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COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY FINDINGS IN HIV POSITIVE PATIENTS REFERRED FOR SUSPECTED PULMONARY THROMBO-EMBOLIC DISEASE

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A dissertation in the fulfillment of the requirements for the degree of Master of Medicine in Radiology submitted on this date of:

____7 December 2021____

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Declaration by candidate:

I hereby declare that this research paper is my own original work and has not been submitted before to any other institution for assessment purposes.

I have acknowledged all sources and cited these in the reference section.

There are no conflicts of interest in creating this research paper.

This paper was prepared in a "submissible" format in line with the guidelines of the South African Journal of Radiology.

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The following people contributed as supervisors to the work undertaken by the candidate, Diane Wiese, student number 300284, as part of their research paper entitled "Computed tomography pulmonary angiography findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease" in fulfillment of the requirements for the degree of FC Rad Diag (SA) MMed.

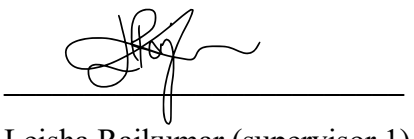
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- Supervisor 1: Leisha Rajkumar (20%)
- Supervisor 2: Susan Lucas (20%)

Contribution of work by supervisors and candidate for the above-mentioned research paper:

- The research paper is the original work of the candidate, Diane Wiese, who drafted the protocol and final research paper for this study.
- Supervisors reviewed draft manuscripts of the protocol and the final research paper and provided guidance regarding research methodology, improvements to content, general conduct, and conceptual ideas.
- This proposal and the research paper were submitted to Turnitin concerning plagiarism. The plagiarism certificates were checked and are satisfactory.

Signed on this day __03__ of ___December_____2021,



Leisha Rajkumar (supervisor 1)



Susan Lucas (supervisor 2)

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This study is dedicated to my wonderful parents.

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Computed tomography pulmonary angiography findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease.

Abstract:

Background: South Africa has a significant HIV burden, and imaging is commonly done as part of the workup for respiratory distress.

Objectives: To document the prevalence of pulmonary thrombo-embolic disease (PTED) and other findings in HIV positive patients referred for computed tomography pulmonary angiography (CTPA) for suspected PTED in a Johannesburg based academic hospital.

Method: 40 CTPA studies of documented HIV positive individuals investigated for suspected PTED during a one-year period were retrieved, anonymised and interpreted by three consultant radiologists. Inter-reader reliability was calculated using Free Marginal Kappa.

Results: A total of 14 out of 40 cases (35%) were positive for PTED. In the PE positive group: 57.14% had peripheral disease and 42.86% had both peripheral and central disease. The most common findings in the PE positive cases were as follows: pulmonary infarcts (17.5%), mosaic attenuation (17.5%), linear atelectasis (7.5%). The most common incidental findings were as follows: solid pulmonary nodules (52.5%), non-wedge-shaped consolidation (45%), cardiomegaly (52.5%), enlarged intra-thoracic lymph nodes (52.5%). Thirty percent of patients had findings related directly to the presence of PTED while most cases in the study (77.5%) had pulmonary findings not related to PTED. In the PE-negative cases, 55% had emergent findings that warranted immediate or urgent medical attention.

Conclusion: CTPA imaging is critical for diagnosing PE, with our study echoing imaging findings of other studies in the literature. However, further investigation into judicious

application of CTPA is required, as CTPA findings in the majority of cases in our study were not related to PE.

Introduction

Causes of respiratory distress in the population affected by human immunodeficiency virus (HIV) are multiple and many pathologies encountered share signs and symptoms of pulmonary embolism (PE). In our clinical setting computed tomography pulmonary angiography (CTPA) is frequently requested in the workup of respiratory distress in these individuals to exclude PE. HIV has been reported to increase venous thrombo-embolism (VTE) risk by two to ten folds, with a frequency reaching up to seven point six percent per year.[1] In Johannesburg South Africa, a retrospective study showed HIV to be the commonest associated risk factor for VTE.[2] The general prevalence of PE is estimated as 600 000 cases per year in the United States,[3] and ranges between 0.14 – 61.5% in medical patients in different African countries.[4] Mortality is largely preventable, thus diagnosis of PE in hospitalised patients remains paramount to patient care and outcomes. Paradoxically, studies of CTPA findings for suspected PE have also demonstrated that many alternate findings did not provide a strong rationale for its increased use.[5, 6] A study in Brazil in 2016 revealed a significant proportion of patients who had undergone CTPA for suspected PE had alternate findings compatible with an alternate diagnosis.[7] This is a relevant consideration for resource-poor settings such as that of South Africa. Our study aimed to document the CT findings and determine the CTPA prevalence of PTED in this population group, given that limited data on this exists in current literature and CTPAs are frequently ordered for the workup of respiratory distress in these individuals which contribute further to the currently overloaded healthcare system.

Methods

A cross-sectional, retrospective, descriptive study was carried out in the Department of Radiology at Helen Joseph hospital in Johannesburg. All adult HIV positive patients who had undergone a CTPA for suspected PTED during the study period (01 January – 31 December

2018) were considered for inclusion in the study. CTPA records with inaccessible digital imaging or request forms with illegible information were excluded. Patient demographics and presenting symptoms were collected from the CTPA request forms. HIV status was collected from request forms and/or the National Health Laboratory Service (NHLS) database. Patient identifiers were removed from the CTPA studies using anonymisation software. Patients in the study were scanned on a Phillips 16 slice CT scanner. 100ml Omnipaque 350 was injected via 18G or 20G intravenous cannulas in the antecubital fossa, using an automated pressure injector at a rate of four millilitres per second followed immediately by fifty millilitres saline bolus chaser.

The anonymised studies were reviewed by three radiologists (readers), each with experience exceeding four years. Readers assessed 15 criteria via questionnaire-format tick sheets for each CTPA study on Research Electronic Data Capture (REDCap). Findings were classified as pulmonary, parenchymal, cardiac, pleural, extra-thoracic and other intra-thoracic findings as detailed in Table 1. CTPAs were classified as PE-positive by a reader based on presence of pulmonary artery filling defects and determined overall to be PE positive if two out of the three readers agreed it was positive. Frequencies and percentages were logged for all findings present using SAS 9.2 statistical software (Tables 2, 3 and 4). Inter-rater reliability (using Randolph's Free Marginal multi-rater Kappa) was utilised to investigate the level of agreement between the three readers. A total of 241 CTPAs were identified for the study period of which: 179 were excluded based on negative or unknown HIV status; 2 due to illegible request forms and 20 due to irretrievable digital images. The final analytical sample consisted of 40 patients.

