Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Low Detection Rate of Pulmonary Embolism in Patients Presenting to the Emergency Department With Suspected Coronavirus Disease 2019 (COVID-19): A Single-Centre UK Study

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A B S T R A C T

Purpose: Critically ill patients with coronavirus disease 2019 (COVID-19) are at increased risk of thrombosis. There are limited data on PE rates in COVID-19 patients at presentation to the emergency department (ED). In this study, we evaluated the detection rates of PE in patients presenting to the ED with suspected and proven COVID-19.

Methods: A single-centre retrospective study was undertaken of 285 consecutive patients undergoing CT pulmonary angiogram (CTPA) in the Emergency Department at Nottingham University Hospitals NHS Trust in the United Kingdom between 25 March and 30 April 2020. At our institution, CTPA is performed in all patients undergoing CT for triage. The study group consisted of patients considered COVID-19 positive based on polymerase chain reaction (PCR) results and CTPA findings. The detection rate of PE in COVID-19 patients was compared to patients undergoing CTPA for suspected PE only and for suspected COVID-19 with no COVID CT findings and negative PCR (control group 1); and CTPAs prior to the coronavirus pandemic (control group 2).

Results: One of 48 patients in the study group had a PE (2%) compared to 25/215 (12%) in control group 1 and 10/50 (20%) in control group 2. Prevalence of PE in the study group was lower than in control group 1 ($P = 0.058$) and compared to control group 2 ($P = 0.005$). Eleven patients undergoing CTPA had negative PCR but positive CT for COVID-19.

Conclusion: Detection rate of pulmonary embolus is low in patients with COVID-19 undergoing CTPA on a triage pathway.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Patients with severe COVID-19 have been shown to have coagulation dysfunction,[1-4] which may lead to venous and arterial thromboembolism.[4,5] This is thought to be due to several factors including increased inflammatory response and cytokine release, hypoxaemia and haemostatic abnormalities related to sepsis such as disseminated intravascular coagulation.[3,5,6] Raised D-dimer may indicate excessive coagulation activation and elevation is common in patients with COVID-19.[1-4,7-9] Numerous studies show a clear association between COVID-19 and pulmonary embolism (PE),[5,10] with a high incidence of PE[4,11,12] in patients with severe disease admitted to intensive care (ITU). The prevalence of PE in these patients has been reported in studies as 14%-23%.[4,5,11]

There is currently limited evidence on detection rates of PE at presentation to the emergency department (ED) in patients with COVID-19. These patients may have mild disease or may be earlier in the disease course. The lack of evidence may relate to variation in use of computed tomography (CT) in patients with COVID-19 at presentation to ED across the United Kingdom. The Nottingham University Hospitals (NUH) COVID-19 Adult Triage pathway for patients presenting to ED (Fig 3) mirrors aspects of the British Society of Thoracic Imaging decision tool for suspected COVID-19.[13] Unwell patients with suspected COVID-19 based on symptoms (dry cough, fatigue, myalgia, fever, dyspnoea and anosmia) undergo a chest x-ray (CXR) and viral nasopharyngeal throat swab for polymerase chain reaction (PCR). If CXR appearances are normal or equivocal, CT is considered to assess for typical COVID-19 features if the PCR result is unavailable. A large meta-analysis[14] of findings in COVID-19 reports that ground-glass density is the most commonly encountered CT finding. Consolidation, interlobular septal thickening and air bronchograms are other commonly reported findings. Abnormality is most commonly bilateral and peripheral in distribution, without particular lobar or

