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Pulmonary thromboembolism in hospitalised patients with COVID-19: a retrospective national study of patients managed in critical care and ward environments in Scotland

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ABSTRACT

Objectives To assess for increase in pulmonary thromboembolism (PTE) in hospitalised patients with COVID-19, in both critical care and ward environments.

Setting We reviewed all CT pulmonary angiograms (CTPA) performed in Scotland between 23 March 2020 and 31 May 2020 and identified those with COVID-19 using either classical radiological appearances or positive COVID-19 PCR swab.

Participants All hospitalised patients in Scotland with COVID-19 between 23 March 2020 and 31 May 2020 who underwent a CTPA.

Primary outcome measure To assess if the rate of PTE was increased in those with COVID-19 compared with previously published figures of hospitalised patients.

Secondary outcome measures To assess the effect of right heart strain or requirement for critical care on mortality.

Results 3401 CTPAs were reviewed. 192 were positive for PTE in patients with evidence of COVID-19 either real-time PCR swab positive for SARS-CoV-2 (n=104) or having radiological changes consistent with COVID-19 (n=88). The total number of hospital admissions in Scotland between 23rd March 2020 and 31st May 2020 with COVID-19 was 5195. The incidence of PTE during this time was 3.7% in all patients admitted to all hospitals in Scotland with COVID-19 during this period. 475 hospitalised patients were managed in critical care (both level 2 and level 3 care), in whom the incidence of PTE was 6% (n=29). 4720 patients did not require admission to critical care, in whom the incidence of PTE was 3.5% (n=163). There was increased risk of death with right heart strain (25/52 vs 128/140 (p<0.01)) and in critical care (15/29 vs 146/163 (p<0.01)).

Conclusions We have demonstrated an increased risk of PTE in critical care and ward-based environments. Further studies are required to establish effective prophylactic anticoagulation in this group.

Strengths and limitations of this study

- ► The strengths of this study are that it captures robust, national data in patients cared for in all hospital settings, including patients managed in critical care as well as those managed at ward level.
- ► The study is retrospective, and, therefore, there are some data missing with regards to biomarkers and demographic data.
- ► We have included both PCR positive and those with classical radiological appearances.
- ► We have not included those with deep vein thrombosis in our analysis in those hospitalised with COVID-19.

BACKGROUND

Since December 2019, there has been a rapid, global spread of infection from the novel coronavirus, SARS-CoV-2. The first case in Scotland was reported in early March 2020. COVID-19, the clinical syndrome of SARS-CoV-2 infection, has been heterogeneous in its presentation.[1] Although over 80% of patients present with a mild illness, it is recognised that up to 20% of patients present with a severe or critical illness,[2 3] characterised by fever, shock, acute lung injury and coagulopathy. These coagulation abnormalities mimic other haematological disorders, such as disseminated intravascular coagulation and thrombotic microangiopathy, and are associated with an increased risk of death.[4 5] COVID-19 also predisposes to thrombotic complications[6–8] and the incidence of these has been reported to be as high as 30% in patients with COVID-19 admitted to the intensive care unit. The incidence of COVID-19-associated

pulmonary thromboembolism (PTE) may be substantially higher than has been reported in association with other viral or bacterial pneumonic illnesses.[6 9] We are in a unique position whereby almost all acute healthcare in Scotland is provided by the state, with a network of databases that allow the identification and collection of data from patients across the country linked by a unique patient-specific identification code (Community Health Index (CHI) number).

Making the diagnosis of COVID-19 and its sequalae can be challenging. Although the use of highly specific real-time PCR testing has been virtually ubiquitous, the use of other diagnostic investigations have been employed to provide additional diagnostic information. Plain chest X-ray or thoracic CT[10] have been used widely to clarify the diagnosis, where there is dubiety and allows the detection and assessment of sequalae SARS-CoV-2 infection. Indeed, classical radiological appearances of COVID-19 pneumonitis are now recognised. However, diagnostic processes are more complex in patients with suspected COVID-19 and, in particular, consideration has to be made to limit the potential spread of infection to staff and other patients. Furthermore, patients often have multi-organ failure and haemodynamic instability, prohibiting safe transfer for investigation.

