HIGH D-DIMER VALUES AND POST-DISCHARGE ACUTE PULMONARY EMBOLISM IN YOUNG PATIENTS WITH COVID-19: A CASE SERIES

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Abstract: Introduction: The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with an inflammatory and prothrombotic state that increases the risk of thromboembolic events. High levels of D-dimer are associated with the severity of the disease and acute pulmonary embolism (PE) is the most common thrombotic complication.

Material and methods: We analyzed a series of four cases of COVID-19 in young patients (under 45 years) who developed PE with a delay of two to four weeks after hospital discharge.

Results: These patients had elevated D-dimer (at least 10 times the upper limit of normal) at the initial admission and at the time of the PE diagnostic, while other parameters which involved inflammation and coagulation (C-reactive protein — CRP; lactate dehydrogenase — LDH; fibrinogen; international normalized ratio — INR) were normal. There were no pre-existing risk factors for PE and all the patients were anticoagulated with prophylactic intermediate doses of enoxaparin.

Conclusions: PE is a complication of the COVID-19 disease which may occur later, especially in young patients with no other risk factors for the condition. The highly elevated levels of D-dimer at COVID-19 admission seem to be associated with the post-discharge appearance of PE. This data suggests the role of extended anticoagulation in selected COVID-19 patients and warrants further investigations.

Key words: D-dimer, COVID-19, young patients, pulmonary embolism, post-discharge.
mittee of the Baia Mare Clinical County Emergency Hospital reviewed and approved the study (decision no. 34978/2020), which was done retrospectively with data collected from patients’ records.

RESULTS

The clinical and laboratory characteristics of the patients are presented in Table 1.

Three of the four patients were male and all of them were between 31 and 45 years of age. None of them had medical antecedents, however, two were overweight with a BMI of 29 and 30. The symptoms were initially respiratory with cough and fever (37.5–38.5 °C); and one of the patients had arthralgia, myalgia, abdominal pain, diarrhea, and dyspnea. CT images displayed the presence of ground-glass opacities in all patients. Two of them had multi-affected lobes, one had two lobes, and the female patient had only one lobe affected. SpO2 was between 84–90% in two patients who had pressurized oxygen therapy for five days, 88–92% in one who had basal oxygen therapy.