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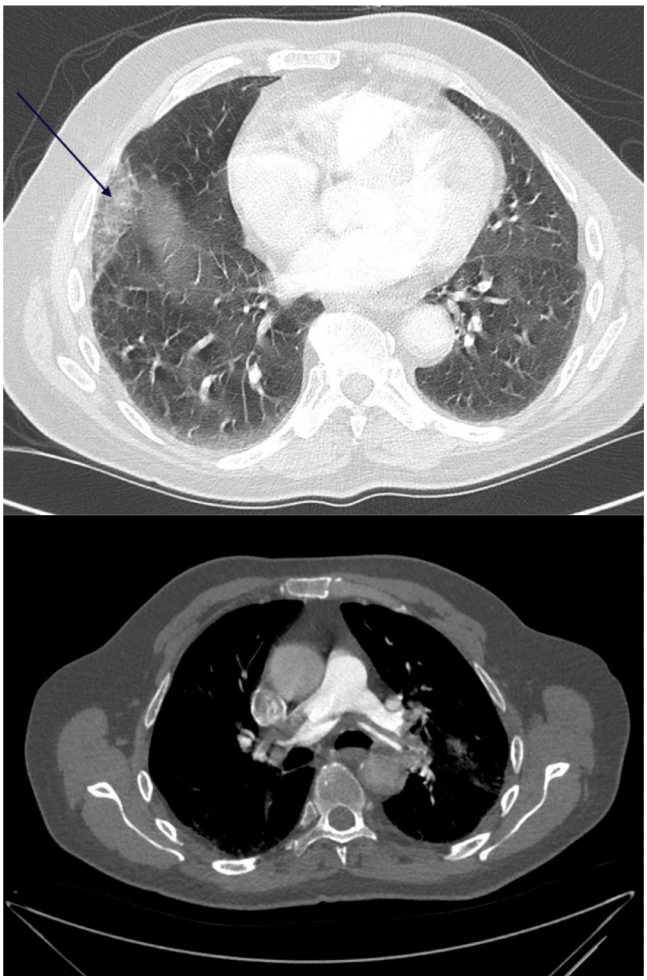

FIG 1. Images from a CTPA demonstrate a right-sided subpleural area of ground-glass density (top image, arrowed) on lung window settings. The CTPA demonstrated extensive saddle embolus (bottom image). The patient had a positive PCR for COVID-19.

zonal predominance. Pleural effusion and lymphadenopathy are rarely encountered. Figures 1 and 2 demonstrate some illustrative CT findings in this cohort of patients. This meta-analysis suggests that CT is sensitive for the detection of COVID-19 but that there is overlap with the imaging findings seen in other infections, so the diagnosis should be confirmed with RT-PCR.

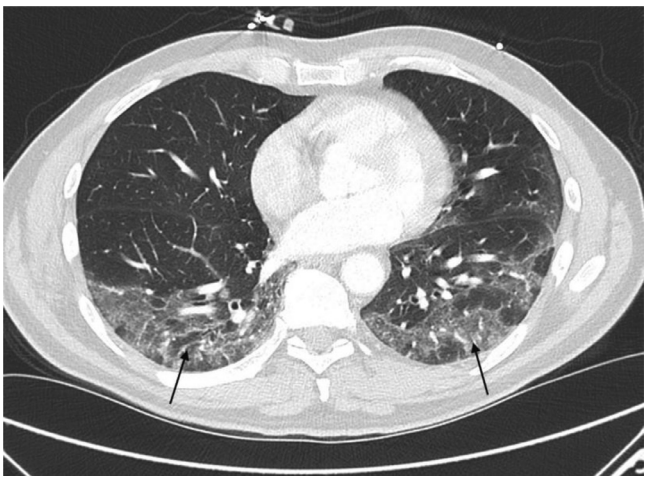

FIG 2. Patient with symptoms of COVID-19 who had a positive PCR. The study demonstrates subpleural posterior ground-glass infiltrates (arrowed) which are consistent with COVID-19.

