Clinical characteristics and computed tomographical features of pulmonary thromboembolic disease associated with COVID-19 infection: A tertiary hospital analysis

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ABSTRACT

Introduction: The co-existence of coronavirus disease 2019 (COVID-19) and pulmonary thromboembolic (PTE) disease poses a great clinical challenge. To date, few researches have addressed this important clinical issue among the South-East Asian populations. The objectives of this study were as follow: (1) to describe the clinical characteristics and computed tomographical (CT) features of patients with PTE disease associated with COVID-19 infection and (2) to compare these parameters with those COVID-19 patients without PTE disease.

Materials and Methods: This cross-sectional study with retrospective record review was conducted in Hospital Tengku Ampuan Rahimah, Selangor, Malaysia. We included all hospitalised patients with confirmed COVID-19 infection who had undergone CT pulmonary angiogram (CTPA) examinations for suspected PTE disease between April 2021 and May 2021. Clinical data and laboratory data were extracted by trained data collectors, whilst CT images retrieved were analysed by a senior radiologist. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.

Results: We studied 184 COVID-19 patients who were suspected to have PTE disease. CTPA examinations revealed a total of 150 patients (81.5%) suffered from concomitant PTE disease. Among the PTE cohort, the commonest comorbidities were diabetes mellitus (n=78, 52.0%), hypertension (n=66, 44.0%) and dyslipidaemia (n=25, 16.7%). They were generally more ill than the non-PTE cohort as they reported a significantly higher COVID-19 disease category during CTPA examination with *p*=0.042. Expectedly, their length of both intensive care unit stays (median number of days 8 vs. 3; *p*=0.021) and hospital stays (median number of days 14.5 vs. 12; *p*=0.006) were significantly longer. Intriguingly, almost all the subjects had received either therapeutic anticoagulation or thromboprophylactic therapy prior to CTPA examination (n=173, 94.0%). Besides, laboratory data analysis identified a significantly higher peak C-reactive protein (median 124.1 vs. 82.1; *p*=0.027) and ferritin levels (median 1469 vs. 1229; *p*=0.024) among them. Evaluation of CT features showed that COVID-19 pneumonia pattern (*p*<0.001) and pulmonary angiopathy (*p*<0.001) were significantly more profound among the PTE cohort. To note, the most proximal pulmonary thrombosis was located in the segmental (n=3, 2.0%) and subsegmental pulmonary arteries (n=147, 98.0%). Also, the thrombosis predominantly occurred in bilateral lungs with multilobar involvement (n=95, 63.3%).

Conclusion: Overall, PTE disease remains prevalent among COVID-19 patients despite timely administration of thromboprophylactic therapy. The presence of hyperinflammatory activities, unique thrombotic locations as well as concurrent pulmonary parenchyma and vasculature aberrations in our PTE cohort implicate immunothrombosis as the principal mechanism of this novel phenomenon. We strongly recommend future researchers to elucidate this important clinical disease among our post-COVID vaccination populations.

KEYWORDS:
COVID-19, pulmonary thromboembolic disease, clinical characteristics, computed tomographical features

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel virus has the potential to cause a multitude of deleterious effects on the host, ranging from acute respiratory distress syndrome, arrhythmia, acute myocardial injury, acute kidney injury and multi-organ failure.[1,2] Lately, the association of pulmonary thromboembolic (PTE) disease and COVID-19 infection has been increasingly recognised. The putative cause of this phenomenon is believed to be due to the combination of both prothrombotic state and widespread pulmonary microvasculature injury created by COVID-19-induced immune hyperactivation. Importantly, the co-existence of PTE disease with COVID-19 infection portends a poor prognosis.[3]

Computed tomography pulmonary angiogram (CTPA) remains to be the imaging modality of choice in the work-up

This article was accepted: 12 February 2023
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of patients with suspected PTE disease. It has the ability to demonstrate thrombus as well as to delineate the thrombotic lesion location.[4] In addition, it also provides additional information which enables the clinician to distinguish between COVID-19 pneumonia changes from non-COVID related changes. To note, we experienced an unprecedented demand in CTPA examination during the peak of COVID-19 pandemic from late April until September 2021, whereby virtually all of our CT suites were running in full tilt during that crisis.

To our best knowledge, PTE disease associated with COVID-19 infection has not been well studied in South-East Asia and most of the data in the literature were generated from the Western populations.[5-7] In an effort to fill this knowledge gap, we undertook this study which aimed to describe the clinical characteristics and computed tomographical (CT) features of patients with PTE disease associated with COVID-19 infection, and compare these to the parameters with those COVID-19 patients without PTE disease.

MATERIALS AND METHODS

Study Setting

This study was conducted in Hospital Tengku Ampuan Rahimah (HTAR) which is a tertiary hospital located in the royal Klang district, Selangor, Malaysia. During the study period, HTAR was designated as a hybrid hospital that served to provide both in-patient treatment for COVID-19 as well as non-COVID 19 patients. In retrospect, Klang district was one of the worst-hit districts at that time. The provision of COVID-19 care was led by infectious disease specialists in close collaboration with multiple disciplines, which included intensivist, acute internal medicine physician, emergency physician, general physician, haematologist, respiratory physician, radiologist and microbiologist.

