Changing face of pulmonary embolism with COVID-19
Bayram Bagırtan, Emine Altuntas, Servan Yasar, Kanber Ocal Karabay

Abstract

Aim: This study aimed to describe the baseline characteristics of coronavirus disease 2019 (COVID-19) patients with pulmonary embolism, and to examine the Geneva score, pulmonary embolism severity index (PESI), radiological and biochemical findings.

Methods: From March 2020 to June 2021, the files of 41 COVID-19 patients with pulmonary embolism were accessed.

Results: Mean D-dimer value was 6.04 mg/dl and 61% of the patients received at least one dose of anticoagulant treatment. In patients receiving deep venous thrombosis prophylaxis, an optimal D-dimer cut-off point was calculated as 5.69 mg/dl. The area under the curve was 0.753 (p=0.007; sensitivity 64%; specificity 62.5%). The mean Geneva score was 4.31, mean PESI was 72.48 and mean Qanadli score was 11.29.

Conclusions: According to this study, traditional clinical predictive scores had little discriminatory power in these patients, and a higher D-dimer cut-off value should be considered to better diagnose patients for pulmonary embolism.

Keywords: COVID-19, thrombosis, pulmonary embolism, D-dimer, anticoagulant therapy

Submitted 12/10/21, accepted 9/2/22
Cardiovasc J Afr 2022; online publication www.cvja.co.za
DOI: 10.5830/CVJA-2022-011

With the emergence of coronavirus disease 2019 (COVID-19) in December 2019, a new pandemic page has been opened in the history of the world. The disease, which was initially thought to be a highly contagious viral infection, later evolved into a multisystem inflammatory and thrombotic disease due to the involvement of cardiovascular and pulmonary structures. Ischaemic stroke and myocardial infarction are examples of complications of the disease. Excessive inflammation, hypoxia, immobilisation, platelet activation and endothelial dysfunction are contributors to the prothrombotic state.

COVID-19 infection affects not only the pulmonary parenchyma but also the pulmonary vascular bed. Autopsy studies have demonstrated the presence of thrombi in the pulmonary arteries and alveolar capillaries of individuals deceased from COVID-19. Recent studies have revealed that patients with COVID-19 had higher PE prevalence than usually encountered in non-infected critically ill patients.

Several prognostic indicators of mortality, such as admission clinical properties and laboratory parameters have been defined in PE. PE severity index (PESI) is a powerful predictor of a worse prognosis, and clinical use of PESI is recommended by the European Society of Cardiology. Also, the Geneva score is a clinical prediction rule to assess PE pre-test probability. This study aimed to describe the baseline characteristics of COVID-19 patients with PE, and assess the Geneva score and PESI.

Methods

The study was retrospective and single centred. From March 2020 to June 2021, the files of all patients admitted to hospital with a diagnosis of PE were accessed. Among them, patients who had simultaneous COVID-19 infection were included in the study. The exclusion criteria were pregnancy and those younger than 18 years.

According to World Health Organisation criteria, COVID-19 infection was determined by positive results from real-time reverse transcription polymerase chain reaction of nasopharyngeal swabs or by typical imaging characteristics on chest computed tomography. Patients without computed tomography pulmonary angiography (CTPA) to diagnose PE were excluded. The study protocol was approved by the local ethics committee.

From the hospital record system, baseline information including demographic characteristics and co-existing medical conditions were obtained. Clinical parameters and biological findings at the diagnosis of PE were recorded for calculation of PESI and Geneva scores. Laboratory data such as complete blood count, albumin, D-dimer, C-reactive protein (CRP), ferritin, fibrinogen, fasting glucose and high-sensitivity (hs) troponin T levels, and kidney and liver function tests were collected on the day of diagnosis of PE. Data on pharmacological therapies, respiratory complications, morbidity and mortality were also gathered during the hospitalisation.

