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Pulmonary embolism in hospitalised patients with COVID-19

Martin B. Whyte[a,b], Philip A. Kelly[a], Elisa Gonzalez[a], Roopen Arya[c], Lara N. Roberts[c,*]

[a] Dept of Medicine, King's College NHS Foundation Trust, London, UK
[b] Dept Clinical and Experimental Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK
[c] King's Thrombosis Centre, Department of Haematological Medicine, King's College NHS Foundation Trust, London, UK

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is characterised by dyspnoea and abnormal coagulation parameters, including raised D-dimer. Data suggests a high incidence of pulmonary embolism (PE) in ventilated patients with COVID-19.

Objectives: To determine the incidence of PE in hospitalised patients with COVID-19 and the diagnostic yield of Computer Tomography Pulmonary Angiography (CTPA) for PE. We also examined the utility of D-dimer and conventional pre-test probability for diagnosis of PE in COVID-19.

Patients/methods: Retrospective review of single-centre data of all CTPA studies in patients with suspected or confirmed COVID-19 identified from Electronic Patient Records (EPR).

Results: There were 1477 patients admitted with COVID-19 and 214 CTPA scans performed, of which n = 180 (84%) were requested outside of critical care. The diagnostic yield for PE was 37%. The overall proportion of PE in patients with COVID-19 was 5.4%. The proportions with Wells score of ≥4 ('PE likely') was 33/134 (25%) without PE *vs* 20/80 (25%) with PE ($P = 0.951$). The median National Early Warning-2 (NEWS2) score (illness severity) was 5 (interquartile range [IQR] 3–9) in PE group *vs* 4 (IQR 2–7) in those without PE ($P = 0.133$). D-dimer was higher in PE (median 8000 ng/mL; IQR 4665–8000 ng/mL) than non-PE (2060 ng/mL, IQR 1210–4410 ng/mL, $P < 0.001$). In the 'low probability' group, D-dimer was higher ($P < 0.001$) in those with PE but had a limited role in excluding PE.

Conclusions: Even outside of the critical care environment, PE in hospitalised patients with COVID-19 is common. Of note, approaching half of PE events were diagnosed on hospital admission. More data are needed to identify an optimal diagnostic pathway in patients with COVID-19. Randomised controlled trials of intensified thromboprophylaxis are urgently needed.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), defined as coronavirus disease 2019 (COVID-19) is a global pandemic. The clinical features of COVID-19 include fever, cough, fatigue, muscle pain, diarrhoea, and pneumonia. Dyspnoea is seen in approximately one-fifth of patients 18.7% [1]. However, in a series from China, COVID-19 produced no radiographic or CT abnormality in 157 of 877 patients (17.9%) with non-severe disease [1]. Severe cases are characterised by acute respiratory distress syndrome, metabolic acidosis, septic shock, coagulation dysfunction, and organ failure [2–4].

In addition to immobility induced by malaise and dyspnoea, COVID-19 predisposes to systemic inflammation which has been reported to increase the risk for deep vein thrombosis (DVT) [5], with PE seen in 16.7–47% of patients admitted to intensive care unit (ICU) [6–9] despite the use of thromboprophylaxis.

Elevated D-dimer values were reported in up to 43% of patients with COVID-19 [10], with higher values seen in patients with more severe disease [11,12]. Therefore, in the context of COVID-19 infection, identifying who to investigate for co-morbid pulmonary embolism (PE) is highly challenging.

D-dimer is a continuous variable, reflecting increasing risk for PE [13], and is used to further risk stratify patients with low pre-test probability - with imaging not required in those with negative D-dimer [14,15]. Patients with PE and significantly raised D-dimers have been shown to be more often hypotensive, tachycardic, and/or hypoxemic [16]. The radiographic burden of pulmonary thrombotic disease may also be greater with high D-dimer values [17,18].

We therefore examined the clinical and radiographic characteristics of patients with COVID-19, who underwent pulmonary imaging for

* Corresponding author at: Dept of Haematological Medicine, 4th Floor Hambleden Wing, King's College Hospital, London SE5 9RS, UK.
E-mail address: lara.roberts@nhs.net (L.N. Roberts).

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possible thrombotic disease. We report the incidence of PE and looked at the utility of D-dimer and Wells score in this patient cohort.