Study Design and Data Collection

This is a retrospective study that involves review of clinical notes as well as CTPA imaging of all hospitalised COVID-19 patients with suspected acute PTE disease between 1st April 2021 and 31st May 2021. The COVID-19 diagnosis was confirmed by either COVID-19 real-time reverse transcriptase-polymerase chain reaction (rRT-PCR), GeneXpert or rapid antigen test (RTK) from nasopharyngeal swab or lower respiratory samples.

Additionally, only subjects who had undergone CTPA examination as well as aged ≥ 18-year-old would be included. In total, we excluded 13 subjects due to the following reasons: at-own-risk discharge (3 cases), severe CTPA image artefacts (1 case), onset of COVID-19 infection more than 30 days at presentation (2 cases), hospital-acquired COVID-19 infection (2 cases) and incomplete or clinical notes (5 cases). All data collected was entered into the pre-tested Google Form which served as the electronic case report form (eCRF) by the trained investigators.

Clinical and Laboratory Data

The clinical stages of COVID-19 were categorised as below: category 1 asymptomatic; category 2 symptomatic but no pneumonia; category 3 symptomatic with pneumonia; category 4a requiring nasal prong or face mask or venturi mask <60%; category 4b requiring high flow mask or venturi mask ≥60%; category 5a requiring non-invasive ventilation including high flow nasal cannula and category 5b mechanical ventilation with or without other organ failures.[8]

On another note, the day of COVID-19 illness was determined with reference to the clinical symptom onset date. In circumstances where the clinical history was unclear or the patient was asymptomatic during diagnosis, the first day of illness was calculated from the day the COVID-19 test first became positive.

Anticoagulant treatment received prior to or during CTPA examination was classified into three regimens, namely prophylactic anticoagulation, intermediate anticoagulation, and therapeutic anticoagulation. The definition of anticoagulation regimens was developed with reference to our institution protocol. Prophylactic anticoagulation is defined as (a) sc. enoxaparin 40mg–60mg daily (if eGFR ≥30 ml/min/1.73m^2); (b) sc. enoxaparin 20mg OD (if eGFR <30 ml/min/1.73m^2)and (c) sc. unfractionated heparin 5000 units q12 hourly or q8 hourly. Therapeutic anticoagulation is defined as (a) sc. enoxaparin 1mg/kg/BD (if eGFR ≥30 ml/min/1.73m^2); (b) sc. enoxaparin 1mg/kg/OD (if eGFR <30 ml/min/1.73m^2); (c) warfarin with INR ranged 2-3 and (d) direct oral anticoagulation therapy as per drug insert recommendation. Any dose in between prophylactic and therapeutic range would be considered as intermediate anticoagulation. In the situation where body weight was unavailable, the clinician would exercise his discretion to determine the anticoagulation regimen based on the clinical notes review.

Pertaining to the laboratory data, D-dimer level was reported in Fibrinogen Equivalent Units (FEU, µg/ml) and a value of less than 0.5 µg/ml was considered as negative. Also, any level above 20 µg/ml would be reported as >20 µg/ml.

The primary outcome measure was death during the hospital stay and 60-day mortality rate after being infected with COVID-19 infection. We did not attempt to determine whether the 60-day mortality was attributable to the PTE disease associated with COVID-19 in view of the retrospective nature of the study. Out-of-hospital death was verified with National Registration Department, Malaysia if such information was not available in our hospital.

Radiological Data

CT image acquisition

Computed tomography pulmonary artery (CTPA) examination was performed on 64-slice multi-detector CT scanners (Toshiba Aquillion CX). The whole chest was craniocaudally scanned from lung apices to the lowest hemidiaphragm for each patient in the supine position. All patients except for intubated cases were instructed to hold their breath to minimise motion artefacts, and CTPA images were acquired during a single breath-hold. Scan parameters were as follows: tube voltage of 120 kV, tube current of 100 to 300 mAs, collimation of 0.6 to 0.625 mm, table speed of 39.37 mm/s, and gantry rotation time of 0.5 s. The soft tissue reconstruction kernel was used. A volume of 50 to 60 mL

Table I: Socio-demographic and clinical characteristics of COVID-19 patients with suspected PTE

