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Pulmonary embolism in COVID-19: Clinical characteristics and cardiac implications

Jason Khoa a, Adam Ioannou b, Koenraad Van den Abbeele a, Amit K.J. Mandal a, Constantinos G. Missouris a,c,*

a Wexham Park Hospital, Frimley Health NHS Foundation Trust, UK
b Royal Free Hospital, Royal Free London NHS Foundation Trust, UK
c University of Cyprus Medical School, Nicosia, Cyprus

A B S T R A C T

Background: The thrombogenic potential of Covid-19 is increasingly recognised. We aim to assess the characteristics of COVID-19 patients diagnosed with pulmonary embolism (PE).

Methods: We conducted a single centre, retrospective observational cohort study of COVID-19 patients admitted between 1st March and 30th April 2020 subsequently diagnosed with PE following computed tomography pulmonary angiogram (CTPA). Patient demographics, comorbidities, presenting complaints and inpatient investigations were recorded.

Results: We identified 15 COVID-19 patients diagnosed with PE (median age = 58 years [IQR = 23], 87% male). 2 died (13%), both male patients >70 years. Most common symptoms were dyspnoea (N = 10, 67%) and fever (N = 7, 47%). 12 (80%) reported 7 days or more of non-resolving symptoms prior to admission. 7 (47%) required continuous positive airway pressure (CPAP), 2 (13%) of which were subsequently intubated. All patients had significantly raised D-dimer levels, lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin and prothrombin times. The distribution of PEs correlated with the pattern of consolidation observed on CTPA in 9 (60%) patients; the majority being peripheral or subsegmental (N = 14, 93%) and only 1 central PE. 10 (67%) had an abnormal resting electrocardiogram (ECG), the commonest finding being sinus tachycardia. 6 (40%) who underwent trans-thoracic echocardiography (TTE) had structurally and functionally normal right hearts.

Conclusion: Our study suggests that patients who demonstrate acute deterioration, a protracted course of illness with non-resolving symptoms, worsening dyspnoea, persistent oxygen requirements or significantly raised D-dimer levels should be investigated for PE, particularly in the context of COVID-19 infection. TTE and to a lesser degree the ECG are unreliable predictors of PE within this context.

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 in Wuhan, China. It rapidly spread and was declared a worldwide pandemic on 11th March 2020 [1]. COVID-19 is primarily a respiratory disease and the most common symptoms reported are fever and dry cough. Most patients experience mild disease, but a small subset of patients develop severe disease requiring hospital admission. The course of the disease may be further complicated by type 1 respiratory failure (T1RF) requiring invasive mechanical ventilation [2]. This is initially due to a viral pneumonia, followed by a cytokine driven inflammatory response that can cause acute respiratory distress syndrome (ARDS), multi-organ failure and death.

However, it is becoming increasingly recognised that COVID-19 infection can lead to a procoagulant state, causing pulmonary embolism (PE). Life threatening COVID-19 cases are often associated with excessive activation of the coagulation cascade which is evidenced by raised D-dimer protein levels and coagulopathy [3,4].

The use of non-contrast-enhanced computed tomography (CT) has been advocated for the diagnosis of COVID-19 pneumonia, particularly when initial Real-Time Reverse Transcripase-Polymerase Chain Reaction (RT-PCR) screening is negative [5]. This imaging modality is also used to assess the severity and progression of disease [6]. Patients with COVID-19 are naturally predisposed to PE because of active inflammation, hypoxaemia and immobility and CTPA should be performed in patients who deteriorate despite supportive therapy or demonstrate clinical features of PE such as worsening dyspnoea, haemoptysis or pleuritic chest pain [7,8].

We aimed to assess the characteristics of hospitalised COVID-19 patients who were subsequently diagnosed with PE and to establish any potential risk factors based on our observations. Our secondary

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aim was to evaluate the diagnostic yield of cardiac investigations with respect to right ventricular dysfunction related to acute PE, such as resting 12-lead ECG and TTE.

2. Methods

We conducted a retrospective analysis of all patients diagnosed with COVID-19 and PE during their hospital admission between 1st March and 30th April 2020. Patient data including demographics, comorbidities, presenting complaints and inpatient investigations were extracted from our local hospital electronic database. RT-PCR assay of nasopharyngeal swabs was used to confirm a diagnosis of COVID-19. In patients where there was a strong clinical suspicion of COVID-19 but negative RT-PCR assay, a radiological diagnosis was made using CT imaging of the chest. Radiological features of COVID-19 included bilateral peripheral subpleural ground-glass opacities, inter/intralobular septal thickening, airspace opacification, traction bronchiectasis and organising pneumonia.

