A retrospective review of CTPA confirmed pulmonary emboli in COVID-19 patients admitted to Groote Schuur Hospital, Cape Town

Student name: Petri Ahlers

Student number: AHLPET002

Supervisor: Dr Qonita Said-Hartley

Division of Radiology, Groote Schuur Hospital, Cape Town

Tel: +27 21 404 4148

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DECLARATION

I, *Petri Ahlers*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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1 List of abbreviations

CTPA **-** Computer tomography pulmonary angiogram

DIC - Disseminated intravascular coagulopathy

DVT - Deep venous thrombosis

ESC - European Society of Cardiology

PE - Pulmonary embolus

RT- PCR - Real-time reverse transcriptase polymerase chain reaction

VTE - Venous thromboembolism

WHO - World Health Organization

ICU - Intensive care unit

DIC- disseminated intravascular coagulation

V/Q - ventilation perfusion

2 Abstract

2.1 Background:

A high incidence of thromboembolic phenomena has been widely reported in patients with COVID-19 pneumonia. There is, however, a paucity of data detailing the incidence and characteristics of pulmonary emboli (PE) in COVID-19 patients in the South African setting. An improved understanding of the presentation and course of these patients is warranted, considering the serious and potentially fatal outcomes.

2.2 Objectives:

To describe the incidence and characteristics of PE confirmed by Computer Tomography Pulmonary Angiogram (CTPA) in patients with COVID-19 pneumonia admitted to a tertiary hospital in the Western Cape, South Africa.

2.3 Methods:

We performed a retrospective-, descriptive study of all adult patients with COVID-19 pneumonia confirmed by Polymerase Chain Reaction (PCR) undergoing CTPA for suspected PE while admitted to Groote Schuur Hospital. The study period was from 1 April 2020 to 30 September 2020.

2.4 Results:

Our study cohort consisted of 116 patients, 59% being female, of whom, 29% were pregnant or in the postpartum period. The median age for both genders combined was 49.5 years .The overall incidence of PE was 19 %, with 20 % in our subset of pregnant and postpartum patients. The majority (64%) of PE's were reported as being segmental in anatomical location.

2.5 Conclusion:

Our study cohort was noteworthy in including pregnant and postpartum patients. The overall incidence of PE was 19 % with no significant differences in demographics, comorbidities or D-dimer levels between patients with or without PE. The importance of a high clinical index of suspicion together with the role of CTPA in diagnosing PE in hospitalised COVID-19 patients is emphasised.

3 CHAPTER 1: LITERATURE REVIEW

3.1 Rationale

A high incidence of thromboembolic phenomena has been widely reported in patients with COVID-19 pneumonia . There is, however,a paucity of data detailing the incidence and characteristics of pulmonary emboli (PE) in COVID-19 pneumonia in the South-African setting.
Considering the potential fatal outcomes in patients with untreated pulmonary emboli, further understanding of the incidence and characteristics of PE in COVID-19 is warranted.

3.2 Introduction

Venous thromboembolism (VTE) is a common disorder worldwide, while the exact incidence of PE is not known, it is estimated to be approximately 60-70 per 100,000 in the general population and is reported as the third most common cause of cardiovascular death. VTE is the umbrella term used to describe pulmonary arterial emboli (PE) and deep venous thrombosis (DVT). (1)(2)(3) PE most commonly results as a complication of deep venous thrombosis (DVT).(2)(4) Rudolf Virchow postulated a triad to help understand the pathophysiology that results in VTE. The three components of Virchow's triad are: (1) hypercoagulability (2) venous stasis and (3) endothelial damage. (5)(2)(6)

Dislodged thrombus from the lower limbs travels along the venous circulation and subsequently enters the pulmonary circulation where it lodges in the pulmonary vasculature resulting in partial or complete vascular obstruction. Large emboli can lodge at the pulmonary trunk bifurcation, a phenomenon also known as a "saddle pulmonary embolus" and can result in near complete occlusion of the pulmonary outflow tract. Furthermore large central pulmonary emboli can result in right ventricular dysfunction with low blood pressure and if left untreated can be fatal. Smaller emboli can lyse spontaneously and cause little clinical sequela or occlude smaller segmental or subsegmental pulmonary arteries.