CTPA examinations with 16-section (Cannon Aquilion Lightning, Canon Medical Systems Europe BV, Zoetermeer the Netherlands) and 128-section (D Revolution Evo Gen 3,
GE Healthcare, Waukesha, WI, USA) multislice CT devices were carried out. The CTPA protocol was performed using a multidetector scanner after intravenous injection of 50–75 ml of high-concentration iodinated contrast agent at a flow rate of 3–4 ml/s, which was triggered on the main pulmonary artery.

The Qanadli score or CT obstruction index is calculated by regarding the arterial tree of each lung as having 10 segmental arteries (three to the upper lobes, two to the middle lobe and lingula, and five to the lower lobes). Embolus in a segmental artery = one point; embolus in the most proximal arterial level = a value equal to the number of segmental arteries arising distally. Weighting factor (for residual perfusion) = the degree of vascular obstruction (no thrombus = zero; partially occlusive thrombus = one; total occlusion = two). The maximal CT obstruction index = 40 for each patient (10 × maximum weighting of 2 = 20 for each side). Isolated subsegmental embolus is considered equal to a partially occluded segmental artery.14

In addition, a CT severity score of one to five was given using ground-glass opacities and consolidations and the extent of COVID-19 lung lesions and the percentage of lung volume affected.15 The CTPA results of COVID-19 and the presence of PE were analysed by an experienced radiologist.

Statistical analysis

In this study, the Statistical Package for Social Sciences (SPSS) 20.0 for Windows (USA, Armonk, New York) program was used for statistical analysis. Distribution of continuous data was assessed with the Kolmogorov–Smirnov test. Normally distributed variables are expressed as mean ± standard deviation, whereas non-normally distributed variables are given as median and interquartile range. Categorical variables are reported as numbers and percentages. Categorical variables were compared with the chi-squared test or Fisher’s exact test, where appropriate.

Correlation analysis was used to examine the relationships between PESI score, Geneva score, CHA2DS2-VASc score, CRP, procalcitonin, fibrinogen, hs-troponin T, D-dimer and glucose. Receiver operating characteristic (ROC) curve analysis was performed and the Youden index was calculated to determine the optimal D-dimer threshold to predict in patients with COVID-19 lung involvement. Stage 3 to 5 involvement was observed in 29 (70.8%) of the patients. It was determined that 10 (34.5%) of them did not receive thromboprophylaxis (Table 3).

In this study, the Statistical Package for Social Sciences (SPSS) 20.0 for Windows (USA, Armonk, New York) program was used for statistical analysis. Distribution of continuous data was assessed with the Kolmogorov–Smirnov test. Normally distributed variables are expressed as mean ± standard deviation, whereas non-normally distributed variables are given as median and interquartile range. Categorical variables are reported as numbers and percentages. Categorical variables were compared with the chi-squared test or Fisher’s exact test, where appropriate.

Correlation analysis was used to examine the relationships between PESI score, Geneva score, CHA2DS2-VASc score, CRP, procalcitonin, fibrinogen, hs-troponin T, D-dimer and glucose. Receiver operating characteristic (ROC) curve analysis was performed and the Youden index was calculated to determine the optimal D-dimer threshold to predict in patients with COVID-19 lung involvement. Stage 3 to 5 involvement was observed in 29 (70.8%) of the patients. It was determined that 10 (34.5%) of them did not receive thromboprophylaxis (Table 3).

Bivariate analysis showed significant correlations between CHA2DS2-VASc and PESI scores (rho = 0.484, p = 0.001). Furthermore the Geneva score was positively correlated with the Qanadli score. In addition, a positive correlation was observed between the Qanadli score and the right/left ventricular (RV/LV) ratio. Correlation analysis results are given in Table 4.

A ROC curve was performed to determine the optimal threshold for D-dimer to predict PE occurrence on CTPA in patients with COVID-19 receiving thromboprophylaxis. The area under the curve (AUC) was 0.753 (p = 0.007) (Fig. 1).