Table 1. Clinical and laboratory characteristics of PE patients

<table>
<thead>
<tr>
<th>Variables/ Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45</td>
<td>42</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Sex</td>
<td>male</td>
<td>male</td>
<td>female</td>
<td>male</td>
</tr>
<tr>
<td>Medical history</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>29</td>
<td>30</td>
<td>24.5</td>
<td>25</td>
</tr>
<tr>
<td>ECG</td>
<td>110 b/min, sinus tachycardia</td>
<td>115 b/min, sinus tachycardia</td>
<td>incomplete right bundle branch</td>
<td>incomplete right bundle branch</td>
</tr>
<tr>
<td>PE symptoms</td>
<td>acute dyspnea, right thoracic pain, hemoptysis,</td>
<td>left thoracic pain, hypoxia 90 %</td>
<td>acute dyspnoea</td>
<td>acute dyspnoea</td>
</tr>
<tr>
<td>PE after ...days of Covid onset</td>
<td>22</td>
<td>18</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>PE localisation at angio CT</td>
<td>distal bilateral segmental and subsegmental</td>
<td>distal left lower lobe and central lobar right superior</td>
<td>distal bilateral segmental</td>
<td>distal unilateral lower left lobe</td>
</tr>
<tr>
<td>SARS-CoV-2 PCR at PE diagnosis</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>D-Dimer at Covid -19 diagnostic RR: 0.00–0.49 mg/L FEU</td>
<td>4.2</td>
<td>14.4</td>
<td>5.2</td>
<td>8.1</td>
</tr>
<tr>
<td>D-Dimer, at PE diagnostic, RR: 0.00–0.49 mg/L FEU</td>
<td>4.8</td>
<td>16.8</td>
<td>14.3</td>
<td>13.4</td>
</tr>
<tr>
<td>h-CRP (mg/dl) RR: up to 5 mg/L</td>
<td>12</td>
<td>25</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Fibrinogen (g/L) RR: 2.0 to 4.0 g/L</td>
<td>4.3</td>
<td>5.2</td>
<td>4.6</td>
<td>3.7</td>
</tr>
<tr>
<td>LDH (U/l) RR: 100 - 250 IU/l</td>
<td>270</td>
<td>320</td>
<td>260</td>
<td>230</td>
</tr>
<tr>
<td>Serum ferritin RR: 12-300 ng/ml</td>
<td>80</td>
<td>450</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BNP (pg/ml) RR: &lt; 100 pg/ml</td>
<td>485</td>
<td>630</td>
<td>350</td>
<td>180</td>
</tr>
<tr>
<td>Haemoglobin (g/L), RR: 13-15 g/l</td>
<td>15</td>
<td>14</td>
<td>12.5</td>
<td>15</td>
</tr>
<tr>
<td>White-cell count (per mm) RR: 5000-10000</td>
<td>10300</td>
<td>11000</td>
<td>9600</td>
<td>9400</td>
</tr>
<tr>
<td>Platelets (per mm) RR: 150000-450000</td>
<td>410000</td>
<td>520000</td>
<td>245000</td>
<td>375000</td>
</tr>
<tr>
<td>INR, RR: 0.8-1.1</td>
<td>1.1</td>
<td>1.05</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>Anticoagulation before PE onset</td>
<td>Enoxaparin 0.6 ml once daily/ 7 days</td>
<td>Enoxaparin 0.6 ml once daily/ 7 days</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>PE treatment</td>
<td>Enoxaparin therapeutic doses, Dabigatran</td>
<td>Enoxaparin therapeutic doses, Dabigatran</td>
<td>Enoxaparin therapeutic doses, Dabigatran</td>
<td>Enoxaparin therapeutic doses, Apixaban</td>
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</table>

HIGH D-DIMER VALUES AND POST-DISCHARGE ACUTE PULMONARY EMBOLISM IN YOUNG PATIENTS WITH COVID-19... 87

for many days, and more than 92% in the female patient who had only intermittent oxygen therapy. The patients were initially managed in two COVID-19 dedicated hospitals and had anticoagulation therapy for VTE prevention (enoxaparin 0.6 ml or 0.8 ml, or 1 ml SC, once a day–q.d) for 10 days. All of them were treated with antimicrobial therapy for secondary bacterial infection and with hydroxychloroquine (400 mg/day). They were discharged after a second negative SARS-CoV-2 PCR test made after 10 days of hospitalization. All the patients developed dyspnea of acute onset and/or chest pain 16 to 32 days after discharge, and they had to be hospitalized at the Emergency County Hospital Baia Mare under suspicion of PE. One of the four patients was, surprisingly, COVID-19 positive in the nasopharyngeal swab on the admission day. Biomarkers usually involved in inflammation were only slightly elevated in three of them, while the common coagulation test international normalized ratio (INR) was normal. The electrocardiogram presented sinus tachycardia (110–120 bpm) in two patients, while the other two had new development of an incomplete right bundle branch. None of them had signs of deep vein thrombosis at the venous duplex ultrasound scan (VDUS). The angio-CT scans revealed distal bilateral pulmonary emboli in three patients and smaller distal unilateral PE in one. There is no data for the D-dimer values on hospital discharge after COVID-19 treatment. The D-dimer were highly elevated (levels vary between 1.06 and 16.96 mg/L, reference range – RR: 0.00–0.49 mg/L FEU) on the second hospital admission, being the highest in patients with bilateral PE. All patients were started on anticoagulation therapy with enoxaparin SC at therapeutic doses, followed by oral administration of Dabigatran or Apixaban; all of them recovered well.