Ethical consideration

Ethical approval was acquired from the Wits Human Research Ethics Committee (HREC) – Approval no. M200256.

Results

Our study showed that 14 out of the 40 patients (35%) who underwent CTPA had PTED. The

95 percent confidence interval for this population proportion was between 20.63% and 51.58%. The mean and median age of cases overall were 39 and 38 years in the males, and 42 and 37 years in the females, respectively. Mean and median age of PE-positive cases were 40 and 42 years in the males, and 38 and 37 years in the females, respectively. Our study had a higher frequency of females compared to males with a total of 27 females overall (67.5%). Of the 14 PE-positive cases, nine (64.3%) were females. The major presenting symptoms included: shortness of breath (29.85%), chest pain (8.23%), cough (11.8%) and hemoptysis (8.8%).

Table 2 provides a detailed summary of the CTPA findings documented in the PE positive cases. In the PE positive group: 57.14% had peripheral disease and 42.86% had both peripheral and central disease. The right lower lobe was the most frequently affected (20%), with even distributions throughout the rest of the lung lobes (12.5%). Two of the 14 patients with PE had a saddle embolus (Figure 1 a). Fifty-seven percent of cases had a pleural effusion. Twenty seven percent had features of right heart strain with 22.5% having an RV:LV ratio >1. The most common parenchymal findings in this group were as follows: pulmonary infarcts (17.5%), mosaic attenuation (17.5%) and linear atelectasis (7.5%). A positive case of PE with parenchymal and pleural complications is seen in Figure 1 b. A complete list of the incidental findings on CTPA are summarized in Table 3 with examples of pulmonary findings in PE-negative cases illustrated in Figure 2. The most common parenchymal findings were as follows: solid pulmonary nodules (52.5%), non-wedge-shaped consolidation (45%) (Figure 2 a – c), emphysematous changes (17.5%) (Figure 2 d) and lung cavities (10%) (Figure 2 e – f). Pleural effusion was also seen in 17% of PE-negative studies (example shown in Figure 3). One patient in the study had a pneumothorax (Figure 4). The most common incidental cardiac finding was cardiomegaly (52.5%). Various examples of extra-pulmonary incidental findings are demonstrated in Figure 5 including a case of extensive pneumobilia (Figure 5 b) and a patient found to have multiple rib fractures (Figure 5 c). The most common other intra-thoracic finding was enlarged mediastinal/hilar lymph nodes without significant mass effect (52.5%), while seven point five percent had an esophageal abnormality (Figure 5 a). The most common extra-thoracic finding was a hiatus hernia (7.5%). Readers were 86.67% agreeable that of the PE-negative patients in the study, 55% had emergent findings that warranted immediate/urgent medical attention (Table 4). Our study concluded that 30% of the patients had findings related

directly to the presence of PE and 77.5% of the patients in the study (both those with and without PE) had pulmonary findings unrelated to PE (Table 4). In terms of inter-rater reliability, the readers had a "good-to-excellent" overall agreement with Kappa exceeding 0.60. Specifically, for 12 out of the 15 criteria assessed, the readers had an excellent overall agreement with Kappa exceeding 0.75.

Discussion

South Africa has one of the highest HIV burdens worldwide. Statistics South Africa indicates the estimated total population infected with HIV in 2020 to be 13% with a steady increase of cases (from 3.8 million in 2002 to 7.8 million in 2020).[8] One-fifth of those affected are females in their reproductive ages (15 – 49 years).[8] A lowered immune system renders these individuals susceptible to a myriad of typical and atypical diseases including bacterial pneumonias, mycobacterium tuberculosis (TB), pneumocystis pneumonia (PCP), malignancies and PE among others.[1] Pathology encountered on imaging was therefore expected to be severe or atypical and indeed, this study demonstrated many cases of such. Figure 2 (c and f) illustrate diffuse ground glass opacities and cavitatory disease with tree-in-bud nodules respectively – imaging findings seen commonly in patients affected by atypical fungal infections such as PCP and atypical mycobacterium such as TB.

In terms of demographics, most patients with PE in our study were female, consistent with literature on HIV negative patients. [5-7, 9, 10] Average age in males and females with PE ranged from 38 – 42 years. This is younger than studies done on HIV negative patients which ranged from 67 – 62 years, [5-7, 9] and in keeping with literature on HIV positive patients where the mean ages ranged from 40 – 45 years. [2, 3, 11-13]

Presenting symptoms in our study were typical of that described in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) trial including: shortness of breath, syncope, chest pain and haemoptysis – all of which are non-specific.[14]

The CTPA prevalence of PE in our study was 35%. This is similar to the CTPA prevalence found in other studies conducted in South Africa.[3, 12, 13] The HIV prevalence in those with PE in these other studies ranged from 37% [13] to 67% [12]. Literature on the prevalence of PE in the general population in other countries are much lower ranging from 9.5 – 24.6%.[5-7, 9, 10] This contrast shows that CTPA's are indeed a relevant investigation in respiratory distress in HIV-positive patients.

PTED is commonly described as being 'central' or 'peripheral' in terms of location. Some studies on the impact on long-term survival or prognosis of central vs. peripheral disease have associated central PTED with shortened survival and poorer prognosis.[15, 16] A study carried out in China by Zhu et al in 2012 assessed specifically the anatomic distribution of emboli on CTPAs in patients with suspected PE, and demonstrated the central and peripheral (mixed) pattern to be 55.6% and peripheral pattern at 40.9%.[17] Our study demonstrated more patients in the peripheral pattern (57.14%) compared to the mixed pattern (42.86%). Zhu et al also demonstrated that the right lung was more affected than the left and lower lobes affected more than upper lobes.[17] This was echoed in a South African study, where lower lobes were also more commonly affected compared to upper lobes in HIV positive patients.[12] Our study demonstrated the RLL to be most affected (20%) with a near even distribution of PE within the other lobes (Table 2).