At NUH, patients were diagnosed with COVID-19 if the PCR was positive or if the CT had typical features of COVID-19 (Fig 3). CTPA was performed on all patients on this pathway unless contraindicated. The NUH pathway considered several factors including staffing, scanner access (and cleaning) and a 2-site service, with need to isolate and treat COVID-19 patients in a different hospital from where the ED is based. CTPA was specified because of emerging evidence regarding increased risk of thromboembolism and expected raised D-dimer in these patients, to prevent the need for reimaging further down the line when transfer to the scanner might be difficult. This however needed to be balanced against the potential disadvantages of administering intravenous contrast to patients with COVID-19, such as the potential risk of contrast-induced nephropathy and the potential for parenchymal changes on administration of contrast material. This provides us with a unique cohort of patients with COVID-19 presenting to ED that underwent CTPA, in that CTPA is normally only performed in patients with suspected PE. In our study, all patients undergoing CT for triage were also scanned in the CTPA phase.

We conducted a retrospective observational study assessing the prevalence of PE in patients presenting to ED at Queens Medical Centre, Nottingham diagnosed with COVID-19, compared to 2 separate groups without COVID-19.

Methods

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics Approval

The study was approved by the local ethics committee.

Consecutive data were collected from the start of implementation of the NUH ED COVID-19 pathway on 25 March to 30 April 2020. This pathway is illustrated in Figure 3.

The study cohort included all patients attending ED who underwent CTPA on the NUH COVID-19 pathway in whom a diagnosis of COVID-19 was made by PCR on a nasopharyngeal swab or with high suspicion of COVID-19 on CT (irrespective of clinical presentation). The first control group (control group 1) included all patients who underwent CTPA in ED during the same time period to investigate PE only (without suspected COVID-19), based on clinical details provided in the radiology request, and patients undergoing CTPA on the COVID-19 pathway with a negative PCR and negative or equivocal CT for COVID-19.

Exclusion criteria included: nasopharyngeal swabs not sent, if a patient underwent unenhanced CT (due to renal failure or contrast allergy) and if the CTPA was non-diagnostic for PE. Diagnosis of PE and radiological suspicion of COVID-19 was determined on retrospective review of the radiology report. Reporting of suspected COVID-19 on CT followed the British Society of Thoracic Imaging guidance.[15] At our institution, CTPA is reported by Consultant radiologists specialising in body imaging.

Variable sensitivities of PCR have been reported in the literature (34%-80%)[16]; therefore, negative PCR does not exclude COVID-19. It is possible that the first control group included patients with COVID-19 with false-negative PCR and this may have affected the observed prevalence of PE. We therefore also studied a separate smaller cohort of 50 consecutive patients presenting to ED at our institution undergoing CTPA for suspected PE before the coronavirus pandemic in September 2019 (control group 2).

Figure 2 demonstrates the study flowchart.

Analysis

Statistical analysis was performed using Stata version 15.1. The prevalence of PE in the study group was compared with the control groups.