2. Materials and methods

2.1. Study population

This was a retrospective analysis of adult inpatients with suspected COVID-19, having imaging to co-diagnose PE, at King's College Hospital, London, UK, with high regional numbers of COVID-19 cases [19]. Data collection was from 3rd March 2020 and concluded on 7th May 2020. At our institution, patients with suspected PE undergo a two-level PE Wells score, with mandatory recording of all components of the Wells score in the electronic request for PE imaging. Imaging is not undertaken for those considered 'PE unlikely' by the Wells rule (score < 4) in conjunction with a D-dimer result below 500 ng/mL. Hospitalised patients were categorised as ICU patients or ward patients (if they were not transferred to ICU during hospitalisation). Weight based thromboprophylaxis was standard of care for all patients admitted with COVID-19 (in the absence of contraindication). Patients with weight < 50 kg receive enoxaparin 20 mg once daily; weight 50-100 kg, enoxaparin 40 mg od; 100-150 kg, enoxaparin 80 mg once daily and > 150 kg, enoxaparin 120 mg once daily. This was also the case in patients admitted to ICU with eGFR > 30 mL/min, with unfractionated heparin 5000 units twice daily given to those < 100 kg, increasing to three times daily in higher body weight. From 24th April, intermediate dosing was utilised in ICU only (see Supplementary Table 1).

2.2. Materials

D-dimer was measured by a latex photometric immunoassay, with STA-Liatest. Values over 500 ng/mL are considered positive; the intraassay CV at this value is 10%. The upper limit of reporting of D-dimer assay is 8000 ng/mL, we obtained raw values for this study, where available. Fibrinogen was measured by the Clauss method, with STA-Fibrinogen. Prothrombin time (PT was measured by coagulation-based assay with STA NeoPTimal. All reagents were obtained from Diagnostica Stago (Asnières, France), with assays performed on the automated analyzer STA-R Evolution as per manufacturer's instruction (Diagnostica Stago). Detection of COVID-19 was from viral RNA isolated from nasopharyngeal swabs using reverse transcriptase polymerase chain reaction (rtPCR). Computed Tomography Pulmonary Angiogram (CTPA) was performed using a GE Discovery CT750HD (Chicago, Il, USA). The interval between D-dimer and CTPA was less than 48 h.

2.3. Data collection

Using the Electronic Patient Records (EPR; Allscripts Sunrise™, Chicago, Il), we collected data for vital signs (including the National Early Warning Score 2; NEWS2 [20]), components of Wells score from the clinical notes (not the completed imaging request form), basic demographic data, laboratory values and imaging results (CTPA and venous ultrasonography, if performed). PE is most or equally likely was considered present in patients with a sudden unexplained clinical deterioration, e.g. without new changes on chest X-ray. If there was no documentation for a component of the Wells score, it was considered absent. In cases with no documentation in the EPR, a Wells score was not calculated. CT scans were requested by the treating clinician for suspected PE. The free text of EPR was reviewed for clinician entry stating whether COVID-19 was suspected. COVID-19 swab results were obtained from EPR. The date and time of CTPA request was extracted from the EPR. All laboratory and clinical variables were taken as the last values recorded before CTPA request.

2.4. Data analysis

The Wells score was calculated *post hoc* by the authors [21,22], using only data available in the clinical record at the time of CTPA request. PE was considered most, or equally likely where there was an unexplained deterioration in clinical status. Normality was determined by Kolmogorov-Smirnov test. Parametric and non-parametric distributed quantitative variables were compared using the Student's *t*-test and the Mann–Whitney *U* test, respectively. Categorical variables including gender, or presence of a venous thromboembolism (VTE) risk factor were compared using the chi-squared test (two-tailed). Contingency tables were constructed to evaluate the accuracy of using the D-dimer level to diagnose PE, with CTPA as the gold standard. Receiver operating characteristics (ROC) curve analysis was performed and area under the curve (AUC) calculated.

The results are given as the mean ± standard error of mean (SEM), median (interquartile range), or number (percentage), wherever appropriate. A P value of < 0.05 was considered statistically significant. Data analysis was made using SPSS Statistics for Windows, version 26 (IBM Corp, Armonk, New York, USA).

2.5. Ethical considerations

This was a service evaluation based upon the Health Research Authority (HRA) decision tool [23] and ethics approval was not required as agreed by the King's College Hospital Research and Innovation Department.