Admission D-dimer levels and CTPA dates were also recorded, along with each patient's Wells score prior to investigation. Routine COVID-19 blood workup including full blood count, serum biochemistry, troponin-T, lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP) and coagulation profile were recorded. The neutrophil:lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count [9].

The anatomical location of PE on CTPA was compared to the pattern of lung consolidation and infiltrates. The right ventricular (RV) and left ventricular (LV) diameters were measured to calculate the RV:LV ratio, a surrogate marker of embolic burden on the heart [10].

Our hospital's guideline for venous thromboembolism (VTE) prophylaxis is subcutaneous dalteparin and we assessed if VTE prophylaxis was prescribed and administered appropriately according to risk stratification. Following diagnosis of PE, we recorded the weight-adjusted treatment doses of dalteparin prescribed and whether any alternative treatment such as oral anticoagulation was initiated.

We analysed each patient's cardiac conduction on an admission resting 12-lead ECG and documented sinus tachycardia, new right bundle branch block (RBBB), right axis deviation, S1Q3T3 pattern, resting 12-lead ECG and documented sinus tachycardia, new right initiation.

We presented and were readmitted because of worsening symptoms. 7 (47%) patients required continuous positive airway pressure (CPAP), 2 of which were subsequently intubated. Of our study group, 7 (47%) patients had positive nasopharyngeal swabs and the remaining 8 (53%) with negative swabs were diagnosed on the basis of pulmonic radiological changes on CT consistent with COVID-19.

Troponin T (<0.14 ng/mL) was elevated in 5 (33%) patients with a median value of 12 ng/mL (range 4–45 ng/mL). 9 (60%) patients had leucocytosis (4.0–11.0 × 10^9/L) with a median value of 13.2 × 10^9/L (range 11.3–17.7 × 10^9/L) and predominant neutrophilia (2.0–7.5 × 10^9/L), median value of 10.8 × 10^9/L (range 8.1–14.4 × 10^9/L) in addition to high CRP (0–4 mg/L) with a median level of 189 mg/L (range 115–424 mg/L); the remaining 6 patients had a median CRP of 45 mg/L (range 30–86 mg/L).

Only 3 (20%) patients had lymphopenia (1.0–4.0 × 10^9/L) with a median value of 0.86 × 10^9/L (range 0.63–0.95 × 10^9/L) giving NLR > 9. The median prothrombin time (12.0±11.0 s) was 17.0 s (range 15.1–21.7 s), the median LDH level (214–214 U/L) was 317 U/L (range 155–872 U/L) and median ferritin level (15–780 μg/L) was 780 μg/L (range 353–3364 μg/L). Only 1 patient was thrombocytopaenic

3. Statistical analysis

Categorical variables are summarised as frequencies and percentages. Data outside the normal distribution are presented as medians and ranges. All data were analysed with SPSS Version 26 software.

4. Ethics

As a study using clinically collected, non-identifiable data, this work does not fall under the remit of the National Health Service Research Ethics Committees.

5. Results

During the study period, a total of 15 COVID-19 patients were diagnosed with PE during their hospital admission. The median age was 58 years (IQR = 23) and 13 (87%) were male. Patient demographics and comorbidities are summarised in Table 1.

There were 2 (13%) deaths, both of which were male patients aged >70 years (cases 10 and 12). The most common symptom was dyspnoea (N = 10, 67%) followed by fever (N = 7, 47%). 12 (80%) patients reported 7 days or more of non-resolving symptoms prior to admission to hospital. 3 (20%) patients who had initially been discharged after 24 h (all nasopharyngeal swab positive for COVID-19 on RT-PCR) represented and were readmitted because of worsening symptoms. 7 (47%) patients required continuous positive airway pressure (CPAP), 2 of which were subsequently intubated. Of our study group, 7 (47%) patients had positive nasopharyngeal swabs and the remaining 8 (53%) with negative swabs were diagnosed on the basis of pulmonic radiological changes on CT consistent with COVID-19.

