Pulmonary thromboembolic disease associated with COVID-19 infection: a comparison between geriatric and non-geriatric populations

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ABSTRACT

Introduction: The magnitude of Coronavirus Disease 2019 (COVID-19) infection among the elderly population is expected to rise. Our study compares the clinical and computed tomographical (CT) features of pulmonary thromboembolic (PTE) disease associated with COVID-19 infection in geriatric and non-geriatric cases, and explores the 60-day mortality rate in these two groups.

Materials and Methods: We conducted this retrospective cross-sectional study in Hospital Tengku Ampuan Rahimah, Selangor, Malaysia. Patients admitted in April 2021 and May 2021 with concomitant COVID-19 infection and PTE disease were included. Demographic, clinical and laboratory data were retrieved, whilst CTPA images were analysed by a senior radiologist.

Results: A total of 150 patients were recruited, comprising 45 geriatric patients and 105 non-geriatric patients. The prevalence rate of hypertension, diabetes mellitus and dyslipidaemia were higher among the geriatric cohort. Evidently, the percentage of patients with fever and diarrhoea were significantly higher among the non-geriatric cohort. The geriatric cohort also recorded a significantly lower absolute lymphocyte count at presentation and albumin level during admission. Despite earlier presentation, the geriatric cohort suffered from more severe diseases. Analysis of the CT features demonstrated that the most proximal pulmonary thrombosis specifically limited to the segmental and subsegmental pulmonary arteries in both cohorts. The elderly suffered from a significantly higher in-hospital mortality rate and their cumulative probability of survival was significantly lower.

Conclusion: Typical COVID-19 symptoms may be absent among the elderly, prompting a lower threshold of suspicion during the COVID-19 pandemic. Additionally, the elderly demonstrated a higher probability of adverse outcomes despite earlier presentation and treatment.

KEYWORDS:
COVID-19, geriatric vs. non-geriatric populations, pulmonary thromboembolic disease

INTRODUCTION

Coronavirus disease 2019 (COVID-19) virus which is caused by the novel SARS-CoV-2 was first reported in Wuhan, Hubei Province in December 2019, has evolved to become a pandemic of global scale.[1,2] SARS-CoV-2 is a single-stranded RNA virus which binds the angiotensin-converting enzyme-2 receptors on the endothelial cells, especially within the kidneys, heart, lungs and liver.[3] The damage to the endothelial cells can lead to widespread thrombosis that cause numerous thrombotic complications such as deep vein thrombosis, pulmonary thromboembolic (PTE) disease, myocardial infarction, stroke and disseminated intravascular coagulation.[4,5] In severe case, it can lead to acute respiratory distress syndrome or multiorgan failure.[6] Demographics and comorbidities that are associated with COVID-19 infection include older age, male sex, ethnicity, diabetes mellitus, systemic hypertension and chronic cardiorespiratory disease.[7]

There were 601,189,435 confirmed COVID-19 cases and total deaths related to COVID-19 has amassed to 6,475,346 worldwide by September 2022.[8] The elderly populations are at the forefront on this onslaught and studies have consistently proven that they are at the risk of adverse outcomes and fatal disease.[7,9] In recent years, studies on PTE disease have gained renewed interest since the emergence of COVID-19 infection. In the seminal papers by Khismatullin et al and Loo et al, it was postulated that PTE disease associated with COVID-19 is driven by in-situ thrombosis caused by immune system hyperactivation that is distinctly different from the conventional PTE disease.[10,11]

It is well established that the occurrence of PTE disease during COVID-19 infection portends a negative survivor outcome, especially among the geriatric populations.[12] Moreover, the later would continue to bear the brunt of this ongoing

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COVID-19 pandemic which is unlikely to disappear from the community in the foreseeable future.[13] The aim of this study is thus to compare the clinical and computed tomographical (CT) features of PTE disease associated with COVID-19 infection between geriatric and non-geriatric cases as well as to explore the 60-day mortality rate between these two groups.

MATERIALS AND METHODS

Study Setting

Hospital Tengku Ampuan Rahimah (HTAR) is a tertiary hospital located in the royal Klang district, Selangor, Malaysia. HTAR had been providing integrated care to both non-Covid and Covid infected cases since 13th January 2021. During the study period, Klang Valley was one of the worst affected regions in Malaysia with thousands of new COVID-19 cases reported daily and the number of hospitalized cases treated in HTAR was ranked the third highest in Klang Valley, after Hospital Sungai Buloh and Hospital Kuala Lumpur.

Study Design and Data Collection

This was a retrospective cross-sectional study conducted among adult COVID-19 patients with CTPA confirmed PTE who were admitted in HTAR between 1st April 2021 and 31st May 2021. We had screened a total of 197 patients, which involved all the hospitalised adult COVID-19 patients who had CTPA done for suspected acute PTE disease within the study period. Patients aged ≥ 18-year-old diagnosed with COVID-19 either through real time Reverse Transcriptase-Polymerase Chain Reaction (rRT-PCR), GeneXpert test or rapid antigen test from nasopharyngeal swab or lower respiratory tract sample with CTPA confirmed PTE were included in this study. In total, 47 subjects were excluded due to the following reasons: without CTPA evidenced PTE (34 cases), 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 missing clinical notes (5 cases). Therefore, a total of 150 patients were included in the analysis.

Clinical and Laboratory Data

Clinical data and laboratory data were extracted from the clinical case notes and electronic medical systems. We defined "elderly" as whom chronological age is ≥ 65 years (completed age upon admission) and they were categorised as geriatric cohort. Conversely, anyone aged below 65 years was grouped as non-geriatric cohort. For each COVID-19 patient, the clinical and laboratory data were retrieved retrospectively from the case notes as well as the online laboratory systems by two physicians (Tan TL and Niny H).