3. Results

Over the study time-period, there were 1477 patients admitted with COVID-19, including 222 admissions to ICU. At the end of data collection, 8.2% patients remained in hospital and 16% had died.

In total, 339 CTPA scans were performed (Fig. 1). Nineteen patients had more than one CTPA during their admission. After further screening of the cases to remove duplicated hospital number or scans for reasons other than suspected PE, 310 CT scans remained. Of these, 214 were scans in patients for whom COVID-19 had been confirmed (n = 145) or was clinically suspected (n = 69) at the time of CTPA

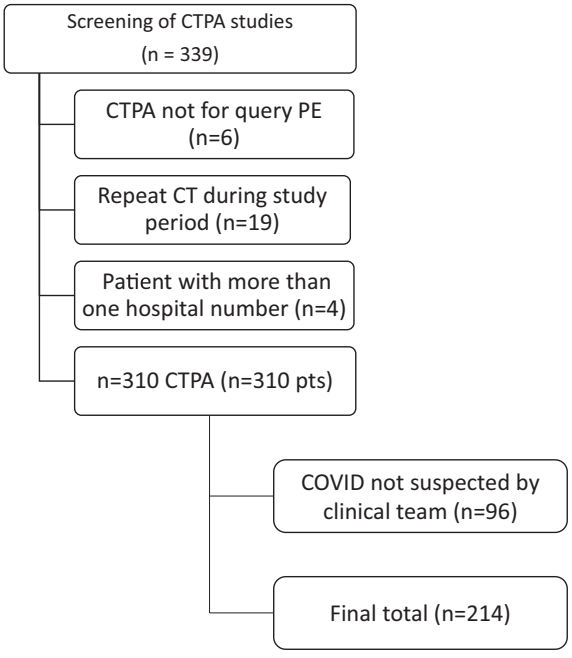

Fig. 1. Study flow-chart.

Table 1
Clinical and demographic features of the study population.

	PE present (n = 80)	PE absent (n = 134)	*P* value
Demographic features			
Males: females	52: 28	77: 57	0.276
Age (yrs)	63.5 ± 1.5	59.6 ± 1.4	0.069
Body weight (kg)	83.1 ± 2.3	81.4 ± 2.4	0.621
Intensive Care Unit (ICU) care	36 (45%)	42 (31%)	0.047
Components of Wells score			
Signs or symptoms of DVT	9 (11%)	2 (1%)	0.0017
PE most or equally likely	17 (21%)	30 (22%)	0.846
Heart rate > 100/min	28 (35%)	56 (42%)	0.325
Immobilisation	45 (56%)	67 (50%)	0.376
History of VTE	7 (9%)	14 (10%)	0.686
Haemoptysis	3 (4%)	9 (7%)	0.361
Malignancy	3 (4%)	13 (10%)	0.109
Wells score[a,b]	3 (1.5–4.5)	2.5 (1.5–4.5)	0.678
Wells score 'Likely'	25 (31)	28 (21)	0.109
Wells score 'Unlikely'	55 (69)	103 (79)	
Laboratory parameters			
D-dimer (ng/mL)[a,c]	8000 (4665–8000)	2060 (1210–4410)	< 0.001
Prothrombin time (PT) > 3 s prolonged[d]	3 (4.8%)	8 (8.2%)	0.530
Serum Creatinine (μmol/L)	83 (68–121)	77 (60–126)	0.405
Platelet count ($x10^9$/L)	302 (218–403)	266 (199–396)	0.270
White cell count ($x10^9$/L)[a]	9.50 (7.43–12.40)	8.60 (6.54–11.32)	0.109
C-reactive protein (CRP) (ng/L)[a]	124.2 (56.9–212.2)	85.7 (21.5–158.0)	0.003

[a] Median (IQR).
[b] no data, n = 3.
[c] n = 161.
[d] n = 168 (excluding those on oral anticoagulants, n = 10 and missing data, n = 34).

request.