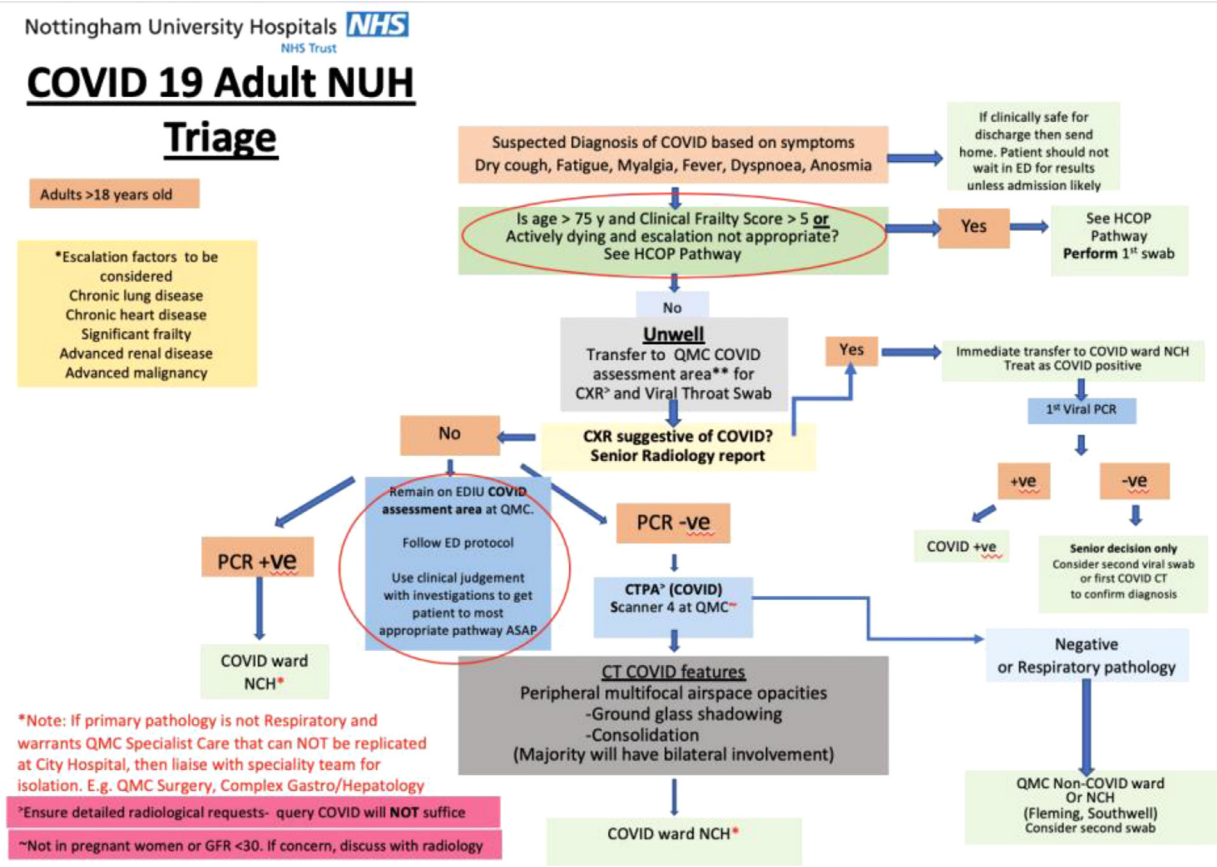

FIG 3. Flowchart for management of patients with COVID-19 at NUH.

Statistical significance was assessed using Fisher's exact test if the expected value in any of the groups was <5 and chi-squared was used if the expected value was ≥ 5. A P value of <0.05 was considered to be statistically significant. Control group 1 was subdivided into patients undergoing CTPA on the COVID-19 pathway and those who had CTPA performed for suspected PE only. The prevalence of PE in the study group was compared with these control subgroups individually. The prevalence of PE in the study group was also compared with control group 2.

Results

Table outlines the clinical characteristics of the study and control groups. Two hundred eighty-five CTPAs (in 285 patients) were performed in Nottingham ED during the study period. Twenty-one patients on the triage pathway did not have PCR and 1 patient had a non-diagnostic CTPA for PE, therefore were excluded. One hundred seventy-four of the remaining CTPAs were performed via the NUH COVID-19 pathway. Of these, 34 patients had positive PCR and 140 were PCR negative. 11/174 (6%) patients undergoing CTPA on the COVID pathway had negative PCR but positive CT for COVID-19. Three of these patients had a second negative PCR the same admission, none of the other patients had a repeat swab.

Eighty-nine patients underwent CTPA outside of the pathway, for suspected PE; however, 3 patients had positive CT for COVID-19 (all had negative PCR). Of interest, 1 patient had an antibody test 3 months later suggesting that the PCR was false negative in this case.