Apart from occlusion, thrombi release vasoactive mediators that can further increase pulmonary vascular resistance and increase the pressure within the pulmonary vasculature. Pulmonary hypertension is the final sequela of large emboli that organize over time and is associated with high morbidity.(2)Inherited and acquired risk factors for the development of VTE have been well described. Hereditary risk factors most commonly involve "dysfunction in clotting factor production or activity". Acquired risk factors can be further grouped into"provoked"and"unprovoked" risk factors.

Provoked risk factors increase a patient's risk of VTE in the acute setting, whereas unprovoked risk factors increase a patient's risk of developing VTE throughout their lifetime. There is overlap between provoked and unprovoked risk factors and the two are not seen as separate entities. Being bedbound, recent surgical intervention, underlying primary tumour, the peripartum period, hormonal therapy and indwelling vascular lines are all examples of provoked risk factors. Increased body mass index, old age, cigarette smoking, underlying cardiovascular conditions, venous stasis, antiphospholipid antibody syndrome and previous PE or DVT are examples of unprovoked risk factors.(2)

PE presents with non-specific signs and symptoms, making the diagnosis of PE challenging.(2)(4)(7) When assessing the likelihood of PE in a patient presenting to hospital , a combination of risk factors, clinical symptoms and examination findings are taken into consideration. Patients can be grouped into certain categories of pre-test or clinical probability for PE. According to the latest guidelines published by the European Society of Cardiology (ESC): Guidelines for the diagnosis and management of acute pulmonary embolism, clinicians can either make use of pre-test probability scoring systems or empirical clinical judgment to assess likelihood of PE in haemodynamically stable patients presenting to hospital with concern for possible PE.(7)

The simplified Wells score and revised Geneva score are widely accepted and validated scoring systems used to predict the probability of PE. (4)(7)Patients are classified by these scoring systems into: " low, intermediate or high probability for PE"or as "PE likely" or "PE unlikely".

D-dimer levels measured in serum plasma is the final fibrin degradation product of fibrin (clot) breakdown. Raised serum D-dimer level indicates that the fibrinolytic pathway is in progress to breakdown fibrin clot. D-dimer levels will be raised in patients presenting with acute thrombus. The D-dimer test has high sensitivity but lacks specificity and a normal D-dimer level can be used to reject the diagnosis of PE in a patient with a low clinical probability of PE. However, due to the lack of specificity, a raised D-dimer level in isolation cannot confirm the presence of PE and further work up with computed tomography pulmonary angiography (CTPA) will be required in patients with a low or intermediate probability for PE and a raised D-dimer level. (7)

CTPA is the current gold standard for the diagnosis of PE. CTPA is reserved for patients with a high clinical probability of PE ("PE likely") or low or intermediate pretest probability ("PE unlikely") with a positive D-dimer. PE presents as a filling defect within the main pulmonary arteries, and/or their lobar, segmental or subsegmental branches on CTPA study.(4)(7)

Increased right ventricular to left ventricular ratio, flattening or bulging of the interventricular septum into the left ventricle and reflux of contrast into the IVC and hepatic veins are CTPA features of right ventricular strain. Right ventricular strain is associated with a poorer prognosis and poor outcome.(8)

3.3 COVID-19 pneumonia

The World Health organization named the disease caused by SARS-COV-2 as Coronavirus disease 2019 (COVID -19). On 30 January 2020, the World Health Organization (WHO) declared the COVID-19 epidemic as a public health emergency and on 11 of March 2020 it was declared a global pandemic.COVID-19 pneumonia has since spread globally. The first case of COVID-19 pneumonia in the African continent was reported in Egypt in February 2020.(9)

The route of transmission is thought to be spread mainly through droplets from the respiratory tract from an infected person to a non infected person. (9)The current gold standard for diagnosing SARS-COV-2 infection is through nucleic acid detection in nasal and throat swabs by real-time reverse transcriptase polymerase chain reaction (PCR). (10)

3.4 COVID-19 pneumonia and coagulation

Available evidence recommends baseline measurement of D-dimer level, platelet count and prothrombin time in patients with COVID-19 pneumonia.(11) D-dimer is the most noteworthy as it not only helps to identify patients at highest risk of VTE but also has the potential to predict outcome.(11)(12)(13) (14) One intensive care unit (ICU) study found that 95 % of patients had elevated D-dimer level on admission.(15) Elevated D-dimer concentration on admission and sudden worsening in clinical condition should raise the suspicion of PE and CTPA should be considered. (16)(17)
A retrospective study reported that D-dimer of < 1,0 ug/ml at baseline had a negative predictive value of 90 % for VTE and 98 % for PE. In contrast the risk of VTE is high when the baseline D-dimer level is > 3 ug/ml. (13)