COVID-19 day of illness was calculated from the onset of clinical symptoms compatible with COVID-19 infections. However, if the clinical history was unclear or the patient was asymptomatic, then the first day of illness would be calculated from the date when the COVID-19 confirmatory test first became positive. The definitions of COVID-19 clinical stages were as follow: category 1-asymptomatic; category 2-symptomatic but no pneumonia; category 3-symptomatic with pneumonia; category 4-symptomatic with pneumonia and requiring supplement oxygen; category 5a-requiring non-invasive ventilation including high flow nasal cannula and category 5b-requiring mechanical ventilation with or without other organ failures.[14]

With reference to our institutional protocols, we developed the following anticoagulation regimen definitions. Prophylactic anticoagulation regimen was defined as follows: (a) subcutaneous enoxaparin 40 to 60 mg daily (if eGFR ≥30 ml/min/1.73 m^2) (b) subcutaneous enoxaparin 20 to 30 mg OD (if eGFR < 30 ml/min/1.73 m^2) and (c) subcutaneous unfractionated heparin 5000 units q12 hourly or q8 hourly. Therapeutic anticoagulation regimen was defined as follow: (a) subcutaneous enoxaparin 1 mg/kg/BD or 40 to 60 mg BD (if eGFR ≥ 30 ml/min/1.73 m^2); (b) subcutaneous enoxaparin 1 mg/kg/OD or 40 to 60 mg OD (if eGFR < 30 ml/min/1.73 m^2); (c) warfarin with INR ranged 2 to 3 and (d) direct oral anticoagulation therapy as per drug insert recommendation. Any dose in between prophylactic and therapeutic range were considered as intermediate anticoagulation. In the circumstances where the body weight was unavailable, the physician would exert his discretion to determine the anticoagulation regimen given.

In addition, we examined the bleeding complications related to anticoagulant therapy. We regarded the following events as major bleeding: (i) fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial or (ii) intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells. If patient fulfilled criteria (ii) in the absence of an apparent bleeding cause, the physician would exert his discretion to decide whether the cause of severe anaemia was attributed to major occult bleeding. Additionally, bleeding events that preceded the initiation of anticoagulant therapy were excluded. Any bleeding event that did not fulfil the-before-mentioned criteria was regarded as minor bleeding complication (adapted from International Society on Thrombosis and Haemostasis criteria).[15]

Acute transaminitis was defined as a two-fold increase in serum aspartate transaminase (AST) or serum alanine transaminase (ALT) level from baseline whilst acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥ 26.5 µmol/L within 48 hours or increase in serum creatinine by 1.5 times baseline.[16]

The primary outcome measure was 60-day mortality after the onset of COVID-19 infection. Due to the retrospective nature of the study, we did not attempt to determine whether 60-day mortality was attributable to the COVID-19 infection. Out of hospital death was confirmed with National Death Registry.

Radiological Data

(a) CT image acquisition and analysis

The 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 in

single breath hold if possible. The scan parameters were as follow: 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. A weight adjusted non-ionic iodinated contrast medium (Ultravist 370) was given with a 40 ml saline flush via a mechanical dual power injector. To optimise the intraluminal contrast enhancement, automatic bolus-tracking technique was used and targeted at the level of the main pulmonary artery with a trigger threshold of 120 HU. Image was reconstructed with a thickness of 1 mm and an increment of 1 mm or 1.25 mm.

(b) Image interpretation

All CTPA images were reviewed by a senior radiologist (Dr Emilia, principal COVID CT thorax analyst with 6 years' experience). Under the mediastinal window setting (width, 250 HU; level, 50 HU), the CTPA images would be analysed. Lung window with a width of 1500 HU and level of 500 HU was set. The anatomical sites of the acute pulmonary thromboembolism were reported based on the most proximal anatomic location. For each PE location, the degrees of lung involvement were reported as multi-lobar (unilateral), multi-lobar (bilateral) or single lobar (unilateral). Lastly, the severity of COVID-19 pneumonia and organising pneumonia changes was reported based on the total areas of lung parenchyma involvement. We separated the aforementioned severity into four categories based on the extent of pneumonia changes detected on CT images in the lung window: (1) minimal (< 25%), (2) mild (25-50%), (3) moderate (51-75%) and (4) severe (>75%).[17]

Statistical Analysis

We performed data analysis using Statistical Package for the Social Sciences (SPSS) software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20. Armonk, NY: IBM Corp.). Geriatric and non-geriatric cohorts were compared using Pearson Chi-square, Fisher's exact test, Student t test and Mann-Whitney U test. Kaplan-Meier curve was used to estimate the probability of survival at 60 days for both geriatric and non-geriatric cohorts. Log-rank test was used to compare if there was any difference between both cohorts in the probability of 60-day mortality. The event of interest was death cases that occurred within 60 days after the onset of COVID-19 infection. For all statistical comparisons, a p value < 0.05 was considered statistically significant.

RESULTS

Comparison of Socio-demographic and Clinical Characteristics Between the Geriatric and Non-geriatric Cohorts

As illustrated in Table I, a total of 150 patients with CT confirmed pulmonary thromboembolic disease were recruited during the study period, which was represented by 45 (30.0%) geriatric patients and 105 (70.0%) non-geriatric patients. The median age of the geriatric cohort was 69 years (IQR 67.0-73.0), while the median age of the non-geriatric cohort was 54 years (IQR 44.5-60.0). Evaluation of gender distribution showed that majority of the study populations were male in both geriatric and non-geriatric cohorts (57.8% vs. 61.9%; p=0.635).