Characteristics	n (%)			*p* value
	Total (n=184)	PTE (n=150)	Non-PTE (n=34)	
Age in years, mean (SD)	56 (13.2)	57 (12.6)	49 (14.1)	**0.002**[a]
Male gender	112 (60.9)	91 (60.7)	21 (61.8)	0.906[b]
With at least one comorbidity	134 (72.8)	110 (73.3)	24 (70.6)	0.745[b]
Comorbidities				
Diabetes mellitus	95 (51.6)	78 (52.0)	17 (50.0)	0.764[b]
Hypertension	80 (43.5)	66 (44.0)	14 (41.1)	0.833[b]
Dyslipidaemia	28 (15.2)	25 (16.7)	3 (8.8)	0.250[b]
Ischemic heart disease	19 (10.3)	17 (11.3)	2 (5.9)	0.534[c]
Obesity	5 (2.7)	4 (2.7)	1 (2.9)	1.000[c]
End stage renal disease	5 (2.7)	4 (2.7)	1 (2.9)	1.000[c]
Chronic kidney disease excluding ESRF	3 (1.6)	3 (2.0)	0 (0.0)	1.000[c]
Malignancy	1 (0.5)	1 (0.7)	0 (0.0)	1.000[c]
Other comorbid*	34 (18.5)	29 (19.3)	5 (14.7)	0.530[b]
Symptomatic at presentation	183 (99.5)	149 (99.3)	34 (100.0)	1.000[c]
Symptoms at presentation				
Cough	143 (77.7)	115 (76.7)	28 (82.4)	0.472[b]
Fever	129 (70.1)	106 (70.7)	23 (67.6)	0.728[b]
Shortness of breath	124 (67.4)	100 (66.7)	24 (70.6)	0.660[b]
Diarrhoea	57 (31.0)	49 (32.7)	8 (23.5)	0.298[b]
Fatigue	37 (20.1)	31 (20.7)	6 (17.6)	0.692[b]
Sore Throat	23 (12.5)	18 (12.0)	5 (14.7)	0.774c
Vomiting	20 (10.9)	16 (10.7)	4 (11.8)	0.768[c]
Anosmia	8 (4.3)	6 (4.0)	2 (5.9)	0.642[c]
Ageusia	8 (4.3)	7 (4.7)	1 (2.9)	1.000[c]
Other symptom#	101 (54.9)	84 (56.0)	17 (50.0)	0.526[b]
Temperature at presentation (degree Celsius), median (IQR)	37.9 (37.0- 38.7)	38.0 (37.0-38.8)	37.5 (36.9-38.2)	0.123[d]
Day of Illness at Presentation, median (IQR)	5 (4.0-7.0)	5 (3.0-7.0)	5 (4.0-7.0)	0.365[d]
Day of Illness during CTPA, median (IQR)	10 (8.0-13.0)	10 (8.0-13.0)	10 (8.0-13.0)	0.772[d]
Category of Illness during CTPA				**0.042**[c]
2	3 (1.6)	1 (0.7)	2 (5.9)	
3	4 (2.2)	2 (1.3)	2 (5.9)	
4a	70 (38.0)	56 (37.3)	14 (41.1)	
4b	44 (23.9)	34 (22.7)	10 (29.4)	
5a	34 (18.5)	30 (20.0)	4 (11.8)	
5b	29 (15.8)	27 (18.0)	2 (5.9)	
Treatment received during/prior to CTPA				
Inotropic support	24 (13.0)	23 (15.3)	1 (2.9)	0.086[c]
Systemic steroids	180 (97.8)	148 (98.7)	32 (94.1)	0.156[c]
Immunomodulators	65 (35.3)	58 (38.7)	7 (20.6)	**0.046**[b]
Favipiravir	129 (70.1)	111 (74.0)	18 (52.9)	**0.015**[b]
Anticoagulation regimen received within the last 48 hours prior to CTPA				0.092[c]
(a) Prophylactic low molecular weight heparin	134 (72.8)	108 (72.0)	26 (76.5)	
(b) Prophylactic unfractionated heparin	3 (1.6)	3 (2.0)	0 (0.0)	
(c) Therapeutic anticoagulation	34 (18.5)	31 (20.7)	3 (8.8)	
(d) Intermediate anticoagulation	2 (1.1)	2 (1.3)	0 (0.0)	
(e) None	11 (6.0)	6 (4.0)	5 (14.7)	
Inotropic support during admission	36 (19.6)	34 (22.7)	2 (5.9)	**0.026**[b]
Highest oxygen support during admission				**0.016**[c]
No oxygen required	7 (3.8)	3 (2.0)	4 (11.8)	**0.023**[c]
Nasal Prong	38 (20.7)	29 (19.3)	9 (26.5)	0.353[b]
Face Mask	21 (11.4)	19 (12.7)	2 (5.9)	0.375[c]
Venturi Mask 40%	1 (0.5)	0 (0.0)	1 (2.9)	0.185[c]
Venturi Mask 60%	11 (6.0)	9 (6.0)	2 (5.9)	1.000[c]
High Flow Mask	25 (13.6)	19 (12.7)	6 (17.6)	0.417[c]
High Flow Nasal Cannula	37 (20.1)	30 (20.0)	7 (20.6)	0.938[b]
Mechanical Ventilatory Support (Intubated)	44 (23.9)	41 (27.3)	3 (8.8)	**0.022**[b]
ICU admission	84 (45.7)	72 (48.0)	12 (35.3)	0.179[b]
Length of ICU stay, median (IQR)	8 (4.0-13.0)	8 (4.0-13.0)	3 (2.3-11.0)	**0.021**[d]
Length of hospital stay, median (IQR)	14 (10.0-19.0)	14.5 (11.0-20.0)	12 (10.0-14.0)	**0.006**[d]
Outcome				0.083[c]
Discharged	162 (88.0)	129 (86.0)	33 (97.1)	
In-hospital death	22 (12.0)	21 (14.0)	1 (2.9)	
Sixty-day all-cause Mortality	23 (12.5)	22 (14.7)	1 (2.9)	0.083[c]