3.1. Cohort description

Of the 214 scans, n = 80 (37%) confirmed PE. Therefore, from 1477 patients admitted with COVID-19, 5.4% were diagnosed with PE. The demographic and clinical features of those with and without PE are in Table 1. At the time of manuscript preparation, of n = 214, n = 36 patients were still receiving hospital treatment and 31 patients had died in hospital. Thirty-two patients had CTPA during a hospital readmission (readmitted within 90 days of discharge; median time to readmission 18.5 days [IQR 7–46 days]). Of these 32 CTPA, nine were positive for PE. Thirty-four patients (16%) were receiving invasive positive pressure ventilation (IPPV), in the intensive care unit (ICU) at the time that CTPA was requested (sixteen of whom showed presence of PE). However, a further n = 44 of the cohort subsequently received ICU care (20 with PE), making a total of 78 ICU-treated patients (Table 1). Thus, the proportion of ICU patients with PE was 16.2%. There were no differences in the distribution of age, gender or body weight between groups. The median NEWS2 score was 5 (IQR 3–9) in those with PE compared to NEWS2 of 4 (IQR 2–7) in those without (P = 0.133).

The incidence of PE in patients with ward-based care was 3.5% (of 1255 admissions to the ward level care). Eighty-two scans (38%) were performed within 24-h of admission (of which n = 31 showed PE); 26 scans (14%, n = 4 showed PE) were performed at 24–72 h. The range of imaging was 0–120 days: one patient having been admitted for over 2-months prior to the first case of COVID-19 recorded. Median duration from admission to imaging was 2 days. Of all admissions, 2.1% were diagnosed with PE within 24 h of admission. Of the patients scanned after 24-h of admission, 124 were receiving anticoagulation (predominantly weight based thromboprophylaxis, n = 95) from admission. Nine commenced therapeutic anticoagulation whilst awaiting imaging, 9 patients were on an unfractionated heparin infusion to maintain haemofilter patency and 11 continued therapeutic anticoagulation for pre-existing comorbidities (e.g. atrial fibrillation). Four patients did not receive any anticoagulant prophylaxis due to a contraindication (active bleeding or severe thrombocytopenia). Data were unavailable for four patients for whom a paper prescription record was in use.

3.2. Wells score

The Wells score was no different between those with and without PE (Table 1). The numbers and proportions with Wells score of ≥4 ('PE likely') was 33/134 (25%) without PE *vs* 20/80 (25%) with PE (P = 0.951). The most frequent Wells score items present were immobilisation (n = 112), heart rate > 100/min (n = 84), and 'alternative diagnosis less likely' (n = 47). Four patients had recent surgery and were suspected to have COVID co-infection. None had a recent long-haul flight. No patients had a history of thrombophilia. Lower limb venous ultrasonography was performed in 19 patients; DVT was confirmed in 11 patients (n = 7 with confirmed PE). The frequency of all components of the Wells score are in Table 1.

3.3. Measures of coagulation

In total, 161 (75.2%) patients had D-dimer results recorded. Of these n = 158 (98.1%) were positive and n = 3 patients negative (with values of 205, 270 and 490 ng/mL). The range of blood D-dimer levels were between 270 and 19,450 ng/mL. D-dimer values were significantly higher in those with confirmed PE (Table 1), with higher values seen in those with PE in both the low and high pre-test probability groups (Fig. 2). The performance of the D-dimer assay to determine PE is shown as a receiver operating characteristic (ROC) curve (Fig. 3). The area under the curve (AUC) was 0.772 (95% confidence interval (CI) 0.697–0.847). The Youden Index was 0.54 at a D-dimer value of 4800 ng/mL; this cut-point had a sensitivity of 0.75 and specificity of 0.78. Without knowledge of the background prevalence of PE in COVID-19, the PPV and NPV should be considered indicative but our data suggest that the D-dimer values at this threshold (4800 ng/mL) had a positive predictive value (PPV) of 72.2% (95% CI of 63.3 to 79.7%), and negative predictive value (NPV) of 80.9% (95% CI 73.4 to 86.7%). Combining this D-dimer threshold with low (Wells) pre-test probability did not improve the NPV (82.4%; 95% CI 73.9 to 88.5%). Fibrinogen was measured in n = 13 and was elevated (> 6 g/dL) in n = 9.