A review of the prevalence of comorbidities demonstrated that 73.3% (n=110) of patients had at least one comorbidity. The prevalence rate of hypertension (62.2% vs. 47.6%) diabetes mellitus (55.6% vs. 39.0%) and dyslipidaemia (24.4% vs. 13.3%) in geriatric cohort were higher compared to non-geriatric group. In contrast, subjects with underlying end stage renal disease (n=4, 3.8%) and malignancy (n=1, 1.0%) only occurred among the latter group. Overall, the differences observed were not statistically significant.

Almost all patients were symptomatic at presentation (n=149, 99.3%) and the commonest symptoms were cough (n=115; 76.7%), fever (n=106; 70.7%) and shortness of breath (n=100; 66.7%). Evidently, the percentage of patients with fever (53.3% vs. 78.1%; p=0.002), diarrhoea (17.8% vs. 39.0%; p=0.011) and fatigue (35.5% vs. 14.3%; p=0.003) were significantly different between the geriatric and non-geriatric cohorts. The median temperature at presentation was generally lower among the geriatric cohort in comparison to non-geriatric cohort (median 37.5, IQR 36.7-38.6 vs. median 38.1, IQR 37.1-38.8; p=0.054). Also, none of patients had clinical deep vein thrombosis.

In another note, both day of illness at presentation (median 4, IQR 2.0-6.0 vs. median 6, IQR 4.0-8.0; p=0.001) and day of illness during CTPA (median 9, IQR 6.0-12.0 vs. median 10, IQR 8.0-14.0; p=0.005) among geriatric cohort was significantly earlier as compared to non-geriatric cohort. Though the geriatric cohort presented earlier to the hospital, their categories of illness at presentation were more severe as indicated by higher percentage in category 4b to 5b (42.2% vs. 29.6%). Geriatric cohort had higher percentage of category 5b during CTPA examination as well (26.7% vs. 14.3%). Despite of this, the difference in the category of illness at presentation and during CTPA were not statistically significant between the two cohorts.

Comparison of treatment received during or prior to CTPA examination showed that the proportion of patients on inotropic support was significantly higher among the geriatric cohort (24.4% vs. 11.4%; p=0.043). Other treatments received which included immunomodulators and favipiravir treatment were comparably similar between the two groups. It is noteworthy that almost all patients received systemic steroidal treatment (n=148, 98.7%), as well as prophylactic, therapeutic or intermediate anticoagulation therapy (n=144; 96.0%) prior CTPA examination.

Comparison of Clinical and Survival Outcomes Between the Geriatric and Non-Geriatric Cohorts

As shown in Table I, treatment received throughout admission suggested that the geriatric cohort was generally more ill as the percentage of inotropic (35.5% vs. 17.1%; p=0.014) and mechanical ventilator support (33.4% vs. 24.8%; p=0.028) needed were significantly higher compared to the non-geriatric cohort. Furthermore, major bleeding (22.7% vs. 11.4%) after receiving anticoagulation during admission, predominantly occurred among the geriatric cohort though this was statistically insignificant.

During the hospitalisation period, the prevalence rate of AKI (46.7% vs. 22.9%; p=0.004) and acute coronary syndrome