Available data further suggests that COVID-19 associated coagulopathy is a low-grade disseminated intravascular coagulopathy (DIC) combined with localized pulmonary thrombotic microangiopathy. (17) Interestingly the DIC pattern appears to be different from the DIC pattern observed in sepsis where a more striking thrombocytopenia is appreciated. In addition , the D-dimer concentration is also higher in COVID-19 than observed in DIC secondary to sepsis.(17)(18)

Provoked risk factors such as patients that are bedbound, presence of vascular lines and unprovoked risk factors like advanced age, increase in BMI and underlying cardiovascular abnormalities further increased risk of VTE.(2)In light of the hypercoagulable state of patients with severe COVID-19 pneumonia and the increased risk of thrombosis demonstrated in recent literature, emerging evidence suggest that all hospitalized patients with COVID-19 pneumonia should receive prophylactic anticoagulation in the absence of contraindications. Unfractionated heparin could be used as an alternative.(11)(17)(19)

3.5 Association between COVID-19 pneumonia and VTE

The association between Influenza A H1N1 and risk of VTE has been described in the literature with one study reporting an increased risk of VTE up to 1 year after initial lower respiratory tract infection. (20,21)

An autopsy study on COVID - 19 patients revealed that 21% of patients at time of autopsy had PE.The study further described that the most common cause of death was pneumonia, followed by pulmonary artery emboli together with pneumonia. (22)

Recent studies suggested an alarmingly high incidence of VTE in patients admitted to ICU with severe COVID-19 pneumonia despite systemic anticoagulation, with PE reported as a common complication at an incidence of 16.7 % and 23 % reported in two ICU studies. (15)(19)(23) Another study reported a 22.5% incidence of VTE and 10% incidence of PE in non-ICU patients with COVID-19 pneumonia on thromboprophylaxis.(13) This highlights the need towards more effective anticoagulation treatment in COVID-19 positive patients. (13) One study found that half of the thromboembolic events were diagnosed within 24 hours of hospital admission, further highlighting the need for possible early initiation of therapeutic anticoagulation.(14) The exact incidence of PE in patients with COVID-19 pneumonia remains largely unknown.(16)

Peripheral PE was the most frequent anatomical location reported in the international literature. (24–27).

3.6 COVID 19 pneumonia and pregnancy

Pregnancy and post partum period in the general population is associated with increased risk of VTE and this is especially true in the immediate postpartum period.

The annual incidence of VTE in the pregnant population is estimated at 1 in 1200 pregnancies but is also related to age with lower incidence reported in patients younger than 35 years.(28)

Physiological changes associated with pregnancy, make the use of pretest probability score and D-dimer levels less reliable in pregnant and postpartum patients.

When it comes to imaging in pregnant patients the overall consensus remains that in pregnant patients with suspected PE the potential hazardous risk of ionizing radiation to the unborn fetus should be weighed up to the risk of missing a PE. The risk to the fetus versus benefit to the mother should be weighed up.

Both ventilation/perfusion (V/Q) scan and CTPA can be used in diagnosing PE in pregnant patients with both imaging modalities demonstrating similar doses of radiation to the unborn fetus. (29)

CTPA is more readily available and could potentially offer an alternative diagnosis in case where CTPA is negative for PE and is often regarded as the preferred choice of imaging to exclude PE, especially in hospitalised pregnant patients.

CTPA is the superior imaging modality in patients with abnormal chest radiographs as V/Q scan is less reliable in patients with abnormal chest radiographs.(29)

Literature review conducted by RM Czeresnia et al reports no difference in severity of COVID-19 infection or symptomatology in pregnant patients compared to the non-pregnant population. (30)

Review by Khan et al report no greater risk of maternal mortality among pregnant women compared to non pregnant women.

One study in their review had showed a higher rate of ICU admissions in pregnant women, compared to non-pregnant women, although symptomatology among both groups were similar. From the article it is not clear whether ICU admission was for COVID 19 complications or complication related to pregnancy.

Many of the studies included in the review, were limited by small sample sizes, again highlighting the need for larger studies in pregnant patients with COVID 19 pneumonia.(31)

Studies on PE in COVID 19 patients did not comment on pregnant patients or patients within the postpartum period. It is unclear whether pregnant patients were excluded from these studies or whether there were no pregnant patients in their respective study populations. (13) (14) (22)

There is paucity in the literature on the incidence and characteristics of PE in COVID 19 pregnant patients.