Fifty-seven percent of the PE positive cases in our study had a pleural effusion. This is higher than Sharma et al's [10] study (25.8%) which did not include patient's HIV status and also higher than the Ramlakhan et al [12] study (45%) for their HIV positive group. Most common parenchymal findings in our PE positive group were pulmonary infarcts and mosaic attenuation (17.5% each) which is also comparable to other studies done on both HIV affected and unaffected populations.[7, 10, 12] These findings are traditionally thought to be due to PE.

The presence of right heart strain which is measured on CT by calculating the ratio of the right ventricle to left ventricle diameters (RV:LV ratio) is an important marker of PE severity that affects outcomes and mortality. [18] Our study demonstrated an increased RV:LV ratio in nine out of the fourteen PE positive patients (22.5%). In terms of general mortality from PE, a

systematic review by Danwang et al [4] found the mortality rate of PE to be substantially higher in African countries (40 -69% in medical patients, and case-fatality rate of 60% after surgery) than those reported in more developed countries such as the United States. Outside of Africa, thirty-day mortality rates from PE are reported to vary between six point seven to eleven percent and as high as 30% if not treated.[7] This is a crucial reminder of the importance of diagnosing and treating PE timelessly.

While our PE findings did not deviate substantially from the reported literature on general populations, the incidental findings in our study were quite varied and many were significant. Most of the cases in our study (77.5%) had abnormal lung parenchymal findings unrelated to PE, consistent with other literature.[7, 9, 10, 12, 19]

Of note, our data demonstrated that of the 26 PE negative cases, 55% had emergent findings that warranted urgent medical attention (Table 4). This is significantly higher compared to other studies.[6, 7, 9] It is suspected that the severity of lung changes encountered in our study is likely to have been more extensive compared to that seen in studies done on HIV negative populations. Previous studies in general populations demonstrated lower percentages of major findings in PE negative scans,[6, 7, 9] although our study was limited in having a smaller sample size and also our study comprised only of HIV positive individuals.

The prevalence of non-wedge-shaped consolidation in our study (45%) was higher than similar studies done by Ferreira et al [7] and Sharma et al [10] (21.5% and 25% respectively). The latter two studies [7, 10] examined incidental findings on CTPA for suspected PE in general populations (not HIV specific) which may account for the differences seen. Our study did however have a lower prevalence of non-wedge-shaped consolidation (45% compared to 68%) than that seen in a study by Ramlakhan et al which was undertaken in the Western Cape in a region known with a high TB prevalence.[12] Only one case in our study was rated normal (2.5%) with no alternate findings which is lower than that seen in other studies.[16]

While some findings did not require immediate medical attention, they were still significant in that their presence would have likely resulted in further workup or follow-up for the patient

e.g., such as in the case demonstrated in Figure 5 a.

Obvious limitations exist in our present study. Due to its retrospective nature and small sample size, our study was mainly descriptive.

Our data demonstrated extensive pulmonary pathology on CTPA, the majority of which seemed likely to have been detectable on chest radiographs. Consideration for a future study would be to compare the chest radiograph findings in HIV positive patients referred for suspected PE to their CTPA findings to correlate if findings on initial radiographs and CTPAs lead to markedly different diagnoses and whether this affects the treatment outcome in any significant way. Evidence for this would prove monumentally valuable to clinical decision making for those working in the healthcare setting in South Africa, known with high resource limitations.

Conclusion

The prevalence of PE in our study was 35%. However, 77.5% had pulmonary findings not related to PE, and 55% of the PE-negative cases demonstrated findings requiring urgent medical attention. This suggests that although PE is a cause of respiratory distress in HIV-positive patients and CTPA imaging is warranted where clinically relevant, further investigations into prudent use and the efficacy of PE-risk determining scores should be done with regard to the request of CTPAs. This study illustrates that HIV positive patients presenting with symptoms of respiratory distress are not always straight forward PE cases with a multitude of other important pathologies incidentally encountered on CTPA imaging. While there is an obvious benefit to detecting a variety of emergent conditions on CTPA, further investigation into whether such conditions found in this study could be determined on other appropriate investigations such as chest radiographs, abdominal imaging etc., will also be of value in curbing the widespread application of CTPAs.

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Competing interests

The authors declare that they have no conflict of interest in the article.

Author (s) contributions

SL and RL conceived the original idea and supervised the project. DW developed the study design, data collection and analysis. DW took the lead in writing the manuscript with RL and SL supervising and contributing to the final version submitted.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author, DW, upon reasonable request.

Disclaimer

Views expressed in this submitted article are the authors own and not an official position of the institute.

Keywords used in this article:

CTPA; HIV; pulmonary embolism; imaging; findings; radiological; prevalence.

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Appendix 1: Tables with legends

Table 1: Description of terms

Term:	**Description/defined as:**
Parenchymal	Findings limited to lung parenchyma excluding pulmonary vessels and lymph nodes
Pleural	Findings limited to visceral and parietal pleura
Cardiac	Findings limited to heart and pericardium
RV:LV	Presence of right heart strain recorded as present if value exceeded 1[18]
MAP: AA	PAH recorded as present if value exceeded 1.1 [20]
Extra-thoracic	Findings included soft tissue, visceral, bone and nodal findings above the thoracic inlet or below the diaphragm
Other Intra-thoracic	Findings included abnormalities of mediastinal/hilar lymph nodes, oesophagus, bronchial arteries, and anterior mediastinum
Emergent findings	Recorded as present if findings other than PE were present on the study that the reader deemed severe enough to cause respiratory distress that would warrant urgent or immediate medical attention. Examples provided in the tick sheet included: pneumothorax, massive pleural effusion, extensive consolidation, cardiac failure, significant pericardial effusion, aortic dissection, hemorrhaging aneurysm, massive ascites, severe abdominal disease, tracheal or central bronchial obstruction)

Source: Authors' own work

RV:LV, right ventricle to left ventricle ratio; MPA:AA, ratio of main pulmonary artery diameter to ascending aorta diameter; PAH, pulmonary arterial hypertension.

