Thromboinflammatory state and venous thromboembolic events in patients with coronavirus disease 2019 admitted to a non-intensive care ward: a prospective study

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Article type: Research letter

Received: August 16, 2020.

Accepted: September 20, 2020.

Published online: September 25, 2020.

ISSN: 1897-9483
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Short title: Thromboinflammation in a COVID-19 medical ward

Conflict of interest: none declared.
INTRODUCTION

Most patients with COVID-19 experience a mild disease, but about 19% of them develop a severe illness [1-2]. A striking feature of COVID-19 is the rapid progression of respiratory failure which often requires transfer to intensive care unit (ICU) [2]. Recent reports highlight the role of systemic thromboembolic disease and lung microvascular thrombosis in rapid clinical worsening [3]. Numerous studies conducted in ICU have demonstrated the existence of a COVID-associated coagulopathy (CAC) [1-2]. However, few studies have evaluated whether clotting abnormalities occur even in patients hospitalized outside the ICU.

The main objectives of the study were: a) to assess the values of inflammatory and some coagulation parameters and the rate of venous thromboembolism (VTE) in patients with COVID-19 hospitalized in a non-ICU medical ward; b) to compare the characteristics of patients with mild disease with those with moderate and severe disease.

PATIENTS AND METHODS

Study design and patients

We conducted a prospective, observational, single-center study evaluating 85 patients with laboratory confirmed SARS-CoV-2 infection, consecutively admitted from April 1 to April 30, 2020 to the COVID-19 ward of the San Giovanni di Dio Hospital in Florence, Italy. This 60-bed ward was managed by an internal medicine staff and was dedicated to patients not requiring intensive care. The diagnosis of SARS-CoV-2 infection was confirmed using a single reverse transcriptase-polymerase chain reaction assay on nasopharyngeal swab specimens.

Patients were divided into 3 groups: 1) mild disease: not requiring oxygen (SpO2>94% on room air); 2) moderate disease: requiring oxygen (SpO2<94% on room air); 3) severe disease: requiring non invasive ventilation (SpO2<94% on 60% oxygen).
All patients underwent laboratory evaluations and ultrasound of the whole leg within the first 3 days of hospitalization and every 3-10 days thereafter. Pulmonary CT angiography (CTPA), was performed in case of clinical suspicion of pulmonary embolism (PE), worsening of respiratory conditions or proximal lower limb deep vein thrombosis (DVT).

**Statistical analysis**

Data were presented as number (percentage) for categorical variables and mean (SD) or median (first, third quartiles) when appropriate for continuous ones. Normality of data distribution was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were compared with Student t test; non-normally distributed variables with Mann-Whitney test. Categorical variables were compared with χ² or Fisher exact test. Comparisons between three groups were performed using the analysis of variance or the Kruskal-Wallis test. *P*-values of two-groups post-hoc comparisons were Bonferroni adjusted. Multivariable logistic regression model was performed to identify the predictors of VTE. GNU PSPP Statistical Analysis Software (https://www.gnu.org/software/pspp/) was used for statistical analyses; *P*<0.05 was considered significant.

**Compliance with ethical standards**

Each patient provided a written consent.

All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments. This study was approved by the Institutional Review Board of the Department of Medicine of the “Azienda USL Toscana Centro”.
RESULTS

Among the 85 patients (42 males; 75.9 years) evaluated, 81 (95.3%) were on low-molecular-weight-heparin (LMWH) prophylaxis (76 with 4,000 or 6,000 IU per day and 5 with 4,000 IU twice a day), 2 were on direct oral anticoagulant for atrial fibrillation and 2 were on pneumatic intermittent compression of the legs, due to recent major bleedings.

We detected 20 DVT (8 proximal and 12 distal) in 18 patients. CTPA was performed in 12 patients and PE was diagnosed in 6 patients (2 massive PE, 4 segmental and/or sub-segmental PE). Overall, at least 1 VTE was detected in 21 patients (24.7%). Age, gender, number of co-existing disorders did not significantly differ between patients with and without VTE (Table 1).