3.7 GSH anticoagulation protocol

In the absence of contra-indications all hospitalised COVID 19 patients admitted to Groote Schuur Hospital received either prophylactic or therapeutic doses of enoxaparin. As per the hospital anticoagulation protocol during the 1st COVID 19 wave, therapeutic anticoagulation doses were reserved for patients who required high flow oxygen or mechanical ventilation, a high index of suspicion for PE or DVT or a rising D-dimer level on serial D-dimer measurements or a single D-dimer level > 1.5 x the upper limit of normal(32)

3.8 The study in the context of the literature

A large number of the studies are limited by their retrospective nature and small sample size, and the majority of the studies focused only on patients with severe COVID-19 pneumonia admitted to ICU, where other risk factors could also contribute to risk of VTE. However, a strong association between COVID-19 pneumonia and VTE is described with surprisingly high incidence of VTE in patients on anticoagulation. This highlights the need for further research in this field as VTE and specifically PE can have devastating outcomes if left untreated.(16)

There is, however, paucity in the literature describing the incidence and characteristics of pulmonary emboli (PE) in COVID-19 in the African setting. Improved understanding of the presentation of COVID-19 associated PE in the South African setting is warranted, considering its serious and frequently fatal outcomes.
The aim of our study is to describe the incidence and characteristics of CTPA confirmed PE in patients with COVID-19 pneumonia admitted to a tertiary hospital in Cape Town. Information gained by this study can be invaluable and potentially help refine local hospital protocols.

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5 CHAPTER 2: FULL TEXT JOURNAL ARTICLE FOR SUBMISSION

A retrospective review of CTPA confirmed pulmonary emboli in COVID-19 patients admitted to Groote Schuur Hospital, Cape Town

1P. Ahlers, 2Q. Said-Hartley

1,2 Department of Radiology, Groote Schuur Hospital, University of Cape Town

6 Abstract

6.1 Background:

A high incidence of thromboembolic phenomena has been widely reported in patients with COVID-19 pneumonia. There is, however, a paucity of data detailing the incidence and characteristics of pulmonary emboli (PE) in COVID-19 patients in the South African setting. An improved understanding of the presentation and course of these patients is warranted, considering the serious and potentially fatal outcomes.

6.2 Objectives:

To describe the incidence and characteristics of PE confirmed by Computer Tomography Pulmonary Angiogram (CTPA) in patients with COVID-19 pneumonia admitted to a tertiary hospital in the Western Cape, South Africa.

6.3 Methods:

We performed a retrospective-, descriptive study of all adult patients with COVID-19 pneumonia confirmed by Polymerase Chain Reaction (PCR) undergoing CTPA for suspected PE while admitted to Groote Schuur Hospital. The study period was from 1 April 2020 to 30 September 2020.

6.4 Results:

Our study cohort consisted of 116 patients, 59% being female, of whom, 29% were pregnant or in the postpartum period. The median age for both genders combined was 49.5 years .The overall incidence of PE was 19 %, with 20 % in our subset of pregnant and postpartum patients. The majority (64%) of PE's were reported as being segmental in anatomical location.

6.5 Conclusion:

Our study cohort was noteworthy in including pregnant and postpartum patients. The overall incidence of PE was 19 % with no significant differences in demographics, comorbidities or D-dimer levels between patients with or without PE. The importance of a high clinical index of suspicion together with the role of CTPA in diagnosing PE in hospitalised COVID-19 patients is emphasised.

6.6 Keywords

COVID-19, Pulmonary emboli, Computer tomography pulmonary angiogram, South-Africa, anti-coagulation, pregnant, TB, HIV.

7 Introduction

The strong association between COVID-19 pneumonia and venous thromboembolism (VTE) has been well described. (19)(11)(17)VTE and, specifically pulmonary emboli (PE), can have devastating outcomes if left untreated. (2)

The hypercoagulable state of patients with severe COVID-19 pneumonia increases the risk of thrombosis.(17) Risk factors provoking VTE include bedbound patients, vascular lines, advanced age, high BMI and underlying cardiovascular abnormalities.(2)

Evidence suggests that all hospitalised patients with COVID-19 pneumonia should receive prophylactic anticoagulation in the absence of contraindications.(19)(11)(17)(16)

Yet a surprisingly high incidence persists despite concurrent anticoagulation, also highlighting the need for different and more effective anticoagulation (19)(23)(15)(13)

