Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified?

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Acutely ill medical patients are at heightened risk for venous thromboembolism, a term that combines deep vein thrombosis (DVT) and its more severe complication, pulmonary embolism.1,2 Although the incidence of venous thromboembolism in medical patients might have been overestimated in some instances, according to a recent study,3 treatment by low, prophylactic doses of low molecular weight heparin (LMWH) is recommended for these patients when additional risk factors coexist.1,2 COVID-19 is an acute, complex disorder that is associated with SARS-CoV-2 infection, which, in its most severe presentation, is characterized by the development of interstitial pneumonia and acute respiratory distress syndrome.4 According to many reports, COVID-19 exposes patients to a particularly high risk for venous thromboembolism.5–8 Hence, hospitalized COVID-19 patients are generally treated with higher LMWH doses than recommended for thromboprophylaxis. A recent document by the Italian Drug Agency (AIFA) suggested the use of 80 to 100 mg enoxaparin daily, instead of the usual 40 mg, while in some hospitals, even higher, up to full anticoagulant doses of LMWH or unfractionated heparin9 are used. In our hospital we use 40 mg enoxaparin daily, as recommended for high-risk, acutely ill medical patients.1,2

From the COVID-19 outbreak in Northern Italy until April 14, 388 patients have been admitted to our non-intensive care unit (ICU) wards, none of whom developed symptomatic DVT during their hospital stay. As DVT may be asymptomatic in a proportion of patients at risk, we performed leg compression ultrasonography, which failed to detect DVT in any of the 64 tested patients, independently of the severity of their condition and length of in-hospital bed rest (Table 1). The absence of reports in the literature of DVT in COVID-19 patients under LMWH thromboprophylaxis confirms our experience. This is apparently in contrast with the relatively frequent reports of pulmonary embolism in hospitalized COVID-19 patients,5–8 which is diagnosed based on the clinical observation of rapid worsening of respiratory insufficiency and blood oxygenation that is out of proportion to the extent of pulmonary infiltration and on the evidence of pulmonary vessel occlusions, generally interpreted as caused by pulmonary emboli, when computed tomography angiography (CTA) is performed. These patients, however, usually do not have symptoms or signs of DVT. As an example, a study of 184 severe COVID-19 patients, all hospitalized in ICU and treated mostly with standard doses of LMWH for thromboprophylaxis, reported a high incidence of venous thromboembolism (n = 28).5 However, only one patient had DVT (diagnosed by compression ultrasonography), while pulmonary embolism (diagnosed by CTA) was by far the most frequent thrombotic event (n = 25) (highlighting the importance of performing CTA in symptomatic patients whenever possible), followed by two cases of catheter-related upper extremity venous thrombosis.5 The discrepancy between the frequencies of pulmonary embolism and DVT is surprising, because, although pulmonary embolism may occur in the absence of detectable DVT, this happens in only approximately 20% of studied patients.10 Therefore, we question whether the observed pulmonary vessels occlusions that have been described in reports on COVID-19 patients are exclusively caused by pulmonary embolism. In our experience and in some reports,11,12 filling defects of pulmonary vessels that are detected by CTA scans are in many instances more reminiscent of pulmonary thrombi rather than emboli, because they are not fully occlusive. This observation is compatible with post-mortem descriptions of “...presence of manifestations of...”
Table 1 Characteristics of 64 hospitalized COVID-19 patients who underwent bilateral leg compression ultrasonography to unravel asymptomatic deep vein thrombosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age (y)</td>
<td>70 [min = 35; max = 97; IQR = 58–77.5]</td>
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<tr>
<td>Days of in-hospital bed rest</td>
<td>9 [min = 1; max = 45; IQR = 4–15]</td>
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<tr>
<td>Days in NIV</td>
<td>0 [min = 0; max = 20; IQR = 0–5]</td>
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<td>Respiratory rate (breaths/min)</td>
<td>20 [min = 8; max = 32; IQR = 16–24]</td>
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<tr>
<td>PaO₂/FiO₂</td>
<td>300 [min = 60; max = 600; IQR = 249–392.5]</td>
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<tr>
<td>D-dimer (µg/mL)</td>
<td>0.458 [min = 0.1; max = 11.970; IQR = 0.252–0.903]</td>
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<tr>
<td>Fibrinogen (g/L)</td>
<td>4.76 [min = 1.30; max = 9.50; IQR = 3.878–5.38]</td>
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<tr>
<td>Ferritin (µg/L)</td>
<td>320 [min = 30; max = 9,000; IQR = 185–776]</td>
</tr>
<tr>
<td>Prothrombin time (P/N ratio)</td>
<td>1.13 [min = 0.97; max = 1.51; IQR = 1.07–1.12]</td>
</tr>
<tr>
<td>Platelet count (×10³/L)</td>
<td>286 [min = 126; max = 754; IQR = 222–384]</td>
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<tr>
<td>Sex</td>
<td>Male = 35; Female = 29</td>
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<tr>
<td>Obesity</td>
<td>Yes = 4; No = 60</td>
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<tr>
<td>Previous VTE</td>
<td>Yes = 0; No = 64</td>
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<td>Malignancy</td>
<td>Yes = 7; No = 57</td>
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Notes: For continuous variables, median [min; max]. 

Abbreviations: IQR, interquartile range; NIV, noninvasive ventilation; VTE, venous thromboembolism.

Conflict of Interest
None declared.

References


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