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Table 1

| Case number | Age (y) | Sex | Pre-existing medical conditions | Presenting symptoms | Duration of symptoms prior to admission (days) | Readmission |
|-------------|---------|-----|---------------------------------|---------------------|-----------------------------------------------|------------|
| 1           | 44      | Female | None                           | Fever, dry cough    | 7                                             | No         |
| 2           | 60      | Male   | None                           | Fever, dry cough    | 14                                            | No         |
| 3           | 54      | Female | Hypertension, Obstructive Sleep Apnoea, Asthma, Obesity | Fever, dry cough, dyspnoea | 7                                             | No         |
| 4           | 61      | Male   | Peripheral Vascular disease    | Fever, dry cough, dyspnoea | 10                                            | Yes        |
| 5           | 67      | Male   | Hypertension, Type 2 Diabetes Mellitus | Vomiting, confusion | 2                                             | No         |
| 6           | 56      | Male   | Type 2 Diabetes Mellitus, High Cholesterol, previous Transient Ischaemic Attack, Epilepsy | Fever, dyspnoea | 7                                             | No         |
| 7           | 56      | Male   | None                           | Fever, dry cough    | 14                                            | No         |
| 8           | 30      | Male   | Sickle cell trait              | Pleuritic chest pain | 2                                             | No         |
| 9           | 73      | Male   | Hypertension, Rheumatoid arthritis | Dyspnoea            | 14                                            | Yes        |
| 10          | 94      | Male   | Previous Transient Ischaemic Attack | Lethargy, dyspnoea  | 7                                             | No         |
| 11          | 75      | Male   | Chronic Obstructive Pulmonary Disease | Fever, productive cough | 7                                            | No         |
| 12          | 72      | Male   | Previous knee replacement      | Dry cough, dyspnoea  | 14                                            | No         |
| 13          | 58      | Male   | Hypertension                   | Pleuritic chest pain, dyspnoea | 18                                           | Yes        |
| 14          | 46      | Male   | None                           | Fever, dry cough, pleuritic chest pain | 17                                           | No         |
| 15          | 49      | Male   | Previous deep vein thrombosis, asthma | Dry cough, dyspnoea, pleuritic chest pain | 5                                             | No         |

a 2 patients who died.

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| Case number | D-dimer, ng/mL | Wells scores | Day of admission | Pattern of consolidation | Site of PE | RV: LV ratio | Mechanical ventilation |
|-------------|----------------|--------------|------------------|--------------------------|-----------|-------------|-----------------------|
| 1           | 2124           | 3515         | 5.5              | Lower lobe consolidation | Right main, lobar and segmental pulmonary arteries | 1.0        | Yes, CPAP             |
| 2           | >20,000        | 3            | 2                | Widespread ground-glass changes in periphery and basal patchy consolidation | Lower lobes and upper lobe | 1.0        | Yes, CPAP             |
| 3           | 11,366         | 4            | 7                | Peripheral ground-glass changes, bifocal consolidation | Lower lobes | 1.0        | Yes, CPAP             |
| 4           | 60,700         | 3            | 2                | Left lower lobe consolidation | Bilateral segmental branches | 0.8        | No                     |
| 5           | >20,000        | 3            | 2                | Multifocal peripheral patchy consolidation in right upper lobe with dependent consolidation in lower lobe | Saddle embolus extending into both lower lobe pulmonary arteries and segmental branches | 1.1        | No                     |
| 6           | >20,000        | 3            | 14               | Widespread ground-glass shadowing | Distal right main artery extending into middle and lower segmental vasculature | 1.4        | Yes, CPAP             |
| 7           | 6704           | 4            | 5                | Peripheral ground-glass opacities | Bilateral segmental and subsegmental | 1.0        | No                     |
| 8           | 9572           | 4            | 5                | Left lower lobe consolidation | Right middle and lower lobe | 1.0        | No                     |
| 9           | 6972           | 3            | 2                | Extensive ground-glass changes, predominantly lower lobes | Lobar level of lingula, lower lobe arteries | 1.1        | Yes, CPAP             |
| 10          | >20,000        | 3            | 4                | Basal patches of consolidation and ground-glass opacities | Subsegmental and segmental branches in basal and lower lobe distribution | 1.0        | Intubated and Ventilated |
| 11          | 3447           | 3            | 7                | Multiple ground-glass opacities in upper lobes and diffuse in right lower lobe | Segmental branch of right lower lobe artery | 1.4        | Intubated and Ventilated |
| 12          | 1320           | 3            | 1                | Bilateral peripheral and basal ground-glass opacification | Subsegmental and segmental arteries of right lower and middle lobe | 0.9        | No                     |
| 13          | 2188           | 4            | 5                | Patchy consolidation in peripheral aspects of bilateral lower lobes and subpleural aspect of right upper lobe | Subsegmental in lingula and basal left lower lobe and anteroinferior right upper lobe | 1.0        | No                     |
| 14          | 4540           | 6            | 1                | Bilateral ground-glass changes in right middle lobe and lingula | Distal end of right lower lobe artery with multiple PE in right inferior pulmonary artery and its branches | 1.1        | No                     |