PE presents with non-specific signs and symptoms, making the diagnosis of PE clinically challenging.(2),(4),(7) This is particularly true in those with hypoxic COVID-19 pneumonia, where there is considerable overlap between the systemic and respiratory symptoms associated with COVID-19 and those of PE. (32)

An elevated D-dimer level on hospital admission and sudden worsening in clinical condition in patients with confirmed COVID-19 pneumonia should raise the suspicion of PE and CTPA should be considered.(17)(16)(32) CTPA remains the gold standard in diagnosis of PE. (4) (7)

8 Objective

To describe the incidence and characteristics of CTPA confirmed PE in patients with COVID-19 pneumonia admitted to a tertiary hospital in the Western Cape, South Africa.

9 Research method and study design

A retrospective-, descriptive single-centre study design was used. The study included all adult patients admitted to Groote Schuur Hospital from 1 April 2020 to 30 September 2020 with confirmed COVID-19 pneumonia who underwent CTPA scans.
This was defined by a positive reverse transcriptase polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). The indication for CTPA in all patients was suspected PE.

9.1 Data collection

Radiological images and reports on scans performed in the Department of Radiology at our institution are stored in the Picture Archiving and Communications System (PACS) database system.

A detailed search using query builder (Philips, xiris 8.3.16) database search tool was used to access all CTPA reports/images on the PACS system for the period Apr 2020-Sep 2020.
The search phrases "covid", "sars", "corona", "Cov 2","pui" and "PCR" were used to refine the search results.

The initial search results with these search phrases revealed 269 CTPA studies.
The study investigators manually filtered all 269 CTPA studies, and those patients with history of COVID-19 and confirmed positive RT-PCR SARS CoV-2 results were included in the search criteria.

CTPA studies with a history of "person under investigation" (PUI) for COVID-19 in the CTPA clinical request form were also included in the initial search.
All PUI patients with positive RT-PCR SARS CoV-2 results were re-classified as COVID-19 and included in the study. PUI patients with negative RT-PCR SARS CoV-2 were excluded.

Of the 269 studies, a total of 116 CTPA studies satisfied the search criteria and were included in the study.

All 116 cases either had a confirmed RT-PCR SARS CoV-2 result on the National Health Laboratory Service (NHLS) or a confirmed result documented on the CTPA clinical request form.

9.2 Imaging protocol and data interpretation

All CTPA studies were performed on the 160-slice Toshiba Aquillion PRIME (Tochigi, Japan) 160 Multidetector Computed Tomography (MDT) scanner.

All CTPA studies were performed with intravenous injection of 100 ml of intravenous contrast (Omnipaque 350), using bolus tracking technique. The CTPA acquisition was initiated once the contrast bolus in the pulmonary trunk reached a Hounsfield unit (HU) of 180.

The CTPA images were transferred to the PACS database for viewing in both soft tissue and lung window reconstructions.

All CTPA studies were either reported by a Radiology consultant or reported by Radiology registrar and the final report approved by Radiology consultant.
The final CTPA report was used to confirm the presence or absence of a PE.
PE was defined as a filling defect within the main pulmonary artery/arteries, and/or their lobar, segmental or subsegmental branches on the CTPA study.(4)(7)
The anatomical location (main, lobar, segmental, subsegmental) of the PE was documented. In the case of multiple PEs, the most proximal anatomical location was noted.

We further retrospectively collected data on patient demographics (age, gender), whether the patient was admitted to a general ward, high care or intensive care unit (ICU) and whether the patient had co-morbidities as recorded in the CTPA clinical request form.

The reported comorbidities included diabetes, hypertension, cardiovascular disease, dyslipidemia, pulmonary tuberculosis, other respiratory diseases, human immunodeficiency virus (HIV), malignancy and a history of deep vein thrombosis (DVT).

Only D-dimer levels performed within 3 days of the CTPA study were included in the study. In a case where more than one D-dimer level was performed, the D-dimer result closest to the date of CTPA study was recorded.

9.3 Hospital anticoagulation protocol

In the absence of contra-indications all patients in our cohort received either prophylactic or therapeutic doses of enoxaparin according to our hospital protocol.

As per hospital protocol at the time, therapeutic anticoagulation doses were reserved for patients who required high flow oxygen or mechanical ventilation, a high index of suspicion for PE or DVT, a rising D-dimer level on serial D-dimer measurements or a single D-dimer level > 1.5 x the upper limit of normal(32).