The median values of all the inflammatory parameters were above the normal reference limits. C-reactive protein (C-RP) and Serum-amyloid A protein (SSA) were significantly higher in patients with VTE than in those without VTE. The median value of D-dimer was above the upper reference limits and it was significantly higher in patients with VTE than without VTE, but also in the latter group it was above normal values (Table 1). No patient showed severe thrombocytopenia (<50,000 mm), severe prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) or reduction of fibrinogen (<100 mg/dl).

D-dimer (OR: 1.001, 95% CI: 1.0001-1.002; P=0.01) and C-RP (OR: 1.06, 95% CI: 1-1.12; P=0.03) at admission were predictive of VTE at the multivariable logistic regression analysis.

Length of stay, in-hospital mortality and transfer to ICU were similar between patients with and without VTE (Table 1).
Patients with mild, moderate and severe disease.

Twenty-one patients had mild disease, 24 had moderate disease and 40 had severe disease. The median values of the inflammatory parameters, except interleukin 6 (IL-6), of patients with mild disease were above the normal reference limits (Table 1). In particular, C-RP was above the upper limit of the reference range in 18 patients (86%), ferritin in 14 (67%), SAA in 16 (76%), IL-6 in 14 (67%). The median values of the inflammatory parameters were significantly lower in patients with mild disease than in those with severe disease. In patients with mild disease, the median value of D-dimer was well above the normal reference limits. Fibrinogen and D-dimer were above the upper limit of the normal range in 21 (100%) and 18 (86%) patients with mild disease, respectively.

One patient with mild disease (5%) had VTE in comparison to 7 patients with moderate disease (29%) and to 13 patients with severe disease (33%) ($P=0.05$ and $P=0.02$, respectively).

Length of stay did not significantly differ between the 3 groups. Among patients with mild, moderate and severe disease, we observed 0, 2 and 14 deaths, respectively (Table 1).
DISCUSSION

The main results of this study are: 1) the rate of VTE is remarkably high in patients with COVID-19 admitted to a non-intensive care unit; 2) the great majority of these patients, even those with mild disease, show a profound alterations of the inflammatory and of some coagulation markers.

VTE complications

Systematic venous ultrasound of the legs, together with CTPA, allowed to detect VTE in 24.7% of the patients. A rate of VTE varying from 20 to 79% is reported in ICU patients [4-5]. Few data are available for non-ICU patients: 2 studies reported a prevalence of VTE ranging from 0 to 6%[6-7], while a French study described a prevalence of 22% [8]. The latter percentage and the one we found (24.7%) are much higher than those described in non-COVID patients, which varies from 0.5 to 8% [9]. This figure is even more remarkable if we consider that the vast majority of our patients were receiving thromboprophylaxis with LMWH.

The incidence of VTE was particularly high in patients with moderate (29%) and severe disease (33%), while it was only 5% in those with mild disease.

Hyperinflammation and hypercoagulability: Thromboinflammation

The inflammation indices and some parameters of the coagulation system, such as D-dimer and fibrinogen, were on average very high in our patients, particularly in those with VTE. Furthermore, increasing D-dimer and C-RP values were independent risk factors for VTE. Extremely high values of D-dimer and C-RP were recently reported in a woman with PE associated with COVID-19 pneumonia [10] and the authors suggest that such high values should prompt physicians to rule out PE.

On the other hand, no patients showed severe thrombocytopenia, severe prolongation of PT and aPTT or reduction of fibrinogen. These results support the existence of a new condition of severe hypercoagulability called CAC, characterized by hyperfibrinogenemia.
and elevated D-dimer values [11], distinguished from disseminated intravascular coagulation (DIC) by the absence of thrombocytopenia and consumption of coagulation factors. However, DIC has sometimes been described in the more advanced stages of the disease [11]. Varga et al. [12] have demonstrated viral infection of the endothelial cells across vascular beds of different organs in a series of patients with COVID-19, with induction of endothelialitis. It is likely that endothelial damage triggers a prothrombotic cascade that leads to in situ thrombosis. So it is conceivable that at least some of the distal PE that we have detected are actually expression of thrombotic phenomena occurred at the level of the small pulmonary arteries, rather than consequences of an embolism. The association of hyperinflammation with CAC is summarized by the term thromboinflammation [11], a condition documented so far in ICU patients, but that seems already present in patients with mild disease, in which VTE is rare.