There remain few data available on the incidence of thrombosis and comorbidity potentially associated with the development of thrombosis in hospitalised patients with COVID-19, particularly in patients managed outside the critical care setting. Most reports have been limited to a few hospital centres. We made a retrospective assessment of the incidence of PTE in all patients with COVID-19 admitted to hospitals in Scotland in both critical care and ward environments. In addition, we aimed to assess if right heart strain increased the risk of death or requiring critical care support.

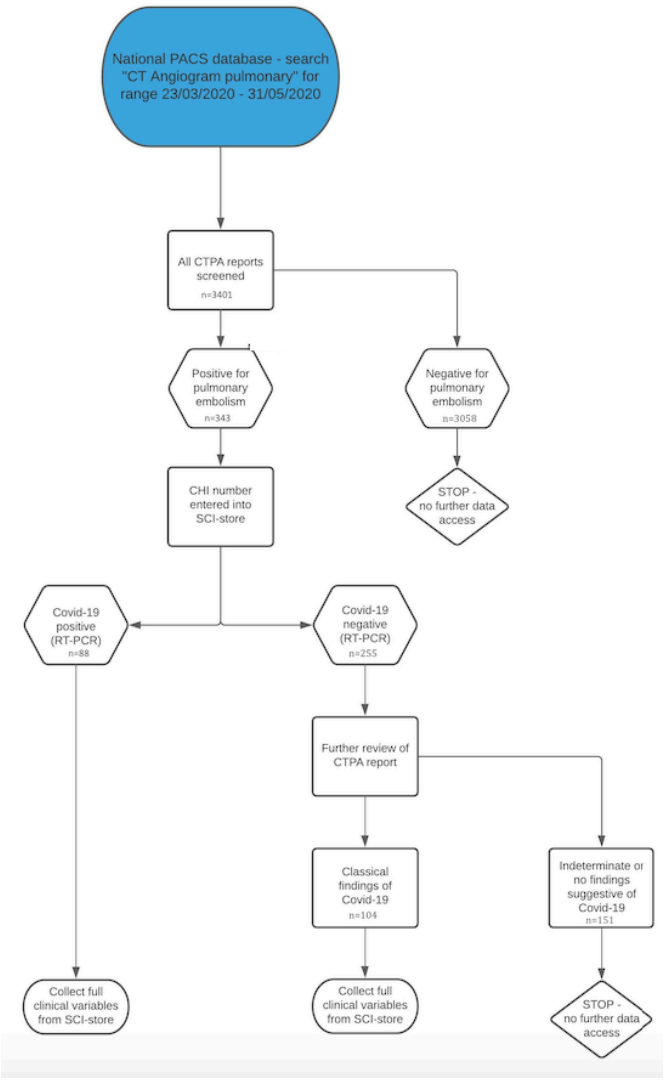

Figure 1 Consort diagram of study data collection. CHI, Community Health Index; CTPA, CT pulmonary angiogram; PACS, Picture Archiving and Communications System; RT-PCR, real-time PCR; SCI, Scottish Care Information.

METHODS

Between 23 March 2020 and 31 May 2020, all patients in Scotland who had a CT pulmonary angiogram (CTPA) were identified using the Scottish National Picture Archiving and Communications System (PACS). This system captures all radiology investigations performed in patients in Scotland. Of these patients, those with evidence of PTE were identified and cross-referred to the Scottish Care Information (SCI store) online platform to identify those with coexisting real-time PCR (RT-PCR) test results for SARS-CoV-2.