The study group therefore consisted of 48 patients. Control group 1 consisted of 215 patients. Control group 2 consisted of 50 patients

TABLE
Clinical characteristics of the study and control groups of patients

Clinical characteristics	Total (study group and control group 1)	Study group	Control group 1	Control group 2
Gender				
Male	114 (43)	16 (33)	98 (46)	19 (38)
Female	149 (57)	32 (67)	117 (54)	31 (62)
Total	263 (100)	48 (100)	215 (100)	50 (100)
Age	61 (19)	65 (19)	60 (19)	64 (19)
Male	62 (17)	63 (21)	62 (17)	62 (14)
Female	59 (20)	67 (18)	57 (20)	65 (22)
Patients that had radiologically confirmed pulmonary embolus on CTPA	27/263 (10)	1/48 (2)	25/215 (12) COVID pathway 12/129 (9) Non-COVID pathway 13/86 (15)	10/50 (20)

The study group consisted of patients who were PCR positive or had CT changes consistent with COVID-19. Control group 1 consisted of patients who were PCR negative and did not have a positive CT. Control group 2 was a consecutive cohort undergoing CTPA at our institution before the pandemic started. Data are number/n (%) for gender, mean (SD) for age, or n/N (%), where N is the total number of patients in the cohort.

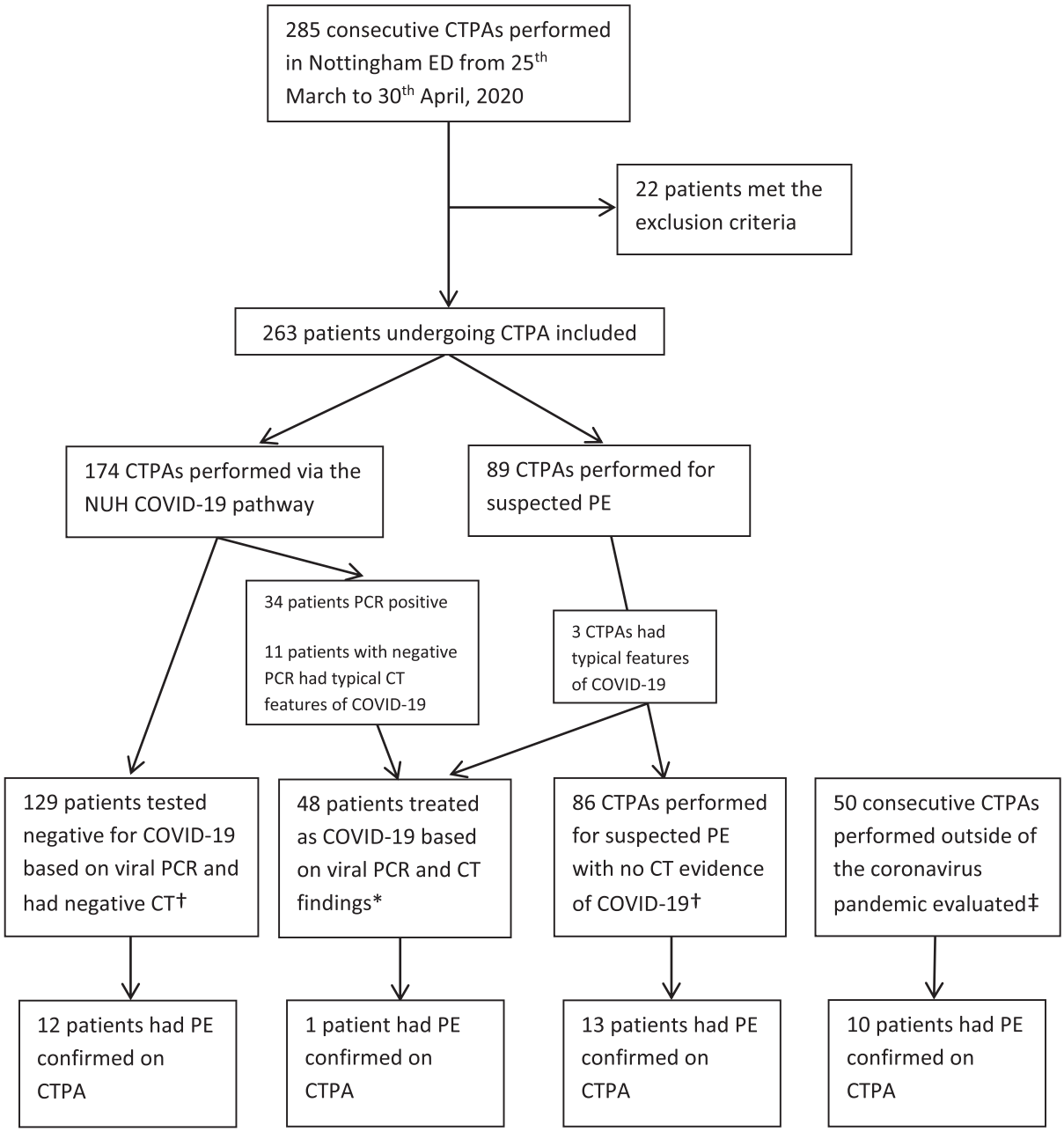

FIG 4. Study flowchart (* represents the study group, † combined represent control group 1 and ‡ represents control group 2). Please note that it was sometimes necessary to proceed to CTPA for triage when the PCR swab result was awaited.

undergoing a CTPA in September 2019. Figure 4 is a study flowchart summarising the groupings. The mean age of all patients undergoing CTPA in the study period was 61 years (standard deviation 19). The COVID-19 positive patients were generally older than those in control group 1 and 2 (mean 65 years vs 60 years and 64 years, respectively). A greater proportion of patients in all groups were female.

In the study group, 1 patient (2%) with PCR-positive COVID-19 had radiologically confirmed PE – a saddle embolus. The patient was an 81-year-old male patient with no risk factors for PE. Parenchymal lung features on CT were equivocal for COVID-19 in this patient as they could have represented pulmonary infarcts. In control group 1, 25 patients (12%) had confirmed PE. Twelve of these patients had CTPA performed via the COVID-19 pathway but tested negative for COVID-19 on PCR or had negative or equivocal CT for COVID-19. Of the patients in control group 1 who had CTPA performed only for suspected PE, 15% had PE. The prevalence of PE in control group 2 was 20%.