10 Ethical consideration

Ethical approval to conduct the study was obtained from the Faculty of Health Sciences Human Research Ethics of the university of Cape town. (HREC reference number:109/2021) and permission to conduct research obtained from Groote Schuur hospital.

11 Statistical Analysis

We recorded the incidence of CTPA confirmed PE in all patients with proven COVID-19 pneumonia with clinical suspicion for PE undergoing CTPA at tertiary hospital during the specified reporting period.

Furthermore, we investigated the association between demographic and clinical variables and CTPA confirmed PE in patients with COVID-19 pneumonia. The appropriate non-parametric tests were conducted where the data violated assumptions of normality. Mann-Whitney U tests were used to compare age and D-dimer levels between COVID-19 patients with and without PE. Chi-square tests investigated the association between PE (positive or negative) and gender, anatomical location of PE, whether the patient was admitted to ICU, high care or general ward, and whether the patient had comorbidities or not. Sub-analyses compared the female patients who were pregnant or within the postpartum period, versus those who were not pregnant.
Data was analysed using SPSS Version 27, with the significance level set at $p = 0.05$.

12 **Results**

Of the study cohort of 116 patients, 69 (59%) were female.
Of these, 18 (26%) were pregnant and 2 (3%) were in the postpartum period (Table1).
The median age for both genders was 49.5years (Table 1).
19% of patients undergoing CTPA for suspected PE had radiological confirmation of PE, with the majority (64%) reported as segmental in anatomical location.

The majority (85 %) of the patients in our study were admitted to general wards, with 13 % admitted to a high care unit and only 2% patients in (ICU).

The majority (71%) of patients in our cohort had comorbidities as tabulated in Table 2, with hypertension and diabetes being the two most common comorbidities.

72% of patients with confirmed PE had more than one or multiple comorbidities compared to 47% in the non-PE group.

There was no significant difference in demographic or clinical variables, including D-dimer levels between patients with and without PE (Table 3).

The incidence and characteristics of PE in the pregnant/postpartum and the non pregnant patients are tabulated in Table 4.

The pregnant and postpartum group was significantly younger compared to the non-pregnant females, and had fewer comorbidities. (Table 4)

Table 1: Clinical characteristics of cohort

	n =116	**PE (n=22)**	**Non PE (n=94)**	***p*-values**
Age (median, IQR)	49.5 (35 – 60)	53.5 (34.5-61)	49 (35-59)	0.585
Female (%, n)	59%, n = 69	63.6%, n = 14	58.5%, n = 55	0.659
*Patients-pregnant or postpartum period (%, n)	29 %, n = 20			
**D-dimer level (ug/ml, IQR, n)		1.05 (0.50-5.13), n = 14	0.61 (0.39-1.00) , n = 47	0.142
***Days between RT-PCR SARS CoV-2 test and CTPA (median, IQR)		13 (5-19), n = 21	17 (5-31), n = 85	0.297

Medians are reported with numbers in brackets indicating IQR's (interquartile range)
*18 patients were pregnant and 2 patients were within the immediate postpartum period
** D-dimer levels within 3 days of CTPA study
***In 10 patients the date of the RT-PCR SARS CoV-2test was not indicated on the CTPA request form

Table 2: Comorbidities

	n=116	PE (n=22)	Non PE (n=94)	p-values
Comorbidities (%,n)	71%, 82	82%, 18	68%, 64	0.311
Patients with more than one comorbidity	52%, 43	72%, 13	47%, 30	0.067
Diabetes	27	6	21	0.832
Hypertension	42	10	32	0.449
Cardiovascular	10	4	6	0.094
Dyslipidemia	6	1	5	1.00
Previous pulmonary Tuberculosis (PTB)	5	1	4	1.00
Active PTB	6	2	4	0.319
*Other respiratory diseases	6	2	4	0.319
HIV	22	6	16	0.423
Malignancy	4	0	4	1.00
DVT	3	1	2	0.471

*Other respiratory diseases include asthma, chronic obstructive pulmonary disease and sarcoidosis
DVT - Deep vein thrombosis
HIV - Human immunodeficiency virus

Table 3: PE characteristics for our cohort

	n = 116
PE on CTPA (%,n)	19 %, n = 22
Anatomical location of PE (%,n)	
Main	22.7%, n = 5
Lobar	13.6%, n = 3
Segmental	63.6%, n = 14
Admitted to Hospital (%,n)	
General ward	85.3%, n = 99
High care	12.9%, n = 15
ICU	1.7%, n = 2