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

Characteristics	n (%)			*p* value
	Total (n = 150)	Geriatric (n = 45)	Non-Geriatric (n = 105)	
Age in years, median (IQR)	59 (49.0-66.0)	69 (67.0-73.0)	54 (44.5-60.0)	**<0.001**[a]
Male Gender	91 (60.7)	26 (57.8)	65 (61.9)	0.635[b]
With at least one comorbidity	110 (73.3)	36 (80.0)	74 (70.5)	0.227[b]
Comorbidities				
Hypertension	78 (52.0)	28 (62.2)	50 (47.6)	0.101[b]
Diabetes mellitus	66 (44.0)	25 (55.6)	41 (39.0)	0.062[b]
Dyslipidaemia	25 (16.7)	11 (24.4)	14 (13.3)	0.094[b]
Ischemic heart disease	17 (11.3)	7 (15.6)	10 (9.5)	0.286[b]
Obesity	4 (2.7)	1 (2.2)	3 (2.9)	1.000[c]
End stage renal disease	4 (2.7)	0 (0.0)	4 (3.8)	0.317[c]
Chronic kidney disease excluding ESRF	3 (2.0)	1 (2.2)	2 (1.9)	1.000[c]
Alzheimer's disease	2 (1.3)	2 (4.4)	0 (0.0)	0.089[c]
Malignancy	1 (0.7)	0 (0.0)	1 (1.0)	1.000[c]
Other comorbid*	27 (18.0)	8 (17.8)	19 (18.1)	0.963[b]
Symptomatic at presentation	149 (99.3)	45 (100.0)	104 (99.0)	1.000[c]
Symptoms at presentation				
Cough	115 (76.7)	31 (68.9)	84 (80.0)	0.140[b]
Fever	106 (70.7)	24 (53.3)	82 (78.1)	**0.002**[b]
Shortness of breath	100 (66.7)	29 (64.4)	71 (67.6)	0.705[b]
Diarrhoea	49 (32.7)	8 (17.8)	41 (39.0)	**0.011**[b]
Loss of appetite	34 (22.7)	12 (26.7)	22 (21.0)	0.444[b]
Fatigue	31 (20.7)	16 (35.5)	15 (14.3)	**0.003**[b]
Sore throat	18 (12.0)	3 (6.7)	15 (14.3)	0.188[b]
Nausea/vomiting	18 (12.0)	2 (4.4)	16 (15.2)	0.062[b]
Chest pain/discomfort	15 (10.0)	2 (4.4)	13 (12.4)	0.233[c]
Arthralgia/myalgia	11 (7.3)	4 (8.9)	7 (6.7)	0.734[c]
Ageusia	7 (4.7)	3 (6.7)	4 (3.8)	0.429[c]
Anosmia	6 (4.0)	3 (6.7)	3 (2.9)	0.365[c]
Haemoptysis	1 (0.7)	0 (0.0)	1 (1.0)	1.000[c]
Other symptom[#]	41 (27.3)	13 (28.9)	28 (26.7)	0.780[b]
Temperature at presentation (°C), median (IQR)	38.0 (37.0-38.8)	37.5 (36.7-38.6)	38.1 (37.1-38.8)	0.054[a]
Day of illness at presentation, median (IQR)	5 (3.0-7.0)	4 (2.0-6.0)	6 (4.0-8.0)	**0.001**[a]
Category of illness at presentation				0.112[c]
2	5 (3.3)	3 (6.7)	2 (1.9)	
3	20 (13.3)	7 (15.6)	13 (12.3)	
4a	75 (50.0)	16 (35.5)	59 (56.2)	
4b	38 (25.4)	13 (28.9)	25 (23.8)	
5a	2 (1.3)	1 (2.2)	1 (1.0)	
5b	10 (6.7)	5 (11.1)	5 (4.8)	
Day of illness during CTPA, median (IQR)	10 (8.0-13.0)	9 (6.0-12.0)	10 (8.0-14.0)	**0.005**[a]
Category of illness during CTPA				0.261[c]
2	1 (0.7)	0 (0.0)	1 (1.0)	
3	2 (1.3)	0 (0.0)	2 (1.9)	
4a	56 (37.3)	18 (40.0)	38 (36.2)	
4b	34 (22.7)	6 (13.3)	28 (26.6)	
5a	30 (20.0)	9 (20.0)	21 (20.0)	
5b	27 (18.0)	12 (26.7)	15 (14.3)	
Treatment received during/prior to CTPA				
Inotropic support	23 (15.3)	11 (24.4)	12 (11.4)	**0.043**[b]
Systemic steroidal treatment	148 (98.7)	45 (100.0)	103 (98.1)	1.000[c]
Immunomodulators treatment	58 (38.7)	15 (33.4)	43 (41.0)	0.380[b]
Favipiravir treatment	111 (74.0)	34 (75.5)	77 (73.3)	0.776[b]
Anticoagulation regimen received within the last 48 hours prior to CTPA				0.121[c]
(a) Prophylactic low molecular weight heparin	108 (72.0)	37 (82.2)	71 (67.6)	
(b) Prophylactic unfractionated heparin	3 (2.0)	2 (4.4)	1 (1.0)	
(c) Therapeutic anticoagulation	31 (20.7)	5 (11.1)	26 (24.8)	
(d) Intermediate anticoagulation	2 (1.3)	0 (0.0)	2 (1.9)	
(e) None	6 (4.0)	1 (2.2)	5 (4.8)	
Haemodialysis during admission	10 (6.7)	2 (4.4)	8 (7.6)	0.724[c]
Inotropic support during admission	34 (22.7)	16 (35.5)	18 (17.1)	**0.014**[b]

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

Characteristics	n (%)			*p* value
	Total (n = 150)	Geriatric (n = 45)	Non-Geriatric (n = 105)	
Highest oxygen support during admission				0.658[c]
No oxygen required	3 (2.0)	0 (0.0)	3 (2.9)	0.554[c]
Nasal prong	29 (19.3)	10 (22.2)	19 (18.1)	0.558[b]
Face mask	19 (12.7)	5 (11.1)	14 (13.3)	0.708[b]
Venturi mask 60%	9 (6.0)	1 (2.2)	8 (7.6)	0.280[c]
High flow mask	19 (12.7)	4 (8.9)	15 (14.3)	0.362[b]
High flow nasal cannula	30 (20.0)	10 (22.2)	20 (19.0)	0.656[b]
Mechanical ventilatory support (Intubated)	41 (27.3)	15 (33.4)	26 (24.8)	**0.028**[b]
Anticoagulation therapy received during admission	149 (99.3)	44 (97.8)	105 (100.0)	0.300[c]
Bleeding complication post anticoagulant				0.204[c]
Major bleeding[$]	22 (14.8)	10 (22.7)	12 (11.4)	
Minor bleeding[@]	5 (3.3)	1 (2.3)	4 (3.8)	
No bleeding complication	122 (81.9)	33 (75.0)	89 (84.8)	
Complications				
Acute transaminitis	82 (54.7)	26 (57.8)	56 (53.3)	0.616[b]
Acute kidney injury	45 (30.0)	21 (46.7)	24 (22.9)	**0.004**[b]
Acute coronary syndrome	5 (3.3)	4 (8.9)	1 (1.0)	**0.029**[c]
Acute stroke	2 (1.3)	2 (4.4)	0 (0.0)	0.089[c]
ICU admission	72 (48.0)	26 (57.8)	46 (43.8)	0.117[b]
Length of ICU stay, median (IQR)	8.0 (4.0-13.0)	7.5 (4.0-12.5)	8.5 (4.8-15.8)	0.235[a]
Length of hospital stay, median (IQR)	14.5 (11.0-20.0)	15.0 (12.0-19.5)	14.0 (10.5-20.0)	0.542[a]
Outcome				**0.001**[b]
Discharged	129 (86.0)	32 (71.1)	97 (92.4)	
In-hospital death	21 (14.0)	13 (28.9)	8 (7.6)	
Sixty-day all-cause mortality	22 (14.7)	14 (31.1)	8 (7.6)	**<0.001**[b]