3.4. Positive cases

Of those with a confirmed PE (n = 80), the CTPA showed 'massive' (saddle embolus) in n = 3 and bilateral PE in 34 cases. Of unilateral cases, the thrombus was segmental (n = 28) and subsegmental (n = 13). One patient had unilateral PE extending from the pulmonary artery and one patient had unilateral lobar thrombus. Right ventricular strain was evident on CT in n = 9. One of the cases of PE was treated with thrombolysis. Of the positive cases, all but one (end of life care) received therapeutic anticoagulation. This was with enoxaparin in n = 36, rivaroxaban n = 15, apixaban n = 8, edoxaban n = 7, unfractionated heparin infusion n = 13.

4. Discussion

This study of hospitalised patients showed that in patients with suspected or confirmed COVID-19, and clinical suspicion for PE, more than one-third of CTPA studies were positive for PE. This compares to the yield of CTPA of inpatients, prior to the COVID-19 epidemic, of 12 to 17% [24–26], and 18% in an ICU environment [25]. Most literature

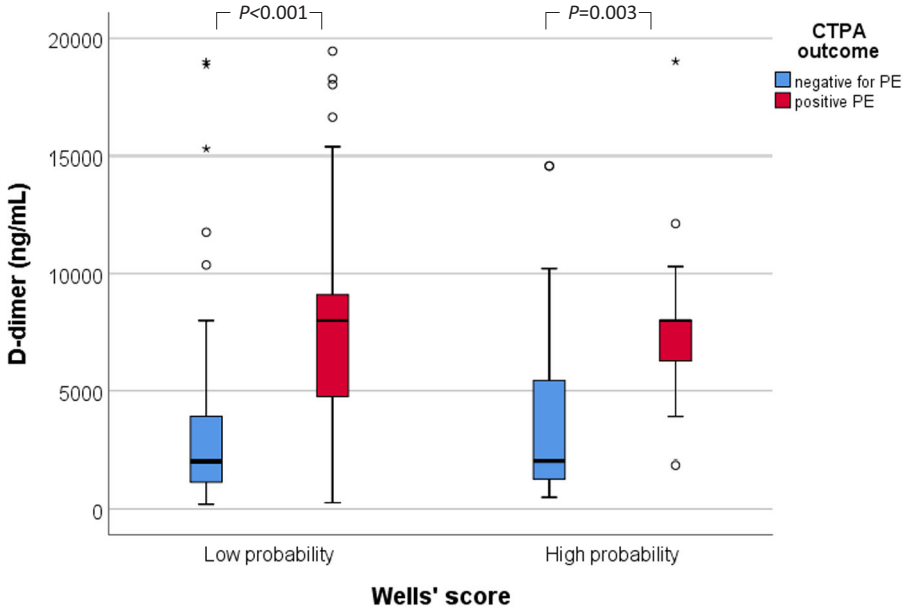

Fig. 2. Distribution of D-dimer values in patients at low- and high-probability for Pulmonary Embolism. Low probability considered as Wells score of < 4.

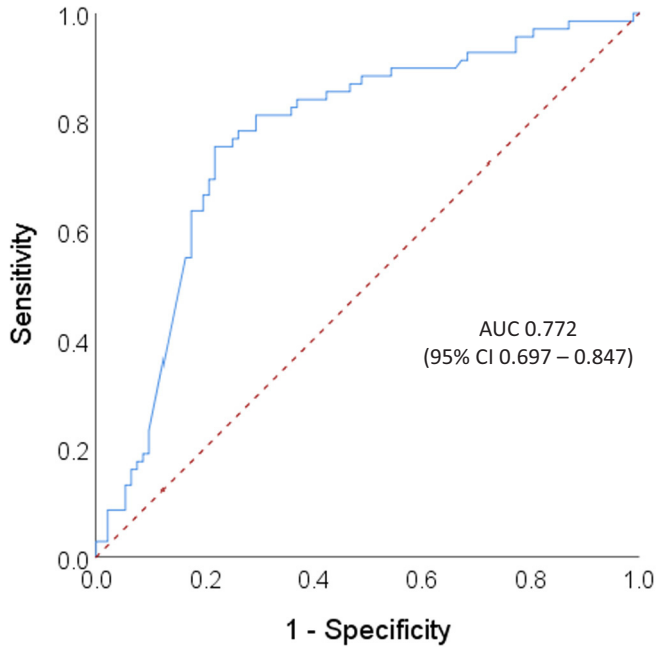

Fig. 3. Receiver Operating Characteristic (ROC) curve for D-dimer for the diagnosis of Pulmonary Embolism.