Table 4: PE characteristics between pregnant, postpartum and non pregnant patients

	Pregnant / Postpartum (n= 20)	**Non pregnant (n = 49)**	***p*-value**
PE on CTPA	20%, n = 4	20.4 %, n = 10	0.969
Anatomical location of PE (%, n)			0.161
Main	0	30 %, n = 3	
Lobar	25 %, n = 1	0	
Segmental	75 %, n = 3	70 %, n = 7	
Admitted to Hospital (%, n)			0.126
General ward	100%, n = 20	81.6%, n = 40	
High care	0	16.3 %, n = 8	
ICU	0	2 %, n = 1	
Comorbidities(%, n)	50 %, n = 10	72.5 %, n = 40	0.008
Age (median, IQR)	30 (23.7-32.7)	55 (41-62)	< 0.001

13 Discussion

According to our knowledge this study is the first to describe the incidence and characteristics of PE confirmed on CTPA in hospitalised COVID-19 patients in South-Africa. The incidence, anatomcal location, patient demographics, d-dimer levels and time interval between RT-PCR test for SARS CoV-2 and CTPA study of patients with COVID-19 pneumonia undergoing CTPA for suspected PE at our institution are discussed. Our study cohort was unique as it included a subset of pregnant and postpartum patients.

The incidence of PE in hospitalised patients with COVID-19 pneumonia undergoing CTPA for clinical suspicion of PE at our institution was 19%. This is similar to the incidence of 23.9 % reported in a meta-analysis by R.Kwee et al.

Their pooled incidence included studies with similar study design to ours, as well as similar indications for CTPA and likewise only included studies with CTPA confirmed PE (27).

The pooled incidence of those admitted to general wards was 23.9 %, with a higher incidence (48.6%) of PE reported in patients admitted to ICU. (27)

Most of the patients in our cohort were admitted to general wards, with only 2 % admitted to the ICU. The General assumption was that patients with severe COVID-19 pneumonia were admitted to either high-care or ICU, leading us to postulate that the majority of our cohort had non-severe COVID-19 pneumonia.

Peripheral PE was the most frequent anatomical location reported in international studies. (24–27). Our study had similar findings, with segmental pulmonary emboli the most common anatomical location.

Interestingly, the mean age of our cohort was younger than reported in similar study population undergoing CTPA for suspected PE.(33,34)

We observed a female predominance, which further consisted of a small subset of young pregnant patients and patients within the postpartum period. This could potentially explain and partially account for the difference in age observed in our cohort compared to the other studies.

Not surprisingly the pregnant and postpartum group was significantly younger compared to the non-pregnant females and had less age-related comorbidities. Other study populations with similar study designs have not commented on pregnant or postpartum patients. It is unclear whether pregnant patients were excluded from these studies or whether there were no pregnant patients in their respective study populations. (27)(34)

Pregnancy and the post partum period in the general population are associated with increased risk of VTE, especially in the immediate postpartum period.(29)

However, there is a paucity of published work on the incidence and characteristics of PE in pregnant patients with COVID-19 pneumonia.

A literature review conducted by RM Czeresnia et al reported no difference in severity of COVID-19 infection or symptomatology in pregnant patients compared to the non-pregnant population. (30)

It is unclear whether, given the hypercoagulable state of pregnancy, COVID-19 pneumonia or interplay between these two entities could have contributed to PE in this subgroup of patients. Larger studies including postmortem studies would need to be conducted to comment on the true underlying pathophysiology.

The incidence of PE in our subset of pregnant and postpartum patients was 20%.

The mean D-dimer levels in our PE group were higher than in the non- PE group, but this was not statistically significant. No significant differences in demographic features or co-morbidities between patients with and without PE were found.

Our study found a median 13 day interval between positive RT-PCR results for SARS CoV-2 and the diagnosis of PE on CTPA. In a study by S.Meiler et al, the majority of PE's were detected on days 11-20 after symptom onset.(33)

In addition, a similar study to assess PE in COVID-19 patients undergoing CTPA reported a median 14 days duration of symptoms prior to CTPA. (34) This highlights the proposal for potentially using a lower threshold for requesting CTPA during the 2nd- and 3rd week of COVID 19 infection.