IQR, Interquartile range
[a]Mann-Whitney U test
[b]Pearson Chi-square test
[c]Fisher's exact test
*Other comorbid: Chronic obstructive pulmonary disease, bronchial asthma, bronchitis, congestive cardiac failure, old cardiovascular accident, Parkinson disease, bipolar disorder, anaemia, hereditary spherocytosis, gastritis, fatty liver, benign prostate hypertrophy, gouty arthritis, obstructive sleep apnoea, hyperthyroidism, scleroderma, uterine fibroid, haemorrhoid, slipped disc, rheumatoid arthritis
[#]Other symptom: runny nose, chills and rigors, acid brash sensation, epigastric pain, orthopnea, parosxysmal nocturnal dyspnea, dizziness, heaviness over head, pre-syncopal attack, syncope, reduced consciousness, unconscious, diaphoresis, reduced urine output, left sided body weakness, alleged fall and slurred speech
[$]Major bleeding: Gastrointestinal bleed, occult bleed, or haematoma causing either (1) a fall in haemoglobin of 2g/dL or more, or (2) transfusion of 2 or more units of whole blood or red cells, or (3) fulfilling both criteria(1) and (2)
[@]Minor bleeding: Haematoma, epistaxis, haematuria, or occult bleed that does not fulfil the criteria for major bleeding

(8.9% vs. 1.0%; *p*=0.029) were significantly higher among the geriatric group. Noticeably, the prevalence rate of acute transaminitis was also remarkably high among both groups. Lastly, two cases of stroke (4.4%) were observed among the geriatric cohort.

Among the geriatric cohort, 57.8% (n=26) of them required ICU admission as opposed to 43.8% (n=46) among the non-geriatric cohort. Despite having shorter median of ICU stay among the former group, the median length of hospital stay was longer when compared to the non-geriatric group.

The in-hospital mortality rate (28.9% vs. 7.6%; *p*=0.001) was significantly higher among the geriatric cohort. As depicted in Figure 1, the cumulative probability of survival was significantly lower in geriatric cohort than non-geriatric cohort (68.9% vs. 92.4%; log rank, *p*<0.001). The mean survival time was 47.5 days in geriatric cohort and 58.1 days in non-geriatric cohort.

Comparison of laboratory data between the geriatric and non-geriatric cohorts

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 significantly lower among the geriatric cohort (median 0.9 × 10^9/L, IQR 0.6-1.3 vs. median 1.0 × 10^9/L, IQR 0.8-1.5; *p*=0.014). In addition, the geriatric cohort also demonstrated a significantly lower peak albumin (median 29g/L, IQR 26.0-32.0 vs. median 32 g/L, IQR 29.0-34.0; *p*=0.001) during admission. Both C-reactive protein (CRP) and ferritin levels were profoundly raised in both cohorts. Other laboratory results including peak AST, peak creatinine, peak procalcitonin and peak D-dimer levels were generally higher among the geriatric cohort. Overall, no significant differences were found between geriatric and non-geriatric cohorts, except serum absolute lymphocyte count at presentation and peak albumin level during admission (Table II).

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

Laboratory data	Normal range	Total (n=150)	Geriatric (n=45)	Non-Geriatric (n=105)	*p* value
Full blood count parameter at presentation, median (IQR)					
Hb (g/dL)	12.0-15.0	13.4 (12.6-14.7)	13.5 (12.7-14.6)	13.3 (12.5-14.9)	0.998[a]
WCC (x10^9/L)	4.0-10.0	6.9 (5.2-8.9)	6.8 (5.2-9.6)	6.9 (5.1-8.8)	0.884[a]
ALC (x10^9/L)	1.0-3.0	1.0 (0.8-1.4)	0.9 (0.6-1.3)	1.0 (0.8-1.5)	**0.014**[a]
Platelet (x10^9/L)	150-410	208 (165.0-267.3)	199 (163.5-238.0)	223 (168.0-275.0)	0.269[a]
Peak level throughout admission, median(IQR)					
Albumin (g/L)	34.0-50.0	31 (28.0-34.0)	29 (26.0-32.0)	32 (29.0-34.0)	**0.001**[a]
CRP (ng/L)	<5	124.1 (86.2-155.1)	137.0 (86.2-155.1)	122.9 (58.7-153.9)	0.164[a]
Ferritin (µg/L)*	10-291	1469 (688.0-2189.0)	1435.5 (688.0-2189.0)	1469.0 (197.5-1506.0)	0.746[a]
AST (U/L)	<34	73 (50.0-121.0)	76 (50.0-121.0)	71 (34.8-105.0)	0.311[a]
ALT (U/L)	10-49	92 (50.8-155.8)	77.5 (50.8-155.8)	97.0 (44.8-137.3)	0.691[a]
Creatinine (µmol/L)	44.2-97.2	97.1 (78.6-135.1)	108.9 (78.6-135.1)	95.5 (75.1-128.2)	0.240[a]
Procalcitonin (ng/ml)[#]	<0.05				0.627[b]
<0.05		14 (11.1)	3 (7.3)	11 (12.9)	
0.05-0.49		82 (65.1)	26 (63.4)	56 (65.9)	
0.50-2.00		19 (15.1)	8 (19.5)	11 (12.9)	
>2.00		11 (8.7)	4 (9.8)	7 (8.3)	
Peak level of D-dimer (µg/ml) pre-CTPA, n (%)	0.0-<0.5				0.319[b]
<0.5		7 (4.7)	0 (0.0)	7 (6.7)	
0.5-5.0		123 (82.0)	39 (86.6)	84 (80.0)	
5.1-20.0		12 (8.0)	3 (6.7)	9 (8.6)	
>20.0		8 (5.3)	3 (6.7)	5 (4.8)	