Table 2: CTPA findings in PE positive cases

PE POSITIVE FINDINGS:		**Frequency**	**Percentage**
Pattern of involvement	peripheral	8	57.14
	Central and peripheral	6	42.86
Lobe affected	RUL	5	12.50
	RML	5	12.50
	RLL	8	20.00
	LUL	5	12.50
	LLL	5	12.50
	All (saddle embolus)	2	5.00
Parenchymal findings	pulmonary infarct	7	17.50
	mosaic attenuation	7	17.50
	linear atelectasis	3	7.00
Presence of Pleural effusion		8	57.14
Presence of right heart strain (RV:LV > 1)		9	22.50
Evidence of PAH (MPA: AA > 1.1)		7	50.00

Source: Authors' own work

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe;

LUL, left upper lobe; LLL, left lower lobe; RV:LV, ratio of right ventricular diameter to left

Ventricular diameter; PAH, pulmonary arterial hypertension;

MPA:AA, ratio of main pulmonary artery diameter to ascending aorta diameter.

CI, confidence interval. Percentage (%), Frequency (n).

Table 3: Incidental findings on CTPAs for HIV positive patients referred for suspected pulmonary thrombo-embolic disease

INCIDENTAL FINDINGS:		**Frequency**	**Percentage**
Parenchymal	non-wedge-shaped consolidation	18	45.00
	Solid pulmonary nodules (> 3 mm)	21	52.50
	Sub-solid pulmonary nodules (> 6 mm)	3	7.50
	Ground-glass opacities	8	20.00
	Emphysematous changes	7	17.50
	Lung cavities	4	10.00
	Lung cysts	2	5.00
	Tree-in-bud	1	2.50
	Pulmonary mass/es	1	2.50
Pleural	Pleural effusion in absence of PE	7	17.50
	Apical pleural thickening	2	5.00
	Pneumothorax	1	2.50
Cardiac	Cardiomegaly	21	52.50
	Pericardial effusion	1	2.50
Other Intra-thoracic	Adenopathy without significant mass effect	21	52.50
	Adenopathy with significant mass effect	2	5.00
	Esophageal Abnormality (thickening/dilatation)	3	7.50
Extra-thoracic	Hiatus hernia	3	7.50
	Massive ascites	2	5.00
	Benign abdominal visceral lesion/s	2	5.00
	Acute severe abdominal pathology[ǂ]	1	2.50
	Vertebral or rib fractures	2	5.00
	Vertebral or rib lesions suspicious for metastases	1	2.50
	Breast mass suspicious for neoplasm	1	2.50
	Significant but discrete axillary/supraclavicular nodes	2	5.00
	Intra-abdominal nodal masses	1	2.50

Source: Author's own work

PE, pulmonary embolus. Frequency (n), Percentage (%).

[ǂ] demonstrated extensive pneumobilia.

Table 4: Frequency and percentages for presence of emergent findings and study impression

		Frequency	Percentage
Emergent findings present		22	55
Study Impression	Findings related to presence of PE	12	30
	Pulmonary findings not related to PE	31	77.5
	Cardiac findings not related to PE	4	10
	Other significant intra-thoracic findings (mediastinal/nodal/esophageal) not related to PE	2	5
	Extra-thoracic significant findings	1	2.5
	Normal study	1	2.5

Source: Author's own work

PE, pulmonary embolus. Frequency (n), Percentage (%).

Appendix 2: Figures with legends

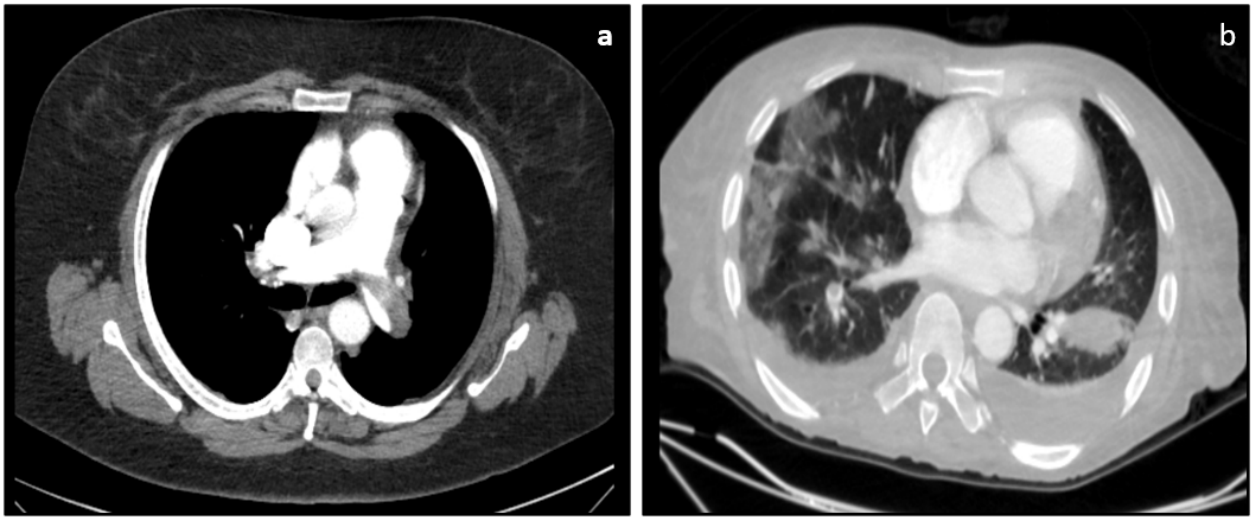


Figure 1: CT axial slices of two different patients with pulmonary embolism. (**a**) Demonstrating a large saddle embolus; (**b**) demonstrates a filling defect in the right descending pulmonary artery complicated by bilateral pleural effusions, peripheral consolidations and wedge-shaped pulmonary infarct on the left.