**Strength and weakness of the study**

The relevance of this study is given by the prospective design and by the systematic search in all patients of VTE. The study population included patients with different stages of COVID-19 severity and this allowed us to evaluate even patients with mild disease, excluded so far in most studies. This study has some limitations: first, it was only performed in a single center; second, it includes a relatively small number of patients.

**Conclusions**

A remarkably high rate of VTE has been detected in COVID-19 patients hospitalized in a non-ICU medical ward. These results, together with the evidence of systemic thromboinflammation even in patients with mild disease, suggest to evaluate the usefulness of early initiation of antinflammatory and anticoagulant therapy.
REFERENCES


Table 1: characteristics and results of patients in the study

<table>
<thead>
<tr>
<th>All patients</th>
<th>Patients with and without VTE</th>
<th>Stages of disease severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VTE patients</td>
<td>Non-VTE patients</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>85</td>
<td>21 (24.7)</td>
</tr>
<tr>
<td>Gender, M/F (%)</td>
<td>42/43</td>
<td>14/7 (67/33)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>75.9 (12.7)</td>
<td>77.5 (8.6)</td>
</tr>
<tr>
<td>Number of coexisting disorders, median (1st-3rd quartiles)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Obesity, number (%)</td>
<td>6 (7.1)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>C-RP, median (1st-3rd quartiles); (reference range: &lt;0.5 mg/dL)</td>
<td>7.5 (2.9-15.1)</td>
<td>13.3 (6.7-19.6)</td>
</tr>
<tr>
<td>Ferritin, median (1st-3rd quartiles); (reference range: 20-200 ng/mL)</td>
<td>611 (275-970)</td>
<td>737 (474-1236)</td>
</tr>
<tr>
<td>SAA, median (1st-3rd quartiles); (reference range: &lt;10 mg/L)</td>
<td>271 (101-827)</td>
<td>529 (204-1.130)</td>
</tr>
<tr>
<td>IL-6 (pg/mL), median (1st-3rd quartiles); (reference range: &lt;16 pg/mL)</td>
<td>22.8 (11.0-43.9)</td>
<td>33 (13.9-61.7)</td>
</tr>
<tr>
<td>Platelets, mean (SD); (reference range: 150-400 x10^3/microL)</td>
<td>222 (93)</td>
<td>245 (98)</td>
</tr>
<tr>
<td>Fibrinogen, mean (SD); (reference range: 150-400 mg/dL)</td>
<td>712 (141)</td>
<td>735 (154)</td>
</tr>
<tr>
<td>D-dimer, median (1st-3rd quartiles); (reference range: &lt;500 ng/mL)</td>
<td>1,443 (576-5,710)</td>
<td>7,014 (1,200-29,236)</td>
</tr>
<tr>
<td>Lenght of stay, days, median (1st-3rd quartiles)</td>
<td>19 (12-26)</td>
<td>20 (14-31)</td>
</tr>
<tr>
<td>In-hospital death, number (%)</td>
<td>16 (19%)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Transfer to ICU, number (%)</td>
<td>3 (3%)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Death + transfer to ICU, number (%)</td>
<td>19 (22%)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

Categorical variables were presented as number and percentage. Continuous variables were expressed as mean (SD) or median (interquartile range) where applicable.

a Post hoc analysis for the stages of disease severity comparisons: P <0.05 for moderate vs severe disease  
b Post hoc analysis for the stages of disease severity comparisons: P <0.05 for mild vs moderate disease  
c Post hoc analysis for the stages of disease severity comparisons: P <0.05 for mild vs severe disease

Abbreviations: C-RP, C-reactive protein; IL-6, interleukin 6; SAA, serum amyloid A protein; VTE, venous thromboembolism; VTE patients, patients with venous thromboembolism; Non-VTE patients, patients without venous thromboembolism