WCC = White cell count; Neut = Neutrophil; Lymph = Lymphocyte; NLR = Neutrophil to Lymphocyte Ratio; Pt = Platelet; CRP = C-reactive protein; Trop = Troponin T; LDH = Lactate Dehydrogenase; PT = Prothrombin Time; APTT = Activated Partial Thromboplastin Time; Na = Sodium; K = Potassium; Cr = Creatinine; Alb = Albumin; Bilirubin; ALP = Alkaline Phosphatase; ALT = Alanine Transaminase.
were characterised by lymphocytic inflammation. 8 deaths were directly attributable to PE. The histopathological features of our patients deviates from that of sepsis where thrombocytopenia is common and from DIC where significant deranged clotting times and clotting disorders may have a low sensitivity for the diagnosis of PE in COVID-19. The predisposition to VTE in COVID-19 patients may occur in several ways. SARS-CoV-2 invades the body by using angiotensin converting enzyme 2 (ACE2) as a coreceptor. ACE2 degrades angiotensin II and acts as counter-regulatory hormone to the vasoconstrictive and proliferative axis of the renin-angiotensin-aldosterone system (RAAS) pathway. Increased expression of angiotensin II has been found to be thrombogenic through the enhancement of platelet activity and coagulation [13]. Viral activation of the innate immune system also leads to cytokine release. Interleukin-6 (IL-6) is the key pro-inflammatory cytokine implicated in the cytokine release syndrome or “storm” and directly activates the coagulation cascade [14]. Activation of RAAS and increased angiotensin II can directly increase the expression of IL-6, further amplifying its thrombogenic potential [15]. Inflammation induced alveolar injury and hypoxaemia can also lead to a vascular endothelial response that augments thrombus formation [16]. More recently, Zhang et al. detected the presence of antiphospholipid antibodies in a COVID-19 case, which might also serve as an explanation for the thrombogenicity [17].

We observed a male propensity to developing PE. Early studies found an association between increased mortality and male gender [18]. It has been hypothesised that the gender differences in severity of disease may be due to sex-based immunology differences, but may also be affected by comorbidities or health inequalities [18,19]. Our data supports the notion that poor outcomes observed in men may be a direct result of higher incidence of PE. A recent study by Li et al. investigated ACE2 expression across various human tissues and found a positive correlation between ACE2 expression and immune signatures in lung tissues of men, suggesting an exaggerated inflammatory response may be more likely to occur in males than females [20].

Most common ECG changes in acute PE are sinus tachycardia and nonspecific T-wave changes, as demonstrated in our case series. Significant embolic burden may manifest as RBBB and ST segment changes which are considered to be poor prognostic markers [21]. Only 10–20% of patients will have a normal ECG [22], TTE, on the other hand, has a reported sensitivity of 53% and specificity of 83% in demonstrating right heart strain, making it a potential rule-in test for patients with a suspicion of PE [23]. The embolic burden in our cohort was sufficient to cause respiratory distress requiring hospital admission, with a few requiring ventilatory support, but overall, PE did not result in cardiac decompensation. Surrogate markers of cardiac compromise, namely, raised serum troponin, increased RV:LV ratio on CTPA or TTE measurements, right ventricular strain pattern/RBBB on ECG and significant pulmonary hypertension on TTE, were, notably, largely absent in our group of patients. TTE performed after the diagnosis of PE failed to demonstrate evidence of significant right heart volume or pressure overload, with normal TAPSE measurements and only trivial TR, suggesting that cardiac investigations may have a low sensitivity for the diagnosis of PE in COVID-19 patients.