Patients were included in the study if they had positive RT-PCR test results for SARS-CoV-2 up to 30 days (mean: 9.5 days) before their CTPA or within 14 days afterwards. If no RT-PCR test had been performed, or if it was negative, patients were deemed to have COVID-19 clinical syndrome if they had classical lung parenchymal changes, as described by the British Society of Thoracic Radiology.[11] Patients who did not have a RT-PCR positive swab and with 'probable' or 'indeterminate' radiographic features of COVID-19 were excluded due to diagnostic uncertainty. See figure 1.

Demographic data, patient location (level 1 (ward-level) care or critical care) and comorbidities were obtained from the SCI store database, as were biomarkers and risk factors for PTE. In accordance with European Society of Cardiology definitions,[12] right heart strain was considered to be present in patients who had serum troponin greater than the local reference limit or had radiological evidence of right ventricular (RV) dilatation (right ventricular:left ventricular ratio (RV:LV) diameter >1). Primary care medical records were used to identify the presence of comorbidities in the patient group. The SCI store includes documents from primary care with the medical history coded for reference.

Publicly available data on the incidence of COVID-19 in hospitalised patients between 23 March 2020 and 31 May 2020, published on the Scottish Government website[13] on

9 June 2020 were used as the denominator for the calculation of the incidence of PTE in hospitalised patients with COVID-19. This denominator was used in order to calculate how many patients from the overall hospitalised COVID-19 population developed PTE.

A control group of 202 patients diagnosed with pulmonary embolus between 11 July 2011 and 4 December 2018 was used to examine for differences between biomarkers in those with and without COVID-19 disease. These patients were a heterogeneous group of hospitalised patients with provoked and unprovoked pulmonary embolus, matched for age who were followed up in the outpatient clinic, when this facility was in its infancy, and, therefore, includes only a small proportion of those diagnosed with PTE during that time. Patients in this group with troponin, above the local reference range, or have RV:LV ratio >1 were identified as having right heart strain. In addition, we obtained data from previously published studies on the incidence of pulmonary embolus in hospitalised patients[14] and those with pneumonia.[15] This was then used as a comparison to the current COVID-19 population.

Statistical analysis

Incidence of PTE percentage was calculated using the total number of hospitalised patients with COVID-19 during the described time period divided by the number of patients with evidence of COVID-19 and a positive CTPA for PTE. Binary logistic regression was used to establish if the presence of comorbidity, increasing age or sex leads to an increased risk of a composite endpoint of critical care admission or death. Survival was calculated using Cox proportional hazard regression in those patients with right heart strain, those in intensive care and in males. We then assessed the comorbidities in the population managed in level 1 care areas and grouping together all those managed in critical care, levels 2 and 3. χ^2 test was used to look for increased frequency of PTE in the critical care groups compared with the ward-based patients. Mann-Whitney U test was used to look for any significant differences between non-parametric data in the biomarker groups. We used multivariable analysis to adjust for age and sex when comparing the presence of right heart strain in the control versus COVID-19 group. Statistical analysis was completed using IBM SPSS Statistics V.27 and Graphpad Prism V.8. P<0.05 was taken to be statistically significant.

Due to the retrospective nature of the study, there are missing data points for both demographic data and biomarkers. As such, all analysis is performed only for those with available complete data.

Patient and public involvement

Given the emergent nature of the COVID-19 pandemic, the patients and public were not involved in the study design. The study was retrospective in nature and, as such, patients were not involved in their recruitment and it will not be possible to disseminate the findings to the patients involved.

RESULTS

A total of 3401 CTPAs were screened using the Scottish National PACS. Of those, 192 were identified as positive for PTE with either coexisting RT-PCR evidence of COVID-19 (n=104) or classical radiological changes consistent with COVID-19 (n=88). The total number of hospital admissions in Scotland between 23 March 2020 and 31 May 2020 with COVID-19 was 5195.