DISCUSSION

We report four cases of late PE in young patients (under 45 years), which appeared 16 to 32 days after discharge after being infected with the COVID-19 virus: the median time delay to the onset of symptoms was 20 days (interquartile range 4–12); the median age of patients was 38.5 years (interquartile range 9.5–6.5) — presented in Table 1. A series of 15 case reports and small series (altogether 26 patients) were retrieved from a PubMed search for papers published up to November 31, 2020, concerning post-discharge PE events after mild COVID-19 cases. These cases reported the occurrence of late thromboembolic complications, especially in young patients (most of them under 50 years), with the absence or with various modalities of thromboprophylaxis during the COVID-19 course (6–20). Patients under 65 years (younger cohort) had a significantly higher PE prevalence of 20.5%, compared to the 14.3% (p < 0.05) observed in those older than 65 years (5).

In a retrospective study, a VTE post-discharge rate of 4.8 per 1000 discharges was found within 42 days, following 1877 hospital discharges associated with COVID-19. The post-discharge rate of PE associated with other medical conditions was 3.1 per 1000 discharges within 42 days. The risk of VTE post-COVID-19 discharge was not significantly higher (odds ratio 1.6) compared with the risk of VTE after other acute diseases. This study was limited to those with symptomatic thromboembolic events and possibly underestimated the total burden of post-discharged VTE after COVID-19, as many events are mild or asymptomatic (21, 22).

The main characteristic of patients with post-discharge PE was the highly elevated D-dimer values, a five to 200-fold increase above the cut-off level used in different studies. The D-dimer values were significantly increased at the initial COVID-19 hospitalization, being the highest at PE admission (7, 10–15, 17–20). They had the same pattern in our patients, with values from 10 to 20 times above the upper limit of normal at first admission and even greater at PE diagnostic, with values from 10 to 34 times higher (Table 1). Therefore, when the patients came with acute dyspnea or respiratory distress after an initial clinical improvement or after discharge, extremely high levels of D-dimer (at least five times higher than normal values) suggested late PE development (6, 9–14, 19). A French retrospective study in 394 COVID-19 patients, proposes a D-dimer cut-off of 2500 ng/ml (normal range < 400 ng/ml) for the PE diagnostic. The study also presented that D-dimer is associated with an increased risk of death (if > 1000) and has an important prognostic role (22). However, a prospective study is required to assess the frequency of late PE and validate the proposed D-dimer cut-off of 2500 ng/mL to indicate the presence of PE in COVID-19 patients.

Another characteristic in our case series is a disproportionally elevated D-dimer value in comparison to other coagulation or inflammatory blood parameters (Table 1). This pattern is like other case series reports of post-discharge PE and should, hence, raise suspicion for pulmonary or venous embolism even in the absence of symptomatology (9, 10, 11).

An important characteristic of most patients was the absence of pre-existing risk factors for VTE and the absence of signs of deep vein thrombosis at VDUS, suggesting that COVID-19 itself — by promoting a prothrombotic status — may be a risk factor (2, 3, 22, 23).
Apart from a female patient in one study, none were found to have inherited thrombophilia to explain the occurrence of the thromboembolic event (10). In our cases, none of the patients had thromboembolic risk factors, and VDUS were performed on all patients with none found with venous thrombosis. Thus, the probable triggers for thrombotic events are the inflammatory status and diffusing the endothelial damage that predisposes to widespread thrombotic vascular lesions (2, 3).

All the patients in our case series during hospitalization had thromboprophylaxis (not full doses) with enoxaparin SC 0.6, 0.8, or 1 ml once daily for seven days. The recommendations of the 2020 - American College of Chest Physicians (ACCP) guideline and expert panel report for the prevention, diagnosis, and treatment of VTE in patients with COVID-19 suggest the current standard dose of anticoagulant (not intermediate) thromboprophylaxis during hospitalization and extended thromboprophylaxis after hospital discharge for those with low risk of bleeding (24). We do not have data for D-dimer values on hospital discharge after COVID-19 treatment and none of the patients had post-discharge oral anticoagulation. This issue could be related to the apparition of late PE. However, until now, no trials were addressing the role and duration of thromboprophylaxis in COVID-19 patients after discharge and no trial evaluating the predictive value of D-dimer for the risk of VTE after anticoagulation withdrawal.