[a]Mann-Whitney U test
[b]Fisher's exact test
*Ferritin level was taken for 139 subjects (not taken for 11 subjects)
[#]Procalcitonin level was taken for 126 subjects (not taken for 24 subjects)

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

Radiological features	n (%)			*p* value
	Total (n = 150)	Geriatric (n = 45)	Non-Geriatric (n = 105)	
Most proximal anatomical location				1.000[a]
Subsegmental	147 (98.0)	44 (97.8)	103 (98.1)	
Segmental	3 (2.0)	1 (2.2)	2 (1.9)	
Degree of involvement				0.369[a]
Single lobar, Unilateral	53 (35.3)	13 (28.9)	40 (38.1)	
Multilobar, Unilateral	2 (1.3)	0 (0.0)	2 (1.9)	
Multilobar, Bilateral	95 (63.3)	32 (71.1)	63 (60.0)	
COVID-19 pneumonia/Organising pneumonia changes				0.216[a]
Mild	48 (32.0)	13 (28.9)	35 (33.3)	
Minimal	6 (4.0)	0 (0.0)	6 (5.7)	
Moderate	56 (37.3)	16 (35.6)	40 (38.1)	
Severe	40 (26.7)	16 (35.6)	24 (22.9)	
Pulmonary angiopathy changes	50 (33.3)	23 (51.1)	27 (25.7)	**0.002**[b]
Other computerized tomography (CT) findings*	76 (50.7)	26 (57.8)	50 (47.6)	0.254[b]

[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, breast lesion, thyroid nodule, renal cyst, splenic cyst

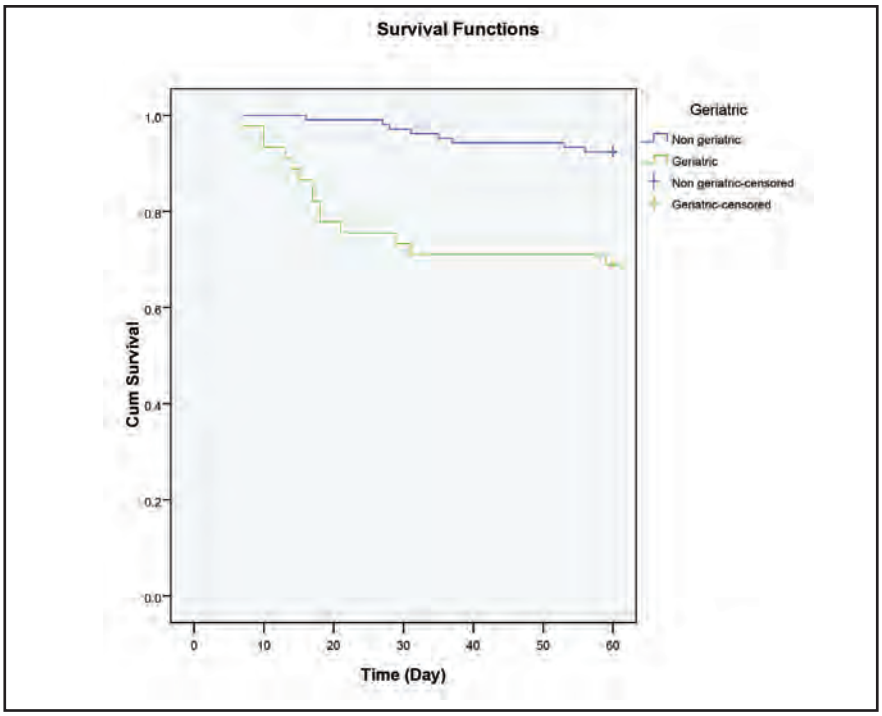

Fig. 1: Kaplan-Meier survival function curve for geriatric versus non-geriatric population