Incidence of PTE in patients admitted to hospital with COVID-19

This incidence of PTE in all patients admitted to Scottish hospitals with COVID-19 was 3.7%. This is higher than the 1% incidence of PTE seen in hospitalised patients (ward based and critical care) in Scotland prior to the COVID-19 epidemic[16] (p<0.01). Of 5195 patients admitted to hospital with COVID-19, 475 were admitted to critical care, in whom the incidence of radiologically confirmed PTE was 6% (n=29). This is also higher than the 2.6%–3.5% seen in other intensive care units prior to the COVID-19 pandemic.[17 18] Four thousand, seven hundred and twenty patients were managed in level 1 care, in whom the incidence of radiologically proven PTE was 3.5% (n=163). One thousand, eight hundred and seven (34%) hospitalised patients with COVID-19 died, 43 (22%) of whom had radiologically confirmed PTE.

Baseline demographics of COVID-19 patients with PTE and historical control patients are presented in table 1. We did not have access to reliable medical records around the length of stay, requirement for critical care or body mass index (BMI) for those in the control group and, as such, these factors have not been included.

The effects of comorbidities on the risk of death or likelihood of requiring critical care

We were able to access all CTPA images and scan reports. We had access to 81% of the patient's primary care records in order to identify the presence of comorbidity. Although we had access to all biomarkers, not all patients had them performed. Numbers of patients included are presented in the data tables. Neither BMI >30 kg/m^2, systemic hypertension, malignancy or cardiovascular disease were associated with the outcome of critical care or death (table 2). We have performed univariate analysis for comorbidities in online supplemental table 1. Differences in the comorbidities between the ward-based patients and critical care are presented in online supplemental table 2.

Survival with PTE

A 30-day survival was significantly worse in those with right heart strain and those requiring critical care, but there was no significant difference between males and females (table 3). This was also seen in survival to 90

Table 1 Demographics of population

Baseline demographics	COVID-19 (n=192)	Control (n=202) Mean (SD)	P value
Age (years)	60.2 (14.1)	59 (16)	0.57*
Sex, male (%)	64.5	46	<0.01†
Right heart strain (%)	27	31	0.61†
Median length of hospital stay until Pulmonary Thromboembolism diagnosis in days (IQR)	1 (9)		
Median length of time between positive RT-PCR and Pulmonary Thromboembolism (days)	8 (14)		
BMI (kg/m^2)	30.2 (8.3)		
Critical Care patients (%)	15		
RT-PCR swab positive (%)	54		

Values listed are mean (SD) unless otherwise stated.
*Wilcoxon signed rank test.
†X^2 test.
BMI, body mass index; RT-PCR, real-time PCR.

days as shown in figure 2. We adjusted for age and sex when comparing the outcomes of right heart strain and there were no differences between the COVID-19 group (p=0.6) and the control group (p=0.1).

Patients in critical care were more likely to have right heart strain: 55% of the patients with PTE in critical care had right heart strain (1 diagnosed using troponin only), compared with 21% of the ward-based patients with PTE (5 of these patients had right heart strain diagnosed via troponin only).

Differences in biomarkers between COVID-19 and historical control patients

In the COVID-19 population, the D-dimer, troponin, neutrophil count and C reactive protein (CRP) were significantly higher compared with the historical control group while the lymphocyte count was reduced. There was a trend towards higher lactate in patients with COVID-19-associated PTE versus historical controls did not reach statistical significance (p=0.07) (figure 3).

Table 2 The effects of comorbidities on the likelihood of admission to critical care or mortality

Comorbidity	Number of patients with comorbidities (n=155)	OR‡	95% CI
Body mass index >30 kg/m^2	47	0.99	0.94 to 1.04
Systemic hypertension	15	0.97	0.41 to 2.33
Malignancy*	31	1.05	0.22 to 5.2
Cardiovascular disease†	19	0.80	0.20 to 3.13
Diabetes mellitus	31	0.45	0.14 to 1.44

*Either current or previous solid organ malignancy coded on primary care records.
†History of ischaemic heart disease or left ventricular systolic dysfunction coded on primary care records.
‡Binary logistic regression.