SD, standard deviation; IQR, interquartile range

[a]Independent T-test [b]Pearson Chi-square [c]Fisher's Exact Test [d]Mann–Whitney U Test

*Other comorbid: Chronic obstructive pulmonary disease (COPD), bronchial asthma, bronchitis, congestive cardiac failure, old cardiovascular accident, Alzheimer's disease, dementia, Parkinson disease, bipolar disorder, anaemia, hereditary spherocytosis, fatty liver, benign prostate hypertrophy, gouty arthritis, obstructive sleep apnoea, hyperthyroidism, scleroderma, uterine fibroid, haemorrhoid, gastritis, slipped disc, rheumatoid arthritis

#Other symptom: runny nose, epistaxis, chills and rigours, pleuritic chest pain, haemotypsis, arthralgia, myalgia, loss of appetite, loss of weight, nausea, acid brash sensation, epigastric pain, diaphoresis, reduced urine output, orthopnea, paroxysmal nocturnal dyspnoea, dizziness, heaviness over head, pre-syncopal attack, syncope, hypoxia, reduced consciousness, unconscious, left sided body weakness, alleged fall and slurred speech

Table II: Laboratory data of COVID-19 patients with suspected PTE

Laboratory data	Normal range	Total (n=184)	PTE (n=150)	Non-PTE (n=34)	*p* value
Full blood count parameter at presentation, median (IQR)					
Hb (g/dL)	12.0-15.0	13.4 (12.3-14.7)	13.4 (12.6-14.7)	13.7 (12.4-14.5)	0.788[a]
WCC (×10^9/L)	4.0-10.0	6.7 (5.1-8.7)	6.9 (5.2-8.9)	6.0 (4.8-8.1)	0.212[a]
ALC (×10^9/L)	1.0-3.0	1.0 (0.7-1.4)	1.0 (0.8-1.4)	1.1 (0.8-1.7)	0.335[a]
Platelet (×10^9/L)	150-410	220 (165.0-272.5)	208 (165.0-267.3)	240 (181.3-322.0)	0.088[a]
Peak level throughout admission, median (IQR)					
CRP (ng/L)	<5.0	119.4 (75.4-155.0)	124.1 (86.2-155.1)	82.1 (58.7-153.9)	**0.027**[a]
Ferritin (ug/L)*	10-291	1369 (648.0-2125.0)	1469 (688.0-2189.0)	1229 (197.5-1506.0)	**0.024**[a]
AST (U/L)	<34	73 (48.3-119.3)	73 (50.0-121.0)	59.5 (34.8-105.0)	0.077[a]
ALT (U/L)	10-49	90 (50.8-152.0)	92 (50.8-155.8)	78 (44.8-137.3)	0.202[a]
Creatinine (µmol/L)	44.2-97.2	97.1 (81.0-135.1)	97 (78.6-135.1)	94.3 (75.1-128.2)	0.366[a]
Procalcitonin (ng/ml)#	<0.05				0.171[b]
<0.05		22 (14.2)	14 (11.1)	8 (27.6)	
0.05–0.49		97 (62.6)	82 (65.1)	15 (51.7)	
0.50–2.00		23 (14.8)	19 (15.1)	4 (13.8)	
>2.00		13 (8.4)	11 (8.7)	2 (6.9)	
Peak level of D-dimer (µg/ml) pre-CTPA, n (%)	0-<0.5				0.242[b]
<0.5		10 (5.4)	7 (4.7)	3 (8.8)	
0.5–5.0		152 (82.6)	123 (82.0)	29 (85.3)	
5.1–20.0		12 (6.6)	12 (8.0)	0 (0.0)	
>20.0		10 (5.4)	8 (5.3)	2 (5.9)	

[a]Mann–Whitney U test.
[b]Fisher's Exact Test.
*Ferritin level was taken for 168 subjects (not taken for 16 subjects).
#Procalcitonin level was taken for 155 subjects (not taken for 29 subjects).

Table III: Radiological features of COVID-19 patients with suspected PTE

Radiological features	n (%)			*p* value
	Total (n=184)	PTE (n=150)	Non-PTE (n=34)	
Covid-19 pneumonia/organising pneumonia changes				**<0.001**[a]
None	1 (0.5)	0 (0.0)	1 (2.9)	
Mild	62 (33.7)	48 (32.0)	14 (41.2)	
Minimal	16 (8.7)	6 (4.0)	10 (29.4)	
Moderate	63 (34.3)	56 (37.3)	7 (20.6)	
Severe	42 (22.8)	40 (26.7)	2 (5.9)	
Pulmonary angiopathy changes	51 (27.7)	50 (33.3)	1 (2.9)	**<0.001**[b]
Other computerized tomography (CT) findings*	81 (44.0)	76 (50.7)	5 (14.7)	**<0.001**[b]
Most proximal anatomical location	Not applicable		Not applicable	-
Segmental		3 (2.0)		
Subsegmental		147 (98.0)		
Degree of involvement	Not applicable		Not applicable	-
Single lobar, Unilateral		53 (35.4)		
Multilobar, Unilateral		2 (1.3)		
Multilobar, Bilateral		95 (63.3)		