Finally, our patients had a favorable therapeutic evolution to parenteral and oral anticoagulants. Usually, much of the late PE after COVID-19 is segmental or subsegmental, and, therefore, the evolutions are generally good (9–11, 22, 23, 25). The pulmonary angio-CT in our patients showed filling defects of the distal segmental and subsegmental arterial branches (two cases) and left lower pulmonary artery (two cases). Pulmonary inflammation caused by COVID-19 and the absence of signs of venous thrombosis at VDUs suggests a pulmonary thrombosis rather than a PE. In a series of 109 hospitalized COVID-19 patients who had suspicions of PE, the patients with confirmed PE were 41/101 (40.6%), while those with deep venous thrombosis at VDUs were 5/41 (12.2%). Thus, the authors hypothesized that the thrombosis due to diffuse pulmonary inflammation explained the PE, rather than the thromboembolism. The question could not be solved due to the limited number of available autopsy studies. Additionally, further research is required to clarify the different PE scenarios seen in the current studies (25).

Our series was retrospective with only four patients presented at the hospital with PE suspicion after the initial COVID-19 discharge. There is no data for the D-dimer values on hospital discharge after the COVID-19 treatment. Therefore, our data should be interpreted cautiously until larger studies bring in more parameters to predict the apparition of late PE in COVID-19 patients.

**CONCLUSION**

PE is a complication of the COVID-19 disease which may occur later, especially in young patients with no other risk factors for pulmonary embolus. The highly elevated levels of D-dimer at COVID-19 admission are correlated not only with the prognostic but also with the risk of thromboembolic complications and seem to be associated with the post-discharge apparition of PE. This data suggests the role of extended anticoagulation in selected COVID-19 patients and warrants further investigations addressing the role and duration of thromboprophylaxis in COVID-19 patients after discharge.

**Abbreviations**

- **SARS-CoV-2** — severe acute respiratory syndrome coronavirus 2
- **COVID-19** — Coronavirus Disease
- **PE** — pulmonary thromboembolism
- **VTE** — venous thromboembolism
- **CRP** — C reactive protein
- **LDH** — lactate dehydrogenase
- **INR** — international normalized ratio
- **SC** — subcutaneous
- **BMI** — body mass index
- **ECG** — electrocardiogram
- **Bpm** — beats per minute
- **FEU** — Fibrinogen equivalent units
- **BNP** — brain natriuretic peptide
- **RR** — reference range
- **CI** — confidence interval

**Authors’ contributions**

Both authors CP and IF were involved in conceptualization, data collection, interpretation of data, writing – original draft, review drafting, and reviewing the submitted manuscript.

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**Licensing**
Sažetak

**VISIKE VREDNOSTI D-DIMERA I AKUTNA PLUČNA EMBOLIJA NAKON OTPUSTA IZ BOLNICE KOD MLADIH PACIJENATA SA KOVID-19: SERIJA SLUČAJEVA**

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Rezultati: Ovi pacijenti su imali povišeni D-dimer (najmanje 10 puta od gornje granice normale) pri prijemu i u vreme dijagnostike PE, dok su ostali parametri, koji su uključivali zapaljenje i koagulaciju (C-reaktivni protein - CRP, laktat dehidrogenaza — LDH, fibrinogen, INR) bili normalni. Nije bilo prethodno postojećih faktora rizika za PE i svi pacijenti su bili antikoagulirani sa profilaktičkim srednjim dozama enoksaparina.

Zaključak: PE je komplikacija bolesti KOVID-19 koja se može javiti kasnije, posebno kod mladih pacijenata bez drugih faktora rizika za to stanje. Čini se da su visoko povišeni nivoi D-dimera pri prijemu KOVID-19 povezani sa pojavom PE nakon otpuštanja. Ovi podaci sugerišu ulogu produžene antikoagulantne terapije kod nekih pacijenata sa KOVID-19 i zahtevaju dalja istraživanja.

Ključne reči: D-dimer, COVID-19, mladi pacijenti, plućna embolija, otpust pacijenata.

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