DISCUSSION

Using a large, robust dataset, we have identified a substantial incidence of PTE in patients hospitalised with COVID-19. This is the first study to capture data, at a national level, contrasting with other work in this area that has been limited to single centre series mainly focusing on patients managed in the intensive care unit.[6 19] Using the Scottish CHI number, assigned to all member of the Scottish population at birth, and linking this with a comprehensive national radiological archiving system, we have captured robust data pertaining to the incidence of COVID-19-associated PTE. These are unique strengths to our study. Of all patients admitted to ward-level or critical care units in Scotland with COVID-19, 3.7% had radiologically confirmed PTE. This incidence of PTE is significantly higher than the reported pre-COVID-19 epidemic incidence of PTE of 1% in hospitalised patients[16] (p<0.01) and, importantly, is higher still than the 1%–2% incidence of PTE previously reported in patients hospitalised with non-COVID-19 pneumonia.[14 15] These data support the recently reported evidence that patients with COVID-19 are at a higher risk of PTE. While this is particularly apparent in the critical care setting, in whom the incidence of PTE was 6%, it is important to note that the incidence of PTE in patients managed in non-critical care areas was also high (3.5%). This is in agreement with another smaller study.[20] This study examined the incidence of all arterial and venous thrombosis over a shorter time period using case report review and only RT-PCR positive results. Our study goes much further and is specific to PTE. The data presented in this current study are on a national level and includes patients who have radiological appearances of COVID-19 infection in addition to those who had a positive RT-PCR test. This gives a more accurate representation of patients infected as the rate of false negative RT-PCR test has been reported as high as 29%.[21]

Despite a higher incidence of COVID-19 in Scottish females (404 per 100 000 compared with 259 per 100

Table 3 30-day survival from admission with pulmonary thromboembolism

Patient status	% survival to 30 days N (%)	Patient status	% survival to 30 days N (%)	OR*	95% CI
Right heart strain (n=52)	25 (48)	No right heart strain (n=140)	128 (91)	4.12	2.24 to 7.55
Critical care (n=29)	15 (55)	Level 1 care (n=163)	146 (89)	1.75	0.86 to 3.57
Male (n=124)	91 (73)	Female (n=68)	46 (67)	1.78	0.88 to 3.62

*Cox proportional hazard regression.

000),[22] we observed a significantly higher rate of thrombosis in men. This may reflect the apparently more severe form of COVID-19 pneumonia observed in men, who are also more likely to admitted to the intensive care unit (17 per 100 000 in males vs 6.3 per 10 000 in females).[22] However, it remains possible that, irrespective of COVID-19 pneumonia severity, men are at a higher risk of developing PTE than women.[23] It is perhaps unsurprising that there was a greater proportion of PTE-associated right heart strain in patients in intensive care unit compared with those in level 1 care. While this may be related to the fact that patients with right heart strain are more unwell with multiorgan dysfunction seen in severe pneumonia, this could also reflect specific effects of severe COVID-19, resulting in a higher clot burden. The significantly higher CRP observed in the COVID-19 population compared with the control group would also support an inflammatory contribution to thrombosis. However, it should be noted that our comparison group consisted of heterogeneous pulmonary thromboembolism aetiologies and not all were in the context of infection.