[a]Fisher's Exact Test.
[b]Pearson Chi-square test.
*Other CT findings: Cardiomegaly, pneumomediastinum, pleural effusion, bronchiectasis with cavitation, aortic aneurysm, emphysema, pulmonary artery hypertension, lung fibrosis, interstitial lung disease, cholelithiasis, sclerotic bone lesion, liver cyst and breast lesion.

(calculated based on the patient's body weight) of non-ionic iodinated contrast medium (Ultravist 370) was injected into an antecubital vein at a flow rate of 4.0–5.0 mL/s followed by a 40-mL saline flush using a mechanical dual power injector. For optimal intraluminal contrast enhancement, the automatic bolus-tracking technique had the region of interest located at the level of the main pulmonary artery with a trigger threshold of 120 HU. Images were reconstructed with a thickness of 1 mm and an increment of 1 mm or 1.25 mm. The imaging data were transmitted to a post-processing workstation for multi-planar reconstruction and picture archiving and communication systems.

CTPA image analysis

All CTPA images were reviewed by a senior radiologist (Dr Emilia, principal COVID CT thorax analyst with 6 years'' experience). The CTPA images were analysed using mediastinal window setting (width, 350 HU; level, 50 HU). The lung window was set with a width of 1500 HU and level of –500 HU. The anatomical sites of the acute pulmonary

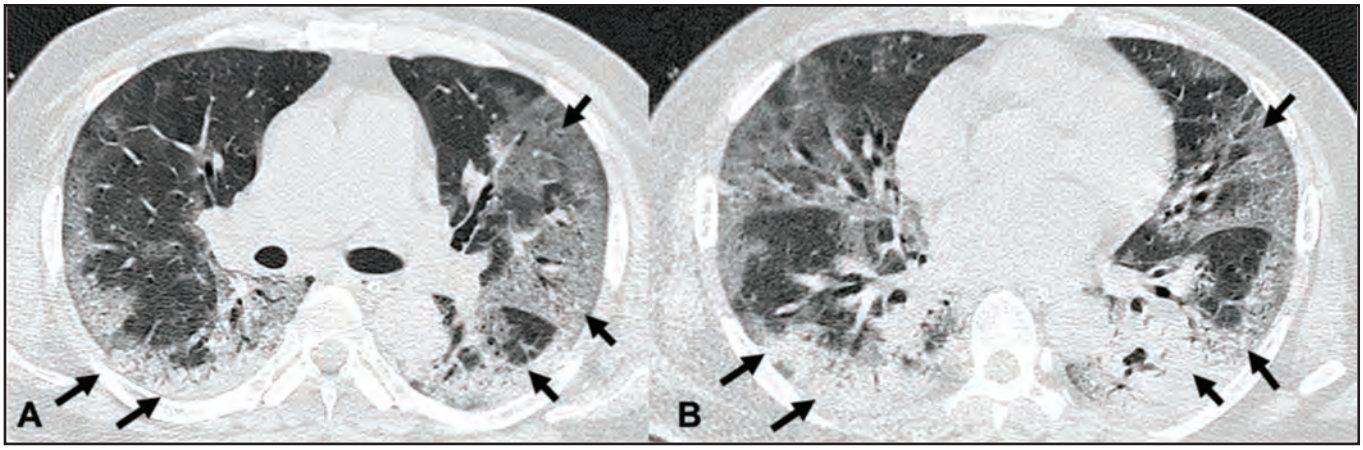

Fig. 1: Computed tomography (CT) pulmonary angiography: A and B: Axial CT images in lung reconstructions at mid and lower lung levels showing typical COVID-19 lesions with bilateral patchy ground-glass opacities and consolidations in predominantly peripheral distribution (black arrows). The pulmonary involvement of COVID-19 lesions was 50% of lung volume.