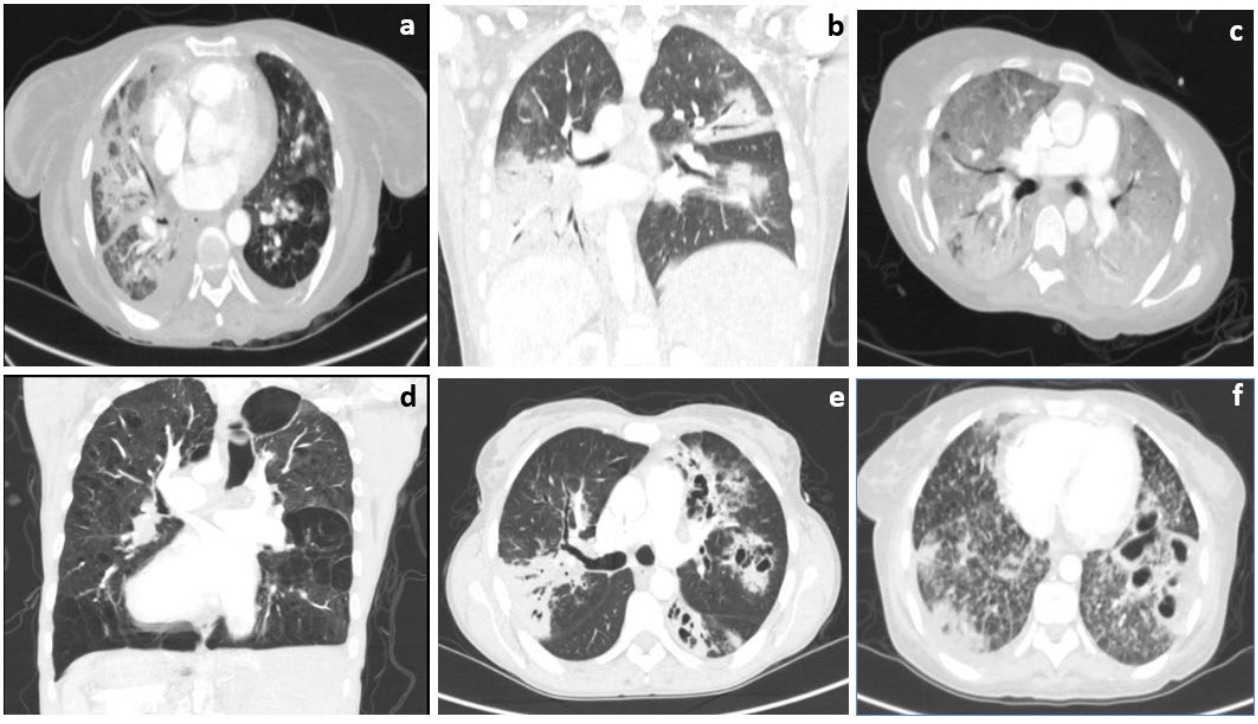


Figure 2: Axial (**a, c, e, f**) and coronal (**b, d**) CT slices of incidental parenchymal findings in patients without PE. (**a – c**) Demonstrate extensive consolidations in three different patients; (**d**) diffuse emphysema; (**e**) cavitatory multi-lobar pneumonia; (**f**) Left lower lobe lung cavitations with superimposed background bilateral tree-in-bud nodules in a patient with pulmonary tuberculosis.

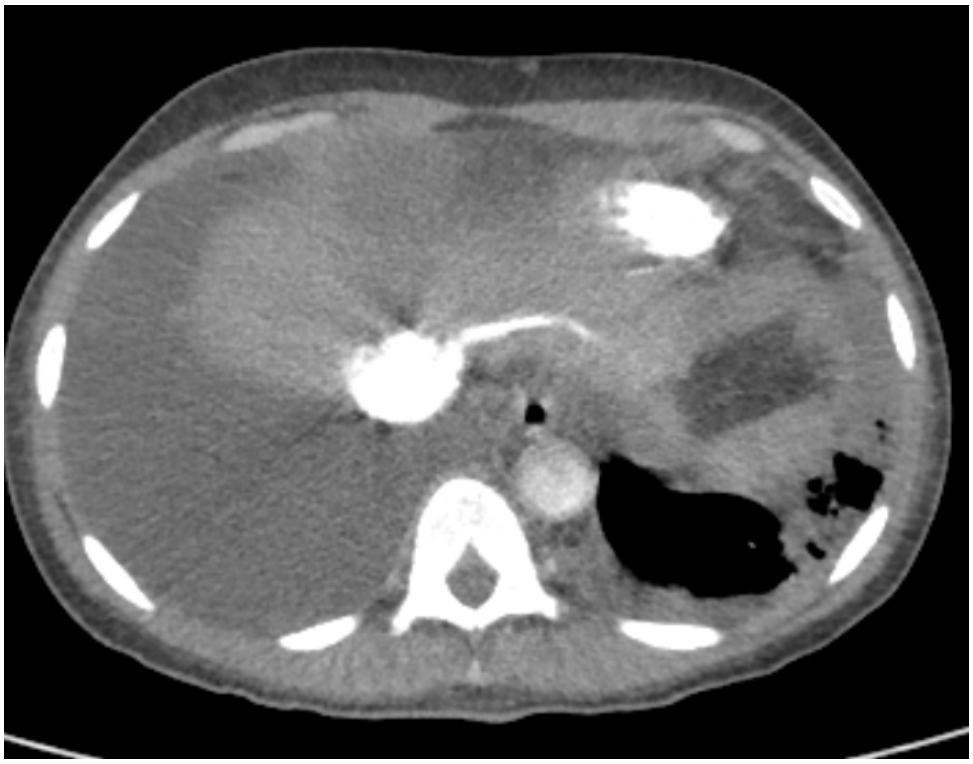


Figure 3: Axial CT of a patient with a large right and smaller left pleural effusions