In agreement with other studies,[24] D-dimer levels at presentation with PTE were noted to be significantly higher in the COVID-19 group compared with the control group. In addition, the lymphocyte count was significantly lower in the COVID-19 group. These findings are now well recognised to be associated with severe COVID-19 infection with the D-dimer levels reflecting the increased systemic and pulmonary macrovascular and microvascular thrombosis.[25] Neutrophil count was also observed to be significantly higher in those with COVID-19, which may have contributed to the immunothrombotic process.[26]

The mean BMI of these patients with COVID-19-associated PTE fell in the obese category and over half of the patients in the intensive care unit had a BMI of greater than 25 kg/m^2. This is also in keeping with other

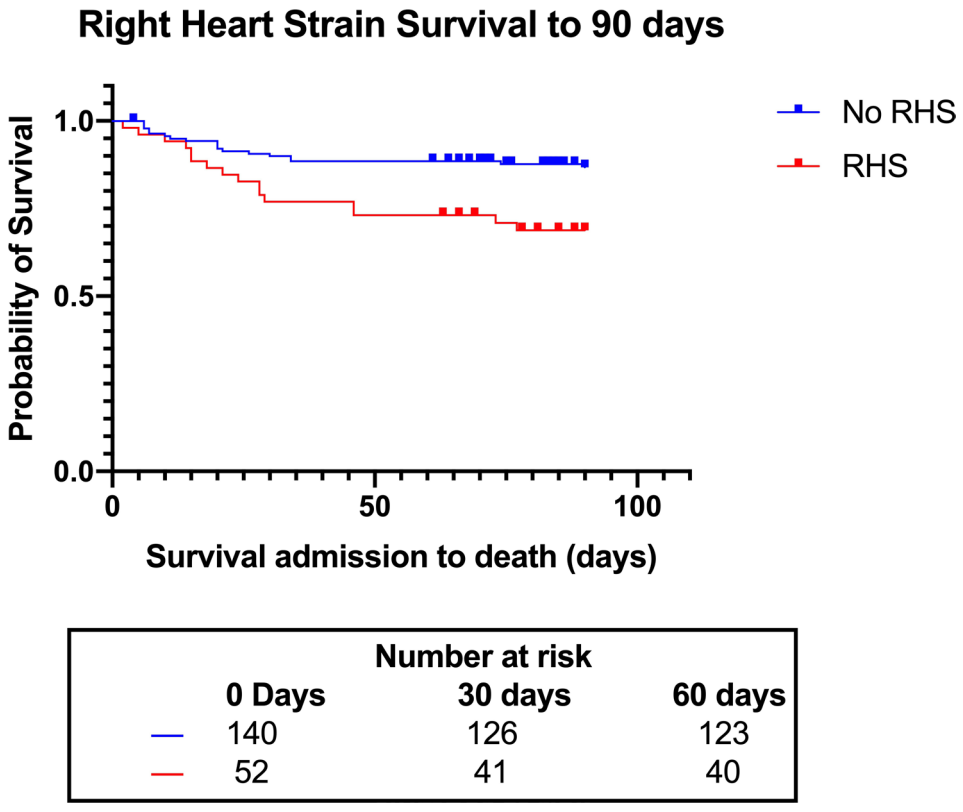

Figure 2 Kaplan-Meier curve of survival in patients with RHS and those without. RHS, right heart strain.