We did not collect information on delay between the onset of symptoms to the time of CTPA, and only reported on the number of days from RT-PCR Cov-2 test to CTPA. This precluded a direct comparison to above mentioned studies with the assumption that symptom onset most likely preceded the date of RT-PCR Cov-2 test. (33)(34)

Identifying a time period when patients are most at risk of developing PE during COVID-19 infection could alert the clinician to have a lower threshold to requesting a CTPA study. This information would be invaluable, especially in view of the clinical challenges created by symptom overlap between PE and severe COVID-19 pneumonia.

14 Study limitations

- Sample size was limited by the retrospective nature of the study.
- Caution should be taken regarding the true incidence of PE in hospitalised COVID-19 patients, as only patients who underwent CTPA for suspicion of PE were included. The incidence reported does not reflect the true incidence in all hospitalised COVID-19 patients.
- All patients included in the study received at least prophylactic anticoagulation, as per our institution guidelines at the time. However, no distinction was made between prophylactic or therapeutic doses, nor were exact doses included in the analysis.
- The small subset of pregnant and postpartum patients was included in our study. Larger studies are required to comment on the true incidence and characteristics of PE in COVID-19 pregnant and post-partum patients.
- We only included D-dimer levels performed within 3 days of the CTPA which resulted in a smaller sample size compared to our overall cohort. This was especially true for the non-PE group.
- We further acknowledge that D-dimer cut off levels used in non-pregnant population are not reliable in pregnancy.(29)

15 Conclusion

The incidence of PE in patients with COVID-19 pneumonia undergoing CTPA for suspected PE at our institution was 19% with majority of PE's reported as segmental in anatomical location.

Our study cohort was unique as it included subset of pregnant and postpartum patients.

We report no significant differences in demographic features, comorbidities or D-dimer levels between patients with and without PE.

Our observations highlight the importance of CTPA, together with high clinical index of suspicion, in diagnosing PE in hospitalised COVID-19 patients at our institution.

Larger multi-centre studies exploring characteristics of PE, together with laboratory markers and historical data to help identify a time interval during the course of COVID-19 infection when patients are most at risk of developing PE could help with clinical decision making and in refining local hospital protocols, especially in resource constrained settings.

16 Acknowledgements

The authors acknowledge the Radiology staff for all the support relating to data collection. Prof S. Beningfield for critical appraisal of the manuscript. M. Henry who conducted the statistical analysis.

17 Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

18 Authors contribution

P. Ahlers was the lead author, gathered the data and prepared the manuscript and Q. Said-Hartley supervised the project, edited and approved the final manuscript for submission.

19 Funding

No external funding was received for conducting of this research.

20 Data availability

Data is available from the authors upon reasonable request.

21 Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect official policy or that of our institution.

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23 Appendix A - South African Journal of Radiology Instructions to Authors

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of five paragraphs labelled Background, Objectives, Method, Results and Conclusion.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)
  Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.
  Research methods and design: This must address the following:
- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution’s name and permit numbers should be stated here.
  Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your

findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings. **Conclusion:** Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- **Competing interests:** This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.
- Author contributions: All authors must meet the criteria for authorship as outlined in the authorship policy and author contribution statement policies.
- **Funding:** Provide information on funding if relevant
- **Data availability**: All research articles are encouraged to have a data availability statement.
- **Disclaimer:** A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

24 Appendix C: GSH Research permission

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHResearch.Request@westerncape.gov.za

Dr Qonita Said-Hartley
RADIATION MEDICINE - RADIOLOGY

E-mail: qshartley@gmail.com / petri.ahlers@gmail.com

Dear Dr Said-Hartley,

RESEARCH PROJECT: Incidence of Pulmonary Emboli In Patients With COVID-19 Pneumonia Admitted To Tertiary Hospital, Cape Town, South Africa (MMed Dr Petri Ahlers)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 March 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACE Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) **Kindly submit a copy of the publication or report to this office on completion of the research.**
n) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
o) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 20 May 2021

C.C. Mr. L. Naidoo
Dr H. Aziz
Professor S. Moosa

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

25 Appendix Ethical Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 March 2021

HREC REF: 109/2021

Dr Q Said-Hartley
Department of Radiology
Email: qshartley@gmail.com
Student: petri.alhers@gmail.com

Dear Dr Said-Hartley

PROJECT TITLE: INCIDENCE OF PULMONARY EMBOLI IN PATIENTS WITH COVID-19 PNEUMONIA ADMITTED TO TERTIARY HOSPITAL, CAPE TOWN, SOUTH AFRICA. (MMED DEGREE – DR PETRI AHLERS)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 March 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Petri Ahlers will also be involved in this study.

Please quote the HREC REF 109/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

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