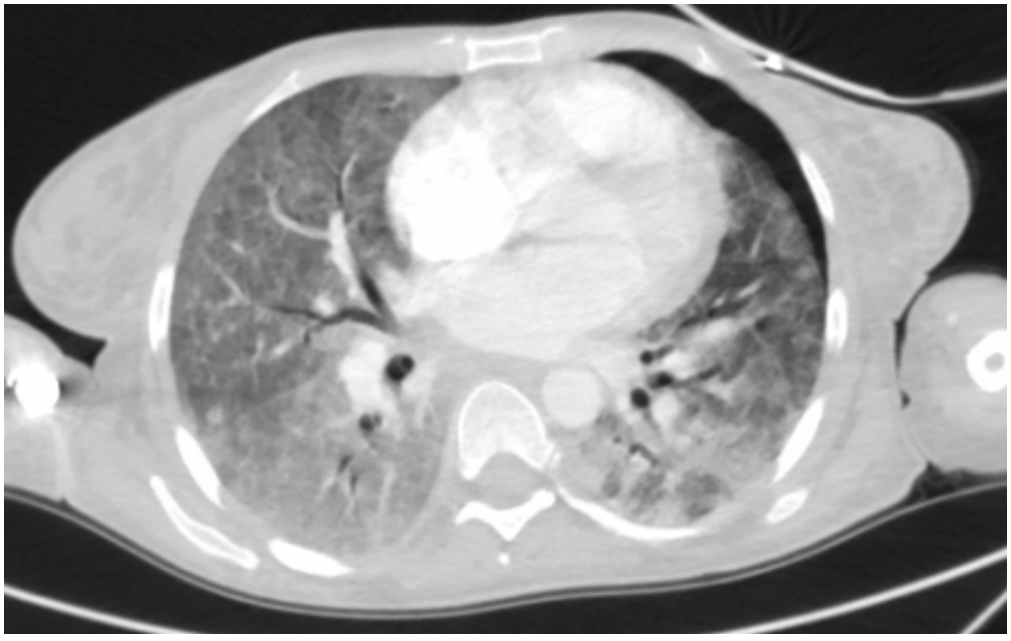


Figure 4: Left pneumothorax, extensive ground-glass opacities, and posterior consolidations in a patient with respiratory distress.

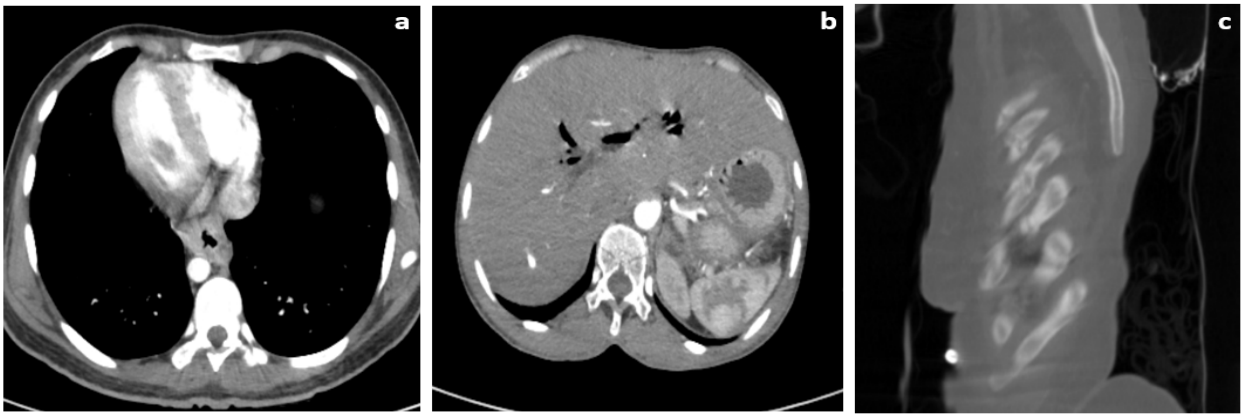


Figure 5: Axial (**a, b**) and sagittal (**c**) CT images of incidental extra-pulmonary findings in three PE-negative patients. (**a**) Demonstrates a patient with circumferential lower esophageal wall thickening; (**b**) extensive pneumobilia in a post-surgical patient; (**c**) patient with multiple chronic rib fractures.

Appendix 3: Ethical clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Diane Wiese

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200256

NAME: (**Principal Investigator**)	Dr Diane Wiese
DEPARTMENT:	Radiology Helen Joseph Hospital
PROJECT TITLE:	Computed tomography pulmonary angiography findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease
DATE CONSIDERED:	28/02/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Leisha Rajkumar and Dr Susan Lucas
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/06/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 01/07/2020

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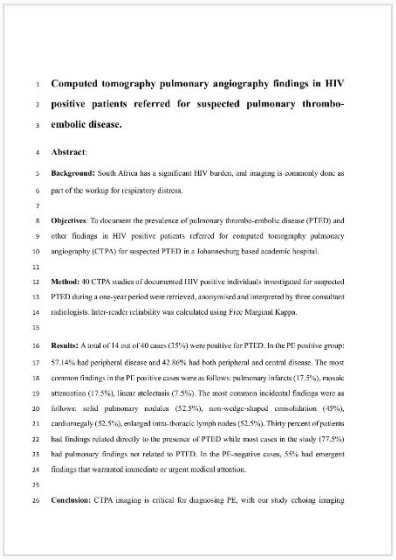
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Computed tomography pulmonary angiography findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease.

Abstract:

Background: South Africa has a significant HIV burden, and imaging is commonly done as part of the workup for respiratory distress.

Objectives: To document the prevalence of pulmonary thrombo-embolic disease (PTED) and other findings in HIV positive patients referred for computed tomography pulmonary angiography (CTPA) for suspected PTED in a Johannesburg based academic hospital.

Method: 40 CTPA studies of documented HIV positive individuals investigated for suspected PTED during a one-year period were retrieved, anonymised and interpreted by three consultant radiologists. Inter-reader reliability was calculated using Free Marginal Kappa.

Results: A total of 14 out of 40 cases (35%) were positive for PTED. In the PE positive group: 57.14% had peripheral disease and 42.86% had both peripheral and central disease. The most common findings in the PE positive cases were as follows: pulmonary infarcts (17.5%), mosaic attenuation (17.5%), linear atelectasis (7.5%). The most common incidental findings were as follows: solid pulmonary nodules (52.5%), non-wedge-shaped consolidation (45%), cardiomegaly (52.5%), enlarged intra-thoracic lymph nodes (52.5%). Thirty percent of patients had findings related directly to the presence of PTED while most cases in the study (77.5%) had pulmonary findings not related to PTED. In the PE-negative cases, 55% had emergent findings that warranted immediate or urgent medical attention.

Conclusion: CTPA imaging is critical for diagnosing PE, with our study echoing imaging

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Appendix 5: Original protocol with updated literature review

CTPA findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease

Diane Wiese

Student number: 300284

Course registered for: MMed (RadD)

Supervisors

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1. Rationale

The aim of this study is to document the CT findings in HIV positive patients referred for CTPA for suspected pulmonary embolism (PE). Findings from this study may be beneficial in future reviews of the adequacy of clinical and scoring criteria regarding assessment of HIV positive patients for PE (as current scoring systems do not consider HIV status of the individual).