There was no statistically significant difference in the prevalence of PE in the study group compared to control group 1 as a whole ($P = 0.058$). This was also the case on subgroup analysis comparing the study group to patients in control group 1 undergoing CTPA on the COVID-19 pathway without COVID-19 (PCR and CT negative), $P = 0.191$. PE prevalence in the study group was significantly lower when compared to patients in control group 1 undergoing CTPA for suspected PE only who had no CT features of COVID-19, $P = 0.018$. PE prevalence was also significantly lower in the study group compared to control group 2 ($P = 0.005$).

We also compared these figures to a consecutive group of inpatients over the same time period who were PCR-positive and underwent CTPA. Eight of 43 (19%) of these scans demonstrated PE.

Discussion

The findings of this study demonstrate our experience of adding a CTPA examination when patients with suspected COVID-19 undergo CT

at our institution for triage. The overall trend was of a lower detection rate of PE in COVID-19 patients based on PCR and CT scanned in ED than in the control groups. The prevalence of PE in patients with COVID-19 was significantly lower than in patients undergoing CTPA in Nottingham ED for suspected PE only, both during and before the coronavirus pandemic. Of note, if only the patients with PCR positivity for COVID-19 are considered to have the disease, and those with CT changes suggesting COVID-19 are not included in the study group, the prevalence of PE remains low at 1/34 (3%). The observed PE prevalence before the pandemic was slightly higher in the patients undergoing CTPA for suspected PE during the pandemic. The reasons for this are unclear but may in part relate to differences in imaging strategy during the different time periods. During the pandemic, CT was used at our institution to triage patients to appropriate parts of the hospital and the CTPA component was employed on every patient undergoing CT for triage to exclude PE (Fig 3). A large US multicentre study[17] cites the rate of PE normally encountered in the ED at 4%.