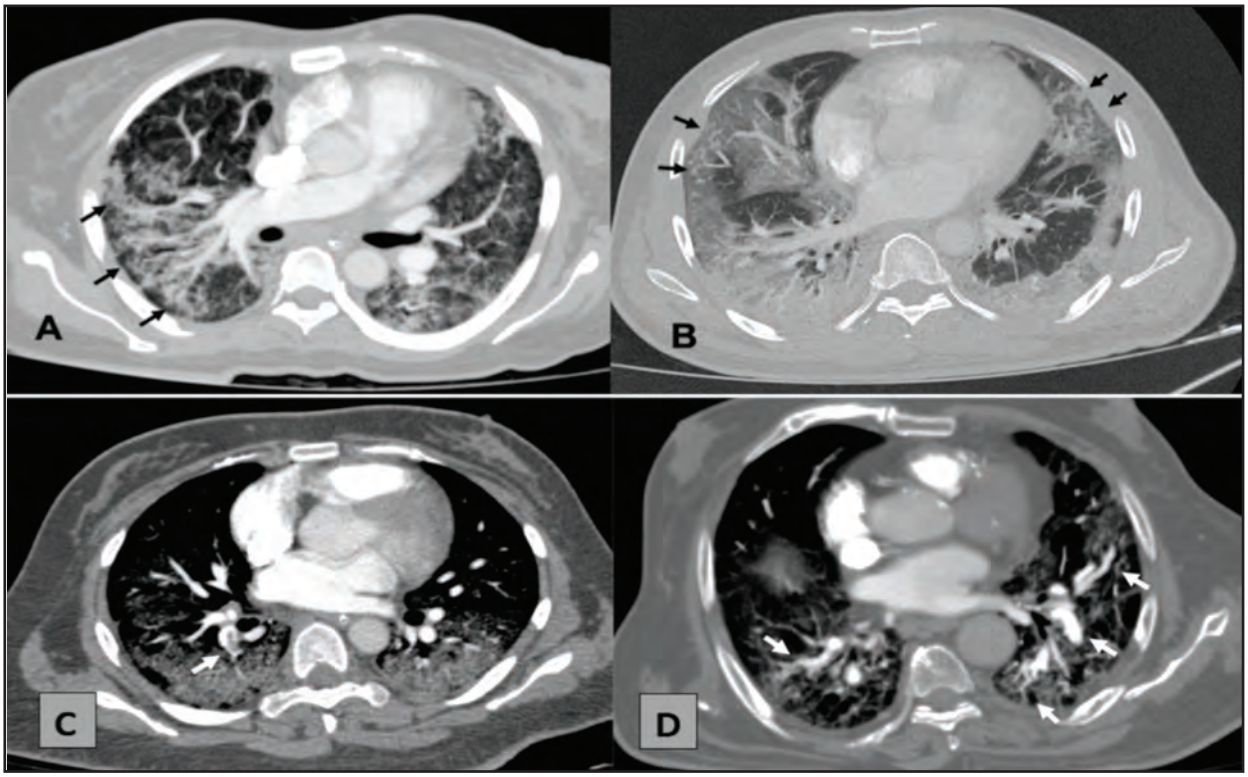

Fig. 2: Axial slice of CTPA demonstrates features of pulmonary angiopathy in two patients with severe COVID-19 pneumonia. (A) Image showed dilated branching and tortuous vessels in the right lower lobe (arrows). (B) There is a bilateral ground-glass opacification with consolidation and vascular tree-in-bud pattern distally, a sign of angiopathy (arrows). (C) CTPA of patient with COVID-19 pneumonia, day 10 after intubation demonstrates filling defects in right lower lobe pulmonary arteries (arrows). (D) CT of elderly patient at day 14 of illness showed dilated branching and tortuous vessels in both lower lobes representing features of pulmonary angiopathy

Comparison of Radiological Features Between the Geriatric and Non-geriatric Cohorts

Analysis of the CT features showed that the thrombotic lesions were primarily located in the peripheral pulmonary arteries with the most proximal anatomical location limited to the subsegmental and segmental arteries in both the geriatric and non-geriatric cohorts. The commonest pattern of PTE involvement was multilobar bilateral, followed by single lobar, unilateral and multilobar unilateral (Figure 2). It is noteworthy that severe degree of COVID-19 pneumonia or organising pneumonic changes were more common among the geriatric cohort, in contradistinction to mild, minimal and moderate changes which were more prevalent among the non-geriatric cohort. All these differences in radiological features were not statistically significant, except for the pulmonary angiopathy changes (51.1% vs. 25.7%; p=0.002) which was significantly higher among the geriatric cohort (Table III).

DISCUSSION

It is well established that the geriatric populations not only stand a greater risk of afflicting COVID-19 infection, but also report a poorer survival outcome due to a myriad of reasons. The foremost explanation for this observation has been well encapsulated under the moniker of immunosenescence or immunoparesis.[18,19] Fundamentally, it describes that due to the physiological ageing process, the host innate as well as cell mediated immune system have weakened, which consequently contribute to the poorer outcome when the hosts are incapable of mounting a robust immune response during infection. Also, the cardinal signs of typical COVID-19 infection, such as fever would be absent due to the blunted immune response.[20] Importantly, they are also having a heightened susceptibility towards thromboembolic complications which are known to be a negative survivor predictor.[12] Considering all these, identification of the common presenting symptoms among the elderly populations with PTE disease complicating COVID-19 infections are of paramount importance as it would enable a timely diagnosis.

In this report, we confirmed that PTE disease associated with COVID-19 infections could manifest in a wide array of symptoms which corroborate with the published literature.[21] It is noteworthy that a significant proportion our geriatric cohort were unable to mount a febrile response during presentation, which were in keeping with the-above-mentioned theory. Paradoxically, the increment in inflammatory markers was comparable to the non-geriatric cohort suggesting their intact ability in generating inflammatory proteins. This observation reaffirms the clinical usefulness of such biomarkers in denoting the hyperinflammatory phase during the clinical course of COVID-19 illness and allowing the clinicians to render the targeted treatment accordingly. Furthermore, atypical symptoms such as gastrointestinal symptoms were more likely to occur among the non-geriatric cohort, whilst neurological deficits only exclusively present among the geriatric cohort. In light of these findings, we recommend the clinicians to maintain a high index of suspicion of COVID-19 infection, especially among the geriatric population during the pandemic as their presenting symptoms could masquerade other common illnesses.[22,23]

There is a growing body of evidence to suggest that COVID-19 infection could trigger a systemic immune hyperactivation leading to cytokine storm that would culminate in a multi-systemic injury as well as hypercoagulable state. The later has been well elucidated under the appellation of immunothrombosis that underpins the pathophysiological process of PTE disease associated with COVID-19.[10,11] In our study, a significant portion of geriatric patients developed AKI and acute coronary syndrome which could be linked to cytokine storm induced by the viral infection. Notwithstanding, the incidence rate of acute transaminitis and acute stroke were equally notable. Though the later was not statistically significant, possibly due to being underpowered from the small event rates, this underscores the predisposition towards multi-organ involvement among the subjects with PTE disease associated with COVID-19.[24] Importantly, none of the subject had associated clinical lower limb deep vein thrombosis. Considering all these, extrapulmonary complications of COVID-19 infection should be actively monitored among hospitalised subjects, especially the elderly group.