2. Introduction

2.1. Venous Thromboembolic disease and Pulmonary Embolism

Venous thromboembolism (VTE) is the third major contributor to cardiovascular disease globally (1, 2). On the spectrum of VTE disease which ranges from deep vein thrombosis (DVT) to Pulmonary embolism (PE), PE is widely accepted as the most devastating sequelae (3) and is a significant concern in hospitalized patients as mortality is largely preventable (4).

2.1.1. Workup Recommendations for suspected PE

Signs and symptoms of PE are non-specific therefore validated clinical decision rules (CDRs) such as the Wells Score or the Revised Geneva Score are used to ascertain the pre-test probability of an individual having a PE(5). In our setting, the Wells Score is more commonly used (see Table 1 below).

Table 1: Wells Score

Criteria (6)	**Point awarded**
Clinical signs + symptoms of a DVT	3
History of PE or DVT	1.5
Immobolisation (more than or equal to three days) or recent operation (less than four weeks)	1.5
Malignancy	1
Haemoptysis	1
Tachycardia (heart rate more than 100)	1.5
Most likely diagnosis is PE; no alternative diagnosis better explaining the symptoms	3

Points are awarded for each criterion met to make up the final Wells Score. Two classification systems exist, a three-tier and a two-tier model. The three-tier model subdivides it into low (0 – 1 point), moderate (2 – 6 points) and high risk (>6 points). The more commonly used two-tier model (which is used in our setting) classifies the pre-test probability as either "PE-unlikely" if points $\leq$ 4 or "PE-likely" if points > 4 (6). Patient's referred for imaging will be those with high scores (>4) or those with low scores but positive D-dimer values (5). D-dimer is a blood marker with a high negative predictive value for VTE, i.e. if the D-dimer value is normal, it precludes the need for further imaging (5). However, increased D-dimer levels are non-specific and may not be useful in the hospital/inpatient setting as many other conditions (e.g. infection, cardiac failure, malignancy and pregnancy) may increase its levels (7). CTPA remains the current gold standard of imaging in suspected PE (5).

Although the Wells Score is an accepted and safe CDR, some controversy exists on the subjective criterion in the Wells Score – the "PE most likely diagnosis with no alternative diagnosis better explaining the symptoms" – a factor that readily lends itself to bias. A study done by the University of Arizona showed significant incongruence between how clinicians determined pre-test probability based on their gestalt versus what they scored on the subjective component of Wells (8).

Whether the differences were secondary to cognitive dissonance or if clinicians intentionally allocated values that would support the diagnostic pathway they favoured is

unknown (8). It is also relevant to note that neither the Wells Score nor the Revised Geneva Score consider a patient's HIV status.

In the Western Cape of South Africa, Bulajic et al (2019) conducted a retrospective study involving a review of the clinical presentation and workup of patients who had undergone a CTPA for suspected PE (9). In their study of 127 patients, they found that CDR scores were poorly documented (Wells Score was documented in only 13% and the Revised Geneva Score was not documented at all) (9). The Revised Geneva Score was retrospectively calculated and found to poorly correlate with CTPA results (9). This study found the CDR score unhelpful in predicting PE in a population with high HIV and TB prevalence (9).

Although not part of standard clinical practice, scoring systems for calculating clot burden and PE severity are available and include the PE Severity Score and Qanadli Score (5).

In terms of the actual symptoms of PE described in the literature, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) trial determined most patients with PE had presented with at least one out of four symptoms that included: sudden breathlessness, chest pain, syncope or haemoptysis (10).

2.1.2 CTPA Findings of PE

PE is diagnosed as intraluminal filling defects within the pulmonary arterial vasculature (5). An acute embolus is described to form an acute angle relative to the vessel wall whilst a chronic embolus will form an obtuse or flattened angle (11). Occluded vessels may be enlarged in the acute setting whilst abrupt vessel narrowing, cut-off, vessel recanalisation, intraluminal bands and webs have been described in the chronic setting (1, 5, 12). Parenchymal changes seen include pulmonary infarcts (wedge-shaped pleural based opacities), focal ground glass attenuation, mosaic perfusion (areas of low attenuation in affected areas), linear atelectasis, and in the chronic setting, bronchial artery dilatation.

Acute or chronic pulmonary thromboembolic disease may cause right ventricular dysfunction as a complication (5). CT signs of right heart dysfunction include the following: a right ventricle (RV) to left ventricle (LV) ratio of >1 on axial plane or >0.9 on four-chamber reconstruction, interventricular septal bowing or flattening, and contrast regurgitation into the IVC and hepatic veins (13). A RV:LV ratio of > 1.5 has been show to correlate with severe

PE (13). Pulmonary arterial hypertension may arise as a sequela of chronic thromboembolic disease (11). Ratio of main pulmonary artery diameter to ascending aorta diameter (MAP:AA) exceeding 1.1 has been found to correlate with pulmonary arterial hypertension measured on CT (14).

2.1.3. Risk Factors

Risk factors for the development of venous thrombo-embolism are broad and multi-factorial but the general principle revolves around factors which affect Virchow's Triad of: amplified coagulability, stasis, and insult to the endothelial lining of blood vessels (15). Prolonged immobilisation, malignancy, operation, oral contraceptive pills, and the peri-partum period are some of the well-recognized risk factors (2). HIV is also a known risk factor for venous thrombo-embolism as elaborated in section 2.2.

2.1.4. PE globally

The prevalence of PE is estimated as 600 000 cases per year in the United States (4) and ranges between 0.14 – 61.5% in medical patients in different African countries (2)

Outside of Africa, thirty-day mortality rates from PE is reported to vary between "6.7 – 11%" and as high as 30% if not treated(16).

Danwang et al (2017) carried out a systematic review in Africa which found the mortality rate of PE to be substantially higher than those reported in more developed countries such as the United States (40 -69% in medical patients, and case-fatality rate of 60% after surgery) (2).

2.1.5. PE in South Africa

In South Africa the prevalence of PE is not known (4, 17), however a previous autopsy series done in Cape Town revealed it to be the 3rd commonest cause of female natural death (18).