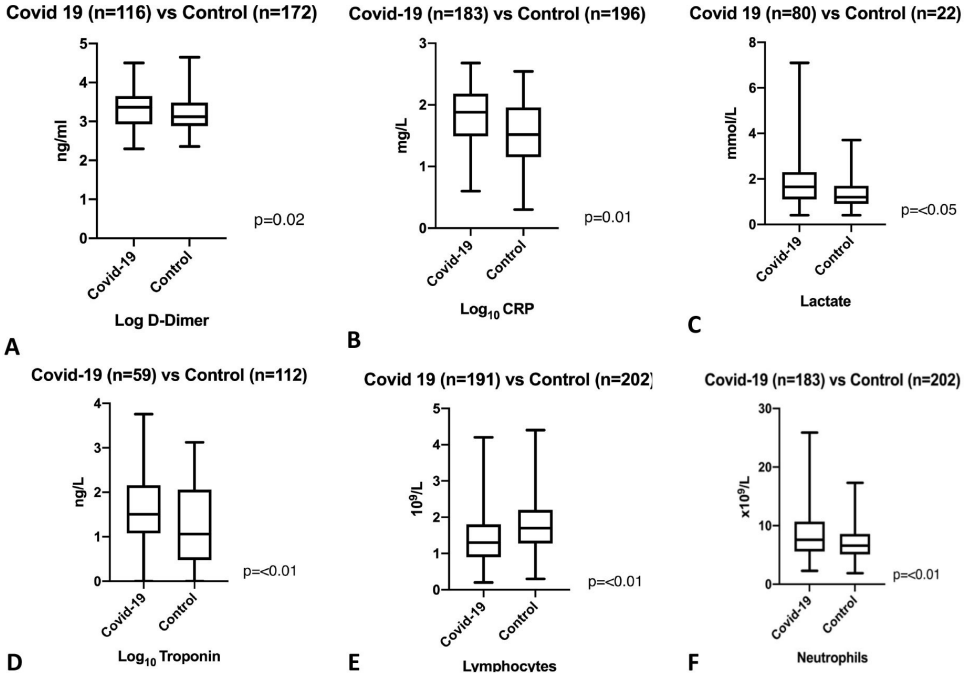

Figure 3 Biomarkers in the COVID-19 vs control group. (A) D-dimer. (B) CRP. (C) Lactate. (D) Troponin. (E) Lymphocytes. (F) Neutrophils. Mann-Whitney U test. CRP, C reactive protein.

studies demonstrating that higher BMI is associated with increasing COVID-19 disease severity but obesity is also an independent risk factor for PTE.[27] However, in the population studied here, we did not demonstrate an association between an elevated BMI and an increased risk for admission to intensive care unit or death. While this may reflect a lack of power to demonstrate this, it may also be due to the population studied.

The median time from RT-PCR sample to presentation with PTE was 8 days and the median time from admission to PTE diagnosis was 1 day. This suggests that clinically relevant PTE in COVID-19 may be a delayed phenomenon. Our cohort included patients who had initial SARS-CoV-2 testing performed in the community prior to admission, in addition to those who had testing performed in hospital and serves to highlight that patients with COVID-19 who are managed in the community are also at risk of PTE. This important observation should reinforce prompt consideration of optimal prophylactic anticoagulation of patients in the very acute phases of admission with COVID-19 and to have a low threshold for early radiological assessment for PTE and treatment.

Our data demonstrating a higher incidence of PTE in the critical care setting support the existing guidance, both nationally and internationally, that these patients should be given higher doses of prophylactic low molecular weight heparin.[28 29] Locally, we have advocated intermediate dose thromboprophylaxis for those in critical care and standard dose prophylaxis for those in ward-based care. In addition, patients with COVID-19-associated PTE managed in critical care were more likely to have right heart strain. While it is possible that this reflects a higher clot burden in these patients, we believe that it is probably more likely to represent the combination of thrombus load, marked parenchymal lung changes and consequent hypoxia seen in severe COVID-19. This multifactorial pathophysiology is also likely to explain the significantly poorer survival observed in patients with right heart strain in this population. Our study supports existing studies that there is an increased risk of thrombosis in patients with COVID-19 in the intensive care unit.[6 30] As such, it is imperative that steps are taken to reduce the risk of thrombosis in these patients using appropriate dose thromboprophylaxis. While there is guidance available, much of this is expert consensus and randomised trials are on-going to establish the most effective way of preventing thrombosis formation in these patients in critical care.

We assessed a range of relevant comorbidities in patients with COVID-19-associated PTE and differentiated between patients managed in the ward and those in critical care. Although the prevalence of comorbidities observed was probably lower than would be observed in non-COVID-19 critical care populations,[31–33] we did not find any significant difference in the prevalence of comorbidity between patients managed in critical care versus those managed elsewhere. Given the severity of COVID-19 pneumonia and the growing understanding of associated potential for very prolonged intensive care stays,[34] it is likely that admission to intensive care unit was not considered to be appropriate for those with multiple comorbidities. The numbers of patients in this group are too limited to make a meaningful assessment of association between comorbidity and the risk of PTE in this population.