It is universally agreed that timely thromboprophylaxis represents the quintessentially important strategy in preventing the development of PTE disease among the hospitalised patients with or without COVID-19 infection.[25,26] It is evident that almost all our subjects had been initiated on either thromboprophylaxis or therapeutic anticoagulations. Similarly, Valle et al and Leonard-Lorant et al reported the percentage of their PTE cases treated with thromboprophylaxis prior to CTPA examination were 83.1% (54/65) and 78.0% (25/32) respectively.[27,28] Nonetheless, a large prospective case control study would be needed to verify the net effects of thromboprophylactic treatment on the incidence of PTE disease associated with COVID-19 which has a distinctive pathophysiological pathway. In another note, recent data from Musoke et al, who reviewed anticoagulation and bleeding risk in patients with COVID-19, indicated that major bleeding regardless of site trends towards association with in-patient fatality (40.0% vs. 21.5%; p=0.054).[29] In this report, the incidence of major bleeding complications is appreciably higher among the elder group. Though it is not statistically significant, it serves to remind us about the judicious use of anticoagulant therapy after weighing in the bleeding risk, and caution against indiscriminate use of therapeutic anticoagulation without clear indication.

There were no discernible differences in regard to the radiological features between two groups, except the pulmonary angiopathy changes which predominantly occurred in the elderly cohort. As alluded earlier, in situ immunothrombosis is the principal cause of PTE disease associated with COVID-19 infection. This dysregulated inflammatory cascade contributes to widespread alveolar injury, disruption of pulmonary vascular endothelial cell thrombo-protective state and systemic coagulopathy. Ultimately, these would result in small vessel thrombi as well as pulmonary angiopathy. According to Yuan et al, the elderly COVID-19 cohort suffered from a more profound

hypercoagulable state as suggested by a significantly higher serum fibrinogen and D-dimer levels compared to the younger cohort.[30] In this report, the insignificant D-dimer levels and unavailability serum fibrinogen levels do not substantiate hypercoagulable state as the cause of pulmonary angiopathy in the elderly cohort. In fact, the hyperinflammatory phenomenon appears to be the more probable driver of pulmonary angiopathy observed among the later.

The unique thrombotic lesions which preferentially affect distal peripheral pulmonary artery branches with a preponderance of multilobar, bilateral involvement are generally in accordance with majority of the published studies. Several studies, for example Ooi et al and van Dam et al have unanimously reported that PTE disease correlate well with the degree of lungs parenchyma affected by COVID-19 pneumonia and our results concur with them.[31,32] Nonetheless, Amaqdouf et al has published a clinical vignette, depicting massive pulmonary embolism complicating mild COVID-19 pneumonia in a 92-year-old man who presented with acute respiratory failure.[33] Hence, our suggestions reflect the recommendations by Sathar et al whereby PTE disease should be suspected on COVID-19 individuals with rapid respiratory deterioration, unexplained tachycardia, haemodynamic instability or moderate to extensive COVID-19 pneumonic X-ray changes.[26]

Despite earlier presentation, the geriatric cohort demonstrated a significantly higher 60-day fatality rate. The clinical characteristic for mortality in our geriatric cohort, such as older age, critically ill, AKI and major bleeding complications were in keeping with the published literature.[29,34-37] Other plausible explanation for the adverse outcome is the immunosenescence phenomenon as alluded earlier. Lastly, significant hypoalbuminaemia and reduced absolute lymphocyte count could also plausibly contribute to a more severe COVID-19 disease and therefore poorer outcome among them.[38,39] In view of the inherently poorer survival outcomes, we recommend close collaboration with geriatrician in discussing the critical care of the elderly, especially pertaining to the resuscitation status as well as ethical consideration at time of pandemic.

We are cognizant of the several limitations in our study. Firstly, there was an unprecedented demand on CTPA examination requests during this study period which coincided with the peak of delta wave in 2021. Therefore, it is understandable that the actual prevalence rate of PTE disease among geriatric populations remained elusive under such circumstances, as those who were moribund or with do not resuscitate status would preclude CTPA examination due to perceived futility of care under such crisis. Also, frailty assessment which has been recognised as a survival predictor among the elderly population was not available due to the retrospective design of this study.[40] Lastly, we were unable to determine the interrater reliability or agreement as we only had single radiologist in this study, though this was not our study objective.

CONCLUSION

Overall, subtle differences in term of presenting symptoms exist between geriatric and non-geriatric patients. There were no major differences in the computerized tomography (CT) representation of both the thrombi distribution as well as the lung parenchyma affected with COVID-19 pneumonia, except the higher incidence of microangiopathic aberration among the elderly. The elderly patients were more susceptible to severe illness with consequent higher fatality outcomes. We recommend future researchers to conduct similar research among our post-vaccination population to further enrich our understanding towards pulmonary thromboembolic (PTE) disease associated with COVID-19.

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ETHICAL APPROVAL

This study was registered with National Medical Research Register (NMRR) and approved by the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH). MREC Approval Letter: KKM/NIHSEC/P21-1451(12) NMRR ID: NMRR-21-1558-59028 (IIR)

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