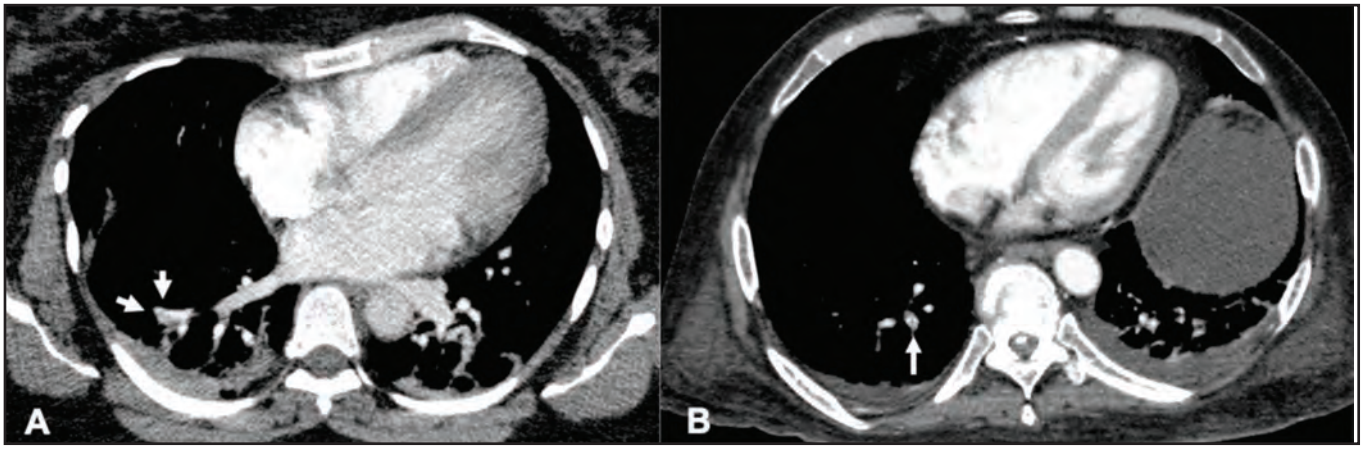

Fig. 2: Computed tomography (CT) pulmonary angiography: A and B: Axial CT images in thin slice demonstrating presence of thrombi (white arrows) in the subsegmental branches of right descending pulmonary artery in different patients with category 4 COVID-19 infection.

thromboembolism were recorded based on the most proximal anatomic location. For each PTE location, the degrees of lung involvement were documented as multi-lobar (unilateral), multi-lobar (bilateral) or single-lobar (unilateral). In addition, the severity of COVID-19 pneumonia and organising pneumonia changes were reported based on the total areas of pulmonary involvement. We divided the aforementioned severity into four categories based on the extent of pneumonia changes detected on CT images at lung window: (1) minimal (<25%), (2) mild (25–50%), (3) moderate (51–75%), and (4) severe (>75%), which was adapted and modified from Pan et al.[9]

Statistical Analysis

The data obtained were analysed using Statistical Package for the Social Sciences (SPSS) software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20. Armonk, NY: IBM Corp.). Demographic data, clinical data, laboratory data and radiological data were presented descriptively. Categorical variables between cases with PTE disease and cases without PTE disease were compared using Pearson Chi-Square or Fisher's Exact test whilst continuous variables were compared using independent t-test or Mann–Whitney U test. For all statistical comparisons, a p value of < 0.05 would be deemed significant.

RESULTS

Clinical Characteristics of COVID-19 Patients with Suspected PTE

A total of 184 COVID-19 patients with suspected PTE who had undergone CTPA were included in this study, and they were further divided into PTE and non-PTE cohorts based on the CTPA findings. Intriguingly, there was a preponderance of PTE among the study populations with a prevalence rate of 81.5% (150 vs. 34).

A review of the clinical characteristics demonstrated that gender distribution was relatively similar between PTE and non-PTE cohorts with a male predominance (60.7% vs. 61.8%, p=0.906). Further, the PTE cohort was significantly elder compared the non-PTE cohort (mean age in years 57 vs. 49; p=0.002). The commonest comorbidities observed were diabetes mellitus (n=95, 51.6%) and hypertension (n=80, 43.5%), which occurred in approximately half of the study population. Also, the prevalence of dyslipidaemia (16.7% vs. 8.8%; p=0.250) and ischaemic heart disease (11.3% vs. 5.9%;

p=0.534) were higher in the PTE cohort although this was not statistically significant. Notably, none of the PTE cohort had clinical deep vein thrombosis.

Almost all of our patients were symptomatic at presentation (n=183, 99.5%), and a wide range of symptoms were reported. There was no significant difference between PTE and non-PTE cohorts in terms of symptoms at presentation. The commonest symptoms documented were cough (n=143, 77.7%), fever (n=129, 70.1%), shortness of breath (n=124, 67.4%), diarrhoea (n=57, 31.0%) and fatigue (n=37, 20.1%). In contrast, anosmia (n=8, 4.3%) and ageusia (n=8, 4.3%) were rarely reported. The median temperature at presentation was 37.9° C (IQR: 37.0–38.7).

Based on the COVID-19 day of illness analysis, the median day of illness at presentation was 5 days (IQR: 4.0–7.0) whilst the median day of illness during CTPA was 10 days (IQR 8.0-13.0). Noticeably, the PTE cohort was generally more severe in contrast to non-PTE cohort as evidence by the former cohort had higher prevalence in more advanced categories with *p* value 0.042. The PTE cohort reported a higher percentage of category 5a (20.0% vs. 11.8%) and category 5b (18.0% vs. 5.9%). On the other hand, category 2 (5.9% vs. 0.7%), category 3 (5.9% vs. 1.3%), category 4a (41.1% vs. 37.3%) and category 4b (29.4% vs. 22.7%) predominantly occurred among the non-PTE cohort.