While our study has key strengths in its capture of robust, national data in patients cared for in all hospital settings, including patients managed in critical care as well as those managed at ward level, there are some limitations. This is a retrospective study, and, therefore, there are some missing data points for our biomarker and comorbidity data, but it should be acknowledged that this was a retrospective study and investigations were clinically directed. There was, therefore, a degree of heterogeneity in the investigations results available to us. We included patients diagnosed on the basis of RT-PCR positive testing for SARS-CoV-2 or, in the absence of RT-PCR test positivity, on the basis of internationally agreed diagnostic radiological criteria for COVID-19.[11] However, despite international agreement for the use of these diagnostic radiological criteria, there remains some diagnostic uncertainty in patients who do not have positive RT-PCR, although we did only select patients with a high likelihood based on radiology. With these diagnostic criteria, we can surmise that the proportion of those with thrombosis is at least 3.7% but could be higher. Although the gold standard investigation for the diagnosis of PTE is CTPA, it is possible that a number of patients treated in intensive care unit were too unstable for transfer for radiological investigation and were treated empirically for PTE. In addition, patients treated at ward level who were deemed too frail, palliative or had a contraindication to CTPA would not have received a formal investigation for PTE. The true incidence of COVID-19-associated PTE may, therefore, be even higher than reported here in the ward-level patients. While we have attempted to be rigorous in our assessment of patients with right heart strain using the European Society of Cardiology guidelines for the diagnostic criteria of right heart strain, it is possible that troponin levels would be influenced by other effects of COVID-19 and not purely from the pulmonary embolus. These patients have a systemic illness, and we accept that there is no perfect way of assessing for right heart strain retrospectively. We did not include patients assessed for peripheral deep vein thrombosis diagnosed by lower limb venous ultrasound. Furthermore, we had limited access to demographic data and details surrounding the management of the control group. As such, we are only able to describe the findings in those with COVID-19 and are unable to compare this with the control group. We have used primary care records in order to gather details of comorbidities on individuals. However, these may be incomplete and, as such, comorbidities may have been present but not included in our analysis. In addition, we have limited access to the comorbidities of the control group, and the same limitation applies to this group.

To the best of our knowledge, this study is the first to report comprehensive national data informing the incidence and characteristics of patients with COVID-19-associated PTE. We have demonstrated that hospitalised patients with COVID-19 have a higher incidence of PTE than would be expected in the general hospitalised population, or those hospitalised with pneumonia. This risk extends to both critical care and to those managed in level 1 care. In the context of COVID-19, PTE may present later in the illness following initial diagnosis and, in this study, can occur up to 14 days after the positive RT-PCR test. Therefore, PTE should be actively considered in deteriorating patients with COVID-19. While our study supports existing data suggesting that COVID-19 presents an important risk for PTE in hospitalised patients, we extend these concerns to patients managed in non-critical care areas. As such, all patients with COVID-19 should receive appropriate thromboprophylaxis in order to reduce the risk of PTE and the threshold for early radiological assessment for PTE should be low.

Contributors MM and AM contributed equally to the manuscript, making substantial contributions to the conception, acquisition, analysis and interpretation of data and drafting of the manuscript. PM substantially contributed to the conception, acquisition of data, drafting of the manuscript and approval of the final manuscript. CB, MJB, NNL and MKJ contributed substantially to the analysis and interpretation of data, drafting and revising of the manuscript and final approval of the published manuscript. ACC contributed substantially to the conception and design of the study, drafting and revising of the study and final approval of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Public Benefit and Privacy Panel for Health and Social Care approved the study on 15 June 2020 and granted access to the national data (reference number: 2021-0049).

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Data availability statement Data are available upon reasonable request.

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