### Table 4

| Case number | ECG findings                          | TTE findings |
|-------------|---------------------------------------|--------------|
|             |                                       | TAPSE, mm    | TR severity | LVEF, % | Probability of pulmonary hypertension | PAP, mmHg |
| 1           | Sinus tachycardia, right ventricular strain pattern, S1Q3T3 | 25.5         | Trivial     | 55–60   | Low                                  | 17        |
| 2           | Nil                                   | –            | –           | –       | –                                    | –         |
| 3           | Right ventricular strain pattern       | –            | –           | –       | –                                    | –         |
| 4           | Right ventricular strain pattern       | –            | –           | –       | –                                    | –         |
| 5           | Nil                                   | 17.8         | Trivial     | 60–65   | Intermediate                         | –         |
| 6           | Nil                                   | 11.0         | Trivial     | 59      | Low                                  | 16        |
| 7           | Sinus tachycardia                      | –            | –           | –       | –                                    | –         |
| 8           | Sinus tachycardia                      | 22.0         | Trivial     | 60–65   | Low                                  | 16        |
| 9           | Sinus tachycardia, right ventricular strain pattern, right axis deviation | –           | –           | –       | –                                    | –         |
| 10          | Sinus tachycardia                      | –            | –           | –       | –                                    | –         |
| 11          | Nil                                   | –            | –           | –       | –                                    | –         |
| 12          | Atrial fibrillation                    | 20.0         | Trivial     | 62      | Intermediate                         | 44        |
| 13          | Nil                                   | –            | –           | –       | –                                    | –         |
| 14          | Sinus tachycardia, right ventricular strain pattern | –           | –           | –       | –                                    | –         |
| 15          | Right ventricular strain pattern       | 25.0         | Trivial     | 60–65   | –                                    | –         |

ECG = Electrocardiogram; TTE = Transthoracic echocardiogram; TAPSE = Tricuspid annular plane systolic excursion; TR = Tricuspid regurgitation; LVEF = Left Ventricular Ejection Fraction; PAP = Pulmonary Arterial Pressures.
The diagnosis of PE in this population appears to depend reliably on clinical history (protracted course of non-resolving respiratory symptoms, presence of pleuritic chest pain and haemoptysis), persistent oxygen requirements disproportionate to the severity of pneumonia, a non-resolving TIRF despite mechanical ventilation, deranged prothrombin times and significantly raised D-dimer levels. Based on our study, a D-dimer levels >2000 ng/mL could be used as a threshold for CTPA. In keeping with other studies, we also observed that male gender may be an independent risk factor for PE and poor prognosis [18]. An NLR > 5.5 has been described to be a useful prognosticator for severe forms of COVID-19 infection [9]; two thirds of our cohort showed an NLR > 5.5, suggesting that raised NLR could potentially be used as a predictor for PE. Another marker of severe COVID-19 infection is elevated LDH levels, as demonstrated in 12 (80%) of our patients including the 2 that died. A pooled analysis by Henry et al. found that elevated LDH levels increased the odds of severe COVID-19 infection by 6-fold and mortality odds by >16-fold and therefore, may be a useful indicator of disease severity and a predictor of mortality [24]. We therefore suggest clinicians be vigilant for the aforementioned risk factors and have a low threshold for performing CTPA because early PE diagnosis and treatment influences outcomes.

Due to the procoagulant profile of COVID-19 infection, conventional doses for thromboprophylaxis may not be adequate; hence the emergence of multiple local hospital guidelines advocating thromboprophylactic dose adjustments according to weight and D-dimer levels [25,26]. This is supported by the preliminary findings from an observational study of 16 COVID-19 patients that demonstrated normalisation of procoagulant profiles (reflected by the reduction in fibrinogen concentrations and D-dimer protein levels) following enhanced doses of thromboprophylaxis [11]. However, at the time of writing, there remains an urgency for a consensus agreement on enhanced VTE prophylaxis in COVID-19 patients.

7. Limitations

Our study was retrospective in nature and based at a single centre with a small cohort of patients. Therefore, our data should be interpreted cautiously until larger studies are conducted to validate our observations. Furthermore, we only included PE identified by CTPA after clinical suspicion. Incidentally diagnosed PE on CT-imaging other than CTPA was not included in our series. A large case-controlled study would be of interest to allow confirmation of parameters that predict PE in COVID-19 patients and to quantify PE as a risk factor in COVID-19 outcomes.

8. Conclusion

Our study suggests that patients who demonstrate acute clinical deterioration, a protracted course of illness with non-resolving symptoms, worsening dyspnoea, persistent oxygen requirements or significantly raised D-dimer levels (>2000 ng/mL) should be investigated for PE, particularly in the context of COVID-19 infection. Cardiac investigations are of limited help in the immediate diagnosis of PE and therefore the decision for CTPA should be based on clinical suspicion, irrespective of the lack of supporting evidence from ECG or TTE.

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Credit author statement

All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.