The findings of our study contrast with much of the published literature, as numerous published studies[1-4,12,18,19] report high prevalence of PE in patients with COVID-19 undergoing CTPA. The high prevalence of PE has prompted some groups to suggest consideration of including CT pulmonary angiography to chest CT examinations in patients with suspected COVID-19, as we have done at our institution.[20] Coagulation dysfunction is however thought to be associated with late or severe disease, with most data from an ITU setting. It may be that the incidence of PE is lower early in the disease, as our cohort has been imaged early in their presentation in ED rather than ITU, as per the management flowchart (Fig 3). We found the PE detection rate in a PCR-positive comparative cohort locally to be 19%; some of these patients were imaged later on in their care and this figure is more comparable to the published literature.

Of interest, Cattaneo et al report a low incidence of deep vein thrombosis in their cohort and postulate that some of the findings on CTPA may relate to thrombosis in ITU patients rather than pulmonary embolus, given that PE often coexists with deep vein thrombosis.[19] The low rate of PE observed in our study early in patient management correlates with the findings of their study and it has been suggested that PE later on in the disease may relate to pulmonary arterial thrombosis. Pathologic studies also suggest that patients with COVID-19 develop in situ vascular changes and thrombosis.[21] The study of Thomas et al also demonstrates increasing incidence of PE in their cohort with duration of stay on ITU,[22] which would suggest incidence is lower earlier in the disease.

D-dimer was not routinely performed in the study group (only 6 out of 34 patients). Anticoagulation status is unknown, but it was not the policy of our ED at the time of admission to routinely commence thromboprophylaxis for patients with suspected or confirmed COVID-19.

The study has several limitations. Firstly, it is a retrospective, relatively small sample single-centre study evaluating local practice. It does not assess all COVID-19 patients (Fig 3) as patients who did not require admission or patients who had a CXR suggestive of COVID-19 did not undergo CTPA. Given the nature of this pathway, we have probably excluded patients with mild disease who were discharged without imaging and patients with severe disease who had classic CXR changes for COVID-19 who did not require CT for triage. Given that all patients were scanned in ED prior to admission, the CT is assumed to have taken place early in their management. The limited sensitivity of PCR in detecting COVID-19 may have led to underestimation of the incidence of COVID-19 in the patient cohort. Although the initial sensitivity of PCR at NUH based on the first swab was quoted as 96% early on in the pandemic (unpublished data), 11 patients had COVID-19 diagnosed on CTPA with negative PCR. This was important because it potentially helped reduce nosocomial transmission by isolating patients in the correct ward environment and aided management and escalation decisions. This cohort is however thought to provide a unique insight into the detection rate of PE associated with adding a CTPA on every patient undergoing triage.

The detection rate of PE in patients presenting to ED diagnosed with COVID-19 is reported in this study at 3%. This is significantly lower than both the PE prevalence in patients without suspected or diagnosed COVID-19 and the baseline PE prevalence outside of the coronavirus pandemic. It is also lower than reported rates of PE in COVID-19 patients in the literature, although many of these reports are in the ITU setting. This may reflect lower prevalence of thromboembolism early in the disease although this is a selected cohort. The low detection rate at this stage would suggest that clinicians should not necessarily be reassured by an initial negative study, which may not obviate the need for a repeat study further down the line, if this is clinically indicated. This may warrant further larger scale studies for clarification. The role of CTPA in evaluating patients with suspected COVID-19 at presentation remains unclear. We hope our experience will be useful for development of strategies for imaging in patients with COVID-19.

Author Contributions

R. Birk, I. Au-Yong, C. Kennedy, D. Shaw and Y. Higashi contributed to the study design and concept. R. Birk, R. Patel, C. Kennedy and I. Au-Yong collected the clinical data. Statistical analysis and interpretation was done by R. Birk and A. Gupta. The final manuscript has been read and approved by all authors.

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