positive CUS based on the incidence, ranging from 20 to 30%, reported in patients with more severe disease [5,7]. The strengths of the study are represented by its prospective, multicentric design and the inclusion of consecutive patients regardless of the presence of symptoms suggestive of DVT and/or of increased D-dimer levels.

In conclusion, the incidence of DVT as detected by CUS in patients with COVID-related pneumonia not requiring admission to an intensive care unit is relatively low and does not warrant proactive actions to detect it in the absence of clinical signs and/or symptoms. Antithrombotic prophylaxis per international guidelines appears safe in these patients.

CRedit authorship contribution statement

Roberta Pancani, Alessandro Celi, Laura Carrozzi designed the study; Roberta Pancani, Liliana Villari, Valentina Foci, Giulia Parri, Filippo Patrucco, Francesco Barsotti collected the data; Alessandro Celi wrote the manuscript; Laura Carrozzi, Rigoletta Vincenti and Mario Malerba critically revised the manuscript; all Authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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