on the use of CTPA centres on over-utilisation, particularly if yields fall below 10% [24–26]. The high-yield from CTPA in our series raises the possibility of relative under-diagnosis of PE in patients with COVID-19. Neither the Wells score, nor NEWS2 (a marker of general illness severity), differentiated between positive and negative studies. Of Wells score components, only the presence of symptoms or signs of DVT were significantly greater in PE, although only evident in just over a tenth of cases. Our data suggest that the D-dimer has a positive predictive value for thrombotic events of approximately 70% when values approach 5000 ng/mL. No D-dimer threshold had an adequate NPV to eliminate the need for diagnostic imaging. We found the overall proportion of patients with PE to be 5.4%, increasing to 16.2% in ICU patients. PE was diagnosed in 3.5% patients receiving ward-based care, similar to that reported in Italy and the Netherlands (6.6% and 3.3% respectively) [8,9]. The higher rate of PE in ICU patients is consistent with previous reports (16.7–47%), albeit at the lower end. This may partly be explained by imaging requested on clinical suspicion, compared to some centres incorporating screening imaging [6–9].

The use of EPR means that data capture of requests and results was very high. However, as with any retrospective dataset evaluation, selection bias is likely. CTPA request would more likely be made after high D-dimer results, making assessment of the performance of D-dimer challenging. We used the D-dimer value closest to the request for CTPA. Evolution of D-dimer values may occur during illness, and evaluation of serial measurement would be of interest in COVID-19 patients. Retrospective calculation of the Wells score based on author evaluation of the notes up to the time of imaging request relies on accurate recording of comorbidities and clinical features within the notes. We adopted this approach as previous audit has demonstrated the Wells recorded is not consistently recorded with accuracy in the imaging request [21].

In our series, very few individuals had fibrinogen measured (outside of ICU) and we are therefore unable to determine the presence of DIC for most of the cohort. Tang et al. [12] highlighted that the majority of COVID-19 patients who died during hospital stay, fulfilled the criteria for disseminated intravascular coagulation (71.6 *vs.* 0.6% in survivors) although overall numbers were low (15 of 21 non-survivors, total cohort n = 182). Of note, other markers of DIC were not prevalent in our cohort (seven patients with platelets < 100 × 10^9/l and 11 with PT prolonged > 3 s). Apart from D-dimer, coagulation markers were not significantly associated with PE.

There is debate as to whether the PE seen in COVID-19 represents true 'thrombus embolisation' or whether this may be localised 'immunothrombosis' [27,28]. 51% of cases in our cohort were limited to unilateral segmental/subsegmental vasculature. A minority of patients (9%) had DVT imaging performed, with DVT confirmed in 11/19 scans including seven patients with confirmed PE. Of note, the majority of events were proximal DVT (n = 8). Of patients with both DVT and PE, only 1 had PE limited to the segmental vasculature with all others demonstrating more proximal thrombosis. We did not collect data on whether segmental/subsegmental PE were co-localised to areas with lung parenchymal disease.

All patients diagnosed with PE during hospitalisation had received at least weight-based thromboprophylaxis beforehand. Whilst this may raise concern regarding the efficacy of thromboprophylaxis, it should

be noted that the overall only 5.4% of patients hospitalised with COVID-19 were diagnosed with PE. Furthermore, in our series, over half of all imaging occurred within the first 72 h of admission (43% of positives) suggesting PE may develop earlier in the disease, *prior* to hospitalisation. We therefore caution against intensified thromboprophylaxis strategies outside ICU without further evaluation in randomised controlled trials.

5. Conclusions

In summary, we have found that the diagnostic yield of CTPA for PE in patients with confirmed or suspected COVID-19 is high. A high index of clinical suspicion for PE in patients with COVID-19 is warranted. An optimal D-dimer threshold to exclude PE without imaging was not identified; further studies to optimise risk stratification of patients for PE imaging are welcomed. Randomised controlled trials to evaluate intensified thromboprophylaxis strategies are urgently needed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2020.07.025.

Addendum

M.B. Whyte data acquisition, data analysis, manuscript writing; E. Gonzalez data acquisition, P. Kelly and R. Arya study conception and data analysis. L.N. Roberts data acquisition and analysis, study conception. All authors were involved in manuscript revision and approved the final version.

Declaration of competing interest

The authors have no disclosures.

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