Interestingly, virtually all subjects received steroidal treatment during/prior to CPTA (n=180, 97.8%.). Conversely, not all subjects received anticoagulation therapy during/prior to CTPA and this was predominantly observed among non-PTE cohort (14.7% vs. 4.0%) despite the suspicion of PTE. Additionally, the percentage of immunomodulator (20.6% vs. 38.7%; *p*=0.046) and favipiravir (52.9% vs. 74.0%; *p*=0.015) therapy were also significantly lower among the non-PTE cohort indicating a milder severity. Moreover, the oxygen requirement also varied between PTE and non-PTE cohort, especially the usage of mechanical ventilatory support (27.3% vs 8.8%; *p*=0.022).

Lastly, the PTE cohort was generally more ill as indicated by a higher proportion of them requiring inotropic support during/prior to CTPA (15.3% vs. 2.9%; *p*=0.086) as well as throughout admission (22.7% vs. 5.9%; *p*=0.026). Despite the absence of a significant difference in intensive care unit (ICU) admission rate (48.0% vs. 35.3%; *p*=0.179), the length of both ICU stays (median number of days 8 vs. 3; *p*=0.021) and hospital stay (median number of days 14.5 vs. 12; *p*=0.006) were significantly longer among PTE cohort. The beforementioned observations translated into a higher proportion of in-hospital death (14.0% vs. 2.9%; *p*=0.083) and 60-day all-cause fatality (14.7% vs. 2.9%; *p*=0.083) among them, though this was not statistically significant (Table I).

Laboratory Data of COVID-19 Patients with Suspected PTE

Analysis of the laboratory parameters showed that the median level of all full blood count parameters at admission was within normal range, except absolute lymphocyte count which was relatively low (median 1.0; IQR 0.7–1.4). Peak C-reactive protein (CRP) (median 124.1 vs. 82.1; *p*=0.027) and ferritin level (median 1469 vs. 1229; *p*=0.024) were significantly higher among the PTE cohort. Other laboratory results including peak serum aspartate transaminase (median 73 vs. 59.5; *p*=0.077), alanine transaminase (median 92 vs. 78; *p*=0.202) and creatinine levels (median 97 vs. 94.3; *p*=0.366) were generally higher among PTE cohort but statistically not significant. Higher peak procalcitonin level (*p*=0.171) and peak D-dimer (*p*=0.242) were noted among PTE cohort as well. Intriguingly, seven PTE patients (4.7%) had a negative D-dimer test and conversely, 31 non-PTE patients (91.2%) recorded a positive D-dimer test. Further, the D-dimer levels from two subjects in the later were raised out of proportion (>20.0 µg/ml) despite the absence of PTE disease. Overall, no significant differences were found between PTE and non-PTE cohort, except peak CRP and ferritin levels(Table II).

Radiological Features of COVID-19 Patients with Suspected PTE

Comparison of the radiological features indicated that the patterns of COVID-19 pneumonia/organising pneumonia changes were significantly more extensive among the PTE cohort with *p*<0.001. For example, the description of moderate (37.3% vs. 20.6%) and severe changes (26.7% vs. 5.9%) was noticeably higher among them (Figure 1). In contrast, mild (41.2% vs. 32.0%) and minimal areas (29.4% vs. 4.0%) of involvement were primarily observed among the non-PTE cohort. Besides, the percentage of pulmonary angiopathy changes was also significantly elevated among PTE cohort (33.3% vs. 2.9%). A myriad of non-COVID pneumonia related radiological changes was also observed, especially among the PTE cohort (50.7% vs. 14.7%)

In the PTE cohort, the thrombotic lesions were mainly located in the peripheral pulmonary arteries, with the most proximal anatomical location restricted to the segmental arteries in 3 patients (2.0%) and in subsegmental arteries in 147 patients (98.0%) (Figure 2). The degree of PTE involvements occurred in single lobar, unilateral among 53 subjects (35.4%), multilobar, unilateral among 2 subjects (1.3%) and multilobar, bilateral among 95 subjects (63.3%) (Table III).

DISCUSSION

Immunothrombosis, which was promulgated during COVID-19 pandemic expounds a distinct pathophysiological pathway for PTE disease associated with COVID-19 infection.[10] In essence, it implicates that dysregulated host immune activation as the primary mechanism for the widespread pulmonary endothelial injury and hypercoagulable state, which would lead to in situ pulmonary thrombosis. This hypothesis is in keeping with the published COVID-19 post-mortem case series, which reported the presence of widespread pulmonary microthrombosis among the deceased.[11,12]

The results derived from this study concurred with the above idea that COVID-19-associated thrombosis primarily occurs due to in situ immunothrombosis. Firstly, none of our PTE cohort had clinical deep vein thrombosis. Furthermore, hyperinflammatory activities appeared to be more rigorous among the PTE cohort as suggested by the disproportionately higher CRP and ferritin values. It is also noteworthy that the thrombosis exclusively affected the subsegmental and segmental as well as peripheral bronchial arteries branches

only, which differs from the conventional embolism-associated PTE described in the non-COVID populations.[13] Moreover, the more extensive involvement of COVID-19 pneumonic changes and existence of microangiopathy support the notion that the thrombosis occurred as result of pulmonary vasculature endothelial damage.