Discussion

The main findings of this study are that the Geneva score and PESI were not high in patients with COVID-19 and PE. Besides, most of the patients developed PE despite anticoagulant therapy. Our study shows that a higher D-dimer threshold (5.69 mg/dl)
gives a better sensitivity and specificity to predict PE in patients with COVID-19 who need oxygen support.

The main features of COVID-19 patients with PE have been described in several studies. The patient characteristics reported in this study confirmed that male gender and longer delay from onset of symptoms to hospitalisation were associated with an increased risk of PE. Also, the patients were younger. The traditional risk factors of PE, as previously described, were not associated with the occurrence of PE in our study.

There is no consensus in the world on the D-dimer cut-off point to suspect PE in COVID-19 patients. The International Society of Thrombosis and Hemostasis considered that a three- to four-fold increase in D-dimer concentration may be significant in terms of guidance for recognition and management of coagulopathy in COVID-19. This cut-off value differs slightly between studies.

In the study of Mouhat et al., workers found that a D-dimer concentration greater than 2,590 ng/ml conferred a 17-fold increase in the risk of PE in 162 hospitalised patients with COVID-19 pneumonitis, with a resultant sensitivity of 83.3% and specificity of 83.8%. Ventura-Diaz et al. placed this threshold at 2,903 ng/ml (resultant sensitivity 81%) in their retrospective cohort of 242 hospitalised patients with COVID-19, with a PE prevalence of 30%.

In another study a total of 193 patients underwent CTPA imaging and were classified into PE-positive (n = 33) and -negative cases.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care unit admission</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>Length of stay in intensive care unit (days)</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>Length of stay in hospital (days)</td>
<td>9 (6.5)</td>
</tr>
<tr>
<td>Mortality in hospital</td>
<td>0</td>
</tr>
<tr>
<td>Duration between CT and swab (days)</td>
<td>13.28 ± 7.69</td>
</tr>
<tr>
<td>Rhythm</td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>40 (97.6)</td>
</tr>
<tr>
<td>AF</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Need for oxygen support</td>
<td>25 (61)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124.75 ± 17.66</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.04 ± 10.95</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>1.3 ± 1.5</td>
</tr>
<tr>
<td>Geneva score</td>
<td>4.31 ± 1.58</td>
</tr>
<tr>
<td>Class of Geneva score</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25 (61)</td>
</tr>
<tr>
<td>High</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>PESI score</td>
<td>72.48 ± 24.62</td>
</tr>
<tr>
<td>Class of PESI score</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td>Class II</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Class III</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>Class IV</td>
<td>2 (4.6)</td>
</tr>
<tr>
<td>Class V</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Under anticoagulant therapy</td>
<td>25 (61)</td>
</tr>
<tr>
<td>No thromboprophylaxis</td>
<td>16 (39)</td>
</tr>
<tr>
<td>DVT thromboprophylaxis dose</td>
<td>14 (34.1)</td>
</tr>
<tr>
<td>Modified thromboprophylaxis dose</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Full thromboprophylaxis dose</td>
<td>9 (22)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>4 (9.8)</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CT: computed tomography; DVT: deep venous thrombosis; PESI: pulmonary embolism severity index; SR: sinus rhythm; AF: atrial fibrillation; CHA2DS2-VASc: congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke, vascular disease, age 65–75 years, sex category; LV: left ventricle; RV: right ventricle.
groups. Physiological, radiological and biochemical parameters were compared and ROC curve analysis was conducted to determine a predictive D-dimer threshold. They proposed that in the absence of other clinical signs, a D-dimer threshold of 2 495 ng/ml could be used with high sensitivity and specificity to predict PE in hospitalised patients with COVID-19 (with 100% sensitivity and 90.6% specificity).21 In our study, the mean D-dimer value of all patients was 6.04 (IQR 9.06) and the cut-off point was 5.69 in patients who received thromboprophylaxis.