CT patterns in our PTE cohort bear close resemblance to the previously published works in numerous aspects.[14,15] The foremost similarity is that virtually all the existing literature describes that thrombosis in COVID-19 shows a predilection for the peripheral and smaller pulmonary arteries. Another common finding is that the sites of thrombosis highly correlate with lung parenchyma which is affected by COVID-19 disease. In this study, we also reported a high prevalence of microangiopathic changes among the PTE cohort. Collectively, these findings strengthen our belief that PTE disease in COVID-19 represents a unique thrombotic phenotype driven by immunothrombosis that should fuel further studies on its pathophysiology.

Admittedly, the number of non-PTE cohort in this study was inadequate to perform multivariate analysis in identifying the risk factors associated with PTE. Nonetheless, we have identified several notable laboratory and radiological features that are highly associated with PTE as mentioned above. To note, the D-dimer value was proven to be not an ideal biomarker in predicting PTE disease as it lacks specificity. Additionally, we did not find discernible symptoms between the two groups. Considering all these, we recommend that suspicion of PTE disease among COVID-19 patients should be based on patient clinical conditions, especially those with rapid respiratory deterioration, unexplained tachycardia, haemodynamic instability or moderate to extensive COVID-19 pneumonic X-ray changes.[4,16]

The landscape of COVID-19 therapy is an evolving field and several medications such as the usage of hydroxychloroquine and favipiravir had become obsolete through the course of time. At present, antiviral, anticoagulant, steroidal and immunomodulator therapies remain to be the cornerstone of treatment still as most complications arise from the prothrombotic state and immune hyperactivation.[8,17] It is evident that almost all the PTE subjects had received ongoing anticoagulant and steroidal treatment prior to CTPA examination. Hence, it is logical to hypothesise that most subjects developed the PTE disease either from the outset or during the course of treatment. Also, treatments mentioned before appeared to be only capable of ameliorating the propagation or progression of the existing thrombosis at best. In our opinion, the most efficacious PTE disease prevention strategy remains to be effective immunisation or timely administration of a potent antiviral or immunomodulator which could circumvent pulmonary vasculature injury caused by the cytokine storm.

To date, notable heterogeneity exists in regard to the study design among the published prevalence study examining PTE disease associated with COVID-19 infection.[5] As a corollary, there exists a large variation in the global PTE disease incidence rate. For instance, Leonard-Lorant et al reported an incidence rate of 30% among the COVID-19 cohort with the suspicion of PTE; whilst Scudiero et al reported an incidence rate of 14% among the COVID-19 cohort with the suspicion of PTE.[3,18] Interestingly, despite the similarity in recruiting both ICU and non-ICU patients in the study, our study recorded a comparatively higher incidence of PTE disease. We postulate that this disparity could arise from the difference in the COVID-19 variant that was ubiquitous during the study time frame as well the study population clinical profiles. It is noteworthy that approximately half of our PTE cohort required ICU admission. Notwithstanding, PTE disease was proven to be a formidable disease as those inflicted with it were generally more ill and reported a higher ICU admission rate as well as fatality rate.

A few limitations exist in this study. Firstly, we would like to cautiously remind the readers that the study population was from the pre-vaccination era, and also, they were infected with the most virulent Delta (B.1.617.2) strain during the course of illness. As well, the CT images were analysed by only a single radiologist. Therefore, the interrater reliability or agreement could not be determined though that is not our study objective. Lastly, the level of important proinflammatory mediators, like serum interleukin and interferon levels, were not measured due to unavailability such test in our centre. Nevertheless, this paper provides a comprehensive review including both ICU and non-ICU COVID-19 patients with suspected PTE disease. Moreover, it also compares and contrasts the important clinical, laboratory and radiological aspects of both PTE and non-PTE cohorts with COVID-19 infection.

CONCLUSION

Our data suggest that PTE disease was common among COVID-19 patients and its' phenotype is different from the conventional PTE disease among patients without COVID-19 infection. Further, the presence of marked hyperinflammatory activities, unique thrombotic lesion sites and concomitant moderate to severe COVID pneumonia substantiate immunothrombosis as the likely cause. Absence of telltale symptoms or biomarkers suggests that the decision to investigate PTE disease should be based on the patient clinical conditions. Lastly, it is hoped that similar research will be undertaken among our post-vaccination populations in order to advance our understanding towards this area.

ACKNOWLEDGEMENTS

We gratefully acknowledge Dr Eashwary, Head of Medical Department, HTAR and Dr Azlina Abdul Manan, Head of Radiology Department, HTAR for their advance review of this article. Lastly, we would like to thank Director General of Health Malaysia for his permission to publish this article.

ETHICAL APPROVAL

This study was registered with National Medical Research Register and approved by the Medical Research and Ethics Committee of the Ministry of Health. MREC Approval Letter: KKM/NIHSEC/P21-1574(11)

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