Because of the prothrombotic state highlighted in COVID-19, previous studies have reported that thrombus described by CTPA was in the majority of cases segmental or subsegmental during COVID-19-related PE. Some authors have suggested that the thrombus load was calculated from CTPA data area.23,24 The mean Qanadli score was 11.29, in our study, the thrombus load was higher.25 The mean Qanadli score was 11.29, in our study, the thrombus load was calculated from CTPA data area.23,24

The development of a thrombus within the lung inflammation during COVID-19-related PE. Some authors have suggested that a localised immunothrombosis process could contribute to the development of a thrombus within the lung inflammation area.25,26

For diagnostic accuracy and assessment of disease severity, in our study, the thrombus load was calculated from CTPA data using the Qanadli score.25 The mean Qanadli score was 11.29, which means that the distribution of thrombus localisation was mostly segmental and subsegmental.

A study of 61 patients investigated the correlation between radiological and clinical–biochemical features in a cohort of hospitalised COVID-19 patients. PE was detected in only 14 patients and deep-vein thrombosis in five. The Qanadli score, RV/LV ratio, revised Geneva score and PESI were calculated in this patient group. It was found that the Qanadli score had a significant correlation with PESI, D-dimer, serum hs-troponin, serum albumin, arterial pressure of oxygen-to-inspired fraction of oxygen ratio (pO2/FiO2) and length of hospital stay.26 In our study, there was a positive correlation between only the Qanadli and Geneva scores.

Silva et al. evaluated the accuracy of the Wells and Geneva scores to predict PE in patients with SARS-CoV-2 infection in their study. There was no statically significant difference between the average Wells score in patients with and without PE (1.04 and 0.89, respectively, p = 0.733) and the AUC demonstrated that the Wells score had no discriminatory power (AUC = 0.5). The Geneva score of the groups was also similar (4.20 vs 3.93, respectively, p = 0.420), with the AUC being 0.54.27

In our cohort, patients who developed PE had a pretest probability in the intermediate to low range, as confirmed by the Geneva score. The spectrum of mortality risk assessed by the PESI score ranged from Class I to III, but no patients died in our study. In the study of Wu et al., the median of the PESI was 88.1 (34–130).28 In our study, the mean of the PESI was 72.48 ± 24.62. This difference may have been due to the fact that our patients were younger.

Although most of the hospitalised patients with COVID-19 were on anticoagulant therapy, the incidence of PE was high. SARS-CoV-2 infection promotes endothelial dysfunction, prothrombotic events and pulmonary microthrombi, and the inflammatory host response leading to PE has been proven in autopsy studies.29 Poissy et al. showed that patients with COVID-19 infection had a higher frequency of PE than patients infected with other infections.29

COVID-19 is now considered a pro-thrombotic disease with systemic inflammation. Post-mortem studies showed widespread alveolar damage and inflammation in patients. In the light of these data, it was determined that the pathogenic mechanism of PE was pulmonary intravascular coagulopathy.29,30 Despite prophylactic anticoagulation in patients with COVID-19, they can still develop thrombotic events.

In a case series of 22 patients followed up in the ICU due to COVID-19 infection, PE was found in 20 patients, although all patients had received thromboprophylaxis.31 Similar results have been supported by other studies.32,33 In our study, 61% of the patients received at least one dose of anticoagulant treatment.

There are several limitations to our study. It was a retrospective analysis of patients admitted with COVID-19 who underwent a CTPA, therefore, there may have been selection bias. In other words, the patients selected for CTPA were suspected of having a high pretest probability of PE. The sample size was small. There was a restriction on accessing different diagnostic tests and complex logistics to confirm PE, such as transthoracic echocardiography.

Conclusion

PE is seen frequently in patients with COVID-19 infection despite thromboprophylaxis. According to our results, traditional clinical prediction scores such as the PESI and Geneva score show little discriminatory power. A high D-dimer cut-off value should be considered a better measure to determine patients with PE.

References