2.2. HIV

HIV on its own has been recognised as an independent risk factor for VTE (19) with frequency of VTE in the affected population reaching up to 7.63 % per year (20). Literature reports a 2 – 10-fold higher risk of VTE in HIV positive patients with increasing risk found with lower CD4 count (those under 200 cells/mm), younger age (less than 50 years) and pro-coagulant conditions such as Protein C or S deficiency (20, 21). Patients with HIV are

also at higher risk for various malignancies and opportunistic infections including Cytomegalovirus (CMV), Pneumocystis jirovecii pneumonia (PCP), Mycobacterium Intracellular Avium and Tuberculosis (TB) which have been linked to a higher incidence of VTE (20). Conflicting data exists on the role of Protease Inhibitors increasing VTE risk in anti-retroviral (ARV) users (20).

Nash et al (2018) reports 25.7 million HIV infected persons in Sub-Saharan Africa of which 40% (10.3 million) are untreated (65% of which are from Eastern/Southern Africa) (22). It is predicted that 1.2 million new infections will occur annually (22). South Africa is known to have one of the highest HIV burdens in the world. Statistics South Africa showed a rise in cases from 3.8 million in 2002 to 7.8 million in 2020 with the estimated total population infected with HIV in 2020 to be 13%(23). One fifth of those infected are females between the ages of 15 – 49 years (23).

Despite the known association with VTE, HIV is not a feature included in common VTE CDRs (19).

2.2.1. HIV and PE globally

In America, Sullivan et al (2000) found the incidence of thrombosis in HIV reactive individual to be "2.6/1000 person-years" (24) with increased risk seen in age >45 years, CMV infection and other AIDS-defining conditions (24).

A Danish cohort study concluded an amplified risk of VTE in the HIV positive population when contrasted to the general population (particularly in the HIV infected intravenous drug users) (25).

Limited data exists on the epidemiology of PE in HIV affected individuals globally (3).

In Europe, Alvaro-Meca et al (2018) revealed that the introduction of combined anti-retroviral therapy (cART) had resulted in a decrease in PE-related incidence and mortality in the HIV-mono-infected individuals and also an inverse increase in those with HIV and hepatitis C co-infection in Spain (3).

In the United states, Howling et al (1999) determined the incidence of PE to be low in patients admitted to the UCL AIDS/HIV unit between 1993 – 1997 (26). However, this study

appears of limited value in our clinical setting where the bulk of HIV- infected individuals are African and of heterosexual sexual orientation.

Ogeng'o et al (2011) carried out a retrospective study describing the pattern of PE among black Africans in Kenya and found HIV to be a frequent co-morbidity (10.9%) in their study population (27).

2.2.2. HIV and PE in South Africa

HIV was determined to be the commonest associated risk factor for VTE followed by Tuberculosis (TB), with some having co-current infection in a retrospective study conducted in a Johannesburg tertiary hospital (19).

This close association was further demonstrated in a retrospective study conducted at Chris Hani Baragwanath hospital which evaluated a total of 498 CTPAs for which 30 % had PE (4). More than 40% of those with PE were documented as HIV positive (4). In addition, this study revealed a higher incidence of PE in HIV positive patients who had a CD4 count under 200cells/ul3 (4) – in keeping with other literature (20). The mortality rate was high (24%) with "advancing age" (>40 years) being the only significant mortality predictor (4).

Ramlakhan et al (2017) undertook the first study in the Western Cape examining the prevalence of HIV in patient's undergoing Computed Tomography for suspected PE. The CTPA prevalence of PE in this study group was found to be 26%, with a prevalence of 67% in the HIV positive group (statistically not different in comparison with PE-negative patients (17).

Ramlakhan et al (2017) looked at the CTPA findings in HIV patients positive for PE and found that, compared with HIV negative group, the HIV positive group had a higher clot burden (partial thrombus-occlusion) in the right middle lobe, and that bilateral lower lobes were most commonly affected (17). Measures of PE severity including the Qanadli score, Right ventricular to left ventricular (RV:LV) ratio and diameter of the pulmonary artery to the aorta (PA:AO) ratio between the HIV reactive and non-reactive groups did not differ to an extent to be considered statistically significant (28). Additionally, the study also revealed a statistically significant association between TB positivity and PE (17).

The study was limited in having a single reader interpreting the scans (17). The study did not look at the radiological findings in HIV patients whose CTPA was negative for PE.

Bulajic et al (2019) conducted a retrospective study in the Western Cape focusing on the clinical presentation and workup of patients who had undergone CTPA for suspected PE (9). The prevalence of PE in their study was 32% of which 37% were HIV positive (9).

2.3. What if it's not PE?

2.3.1. Alternative diagnosis found on CTPA

Ferreira et al (2016) looked at "the prevalence of alternative diagnosis based on Chest CTA in patients with suspected PTE who tested negative for PE as well as whether those alternate diagnosis had been considered prior to the CTA" (16). Their study demonstrated that the majority of patients referred for suspected pulmonary thromboembolic disease did not have a PE (75.4%) and of those without PE, 83.3% had an abnormal finding on CTA (16). "Atelectasis, pulmonary nodules, pleural effusion, consolidation, and emphysema" were listed as the key abnormal findings on the PE-negative scans (16) These common findings are in keeping with other studies which looked at incidental findings on CTPA with majority of them being pulmonary changes (29-31) – refer to Table 2.

The most common alternate diagnosis based on CTA findings was pneumonia (16). Of note, of the 83.8% with abnormal CTA findings, only 20.4% were not picked up on prior chest radiographs (16). Two studies listed heart failure/pulmonary oedema as the major/most relevant cardiac finding explaining the respiratory symptoms seen in PE-negative CT scans for suspected PE (16, 29). Cancer progression/metastasis was also listed within the major findings after pulmonary and cardiac abnormalities in the same studies (16, 29). The study conducted by Perelas et al (2015) listed scarring, stable lung nodule, emphysema and atelectasis as the most common least clinically significant findings(29).

The Ferreira et al (2016) study was conducted in Brazil which has a closer socio-economic background to South Africa (as opposed to Europe or the United States).

In developed countries, the currently most frequently diagnosed lung pathology in HIV infected individuals are bacterial pneumonia, PCP and TB (32). Benito et al says in Africa, TB could be the most common lung complication (32).

2.3.2. Significance of incidental findings on CTPA

Separate studies conducted by Chandra et al (2013) and Kalim and Akthar (2014) demonstrated that poor use of validated CDRs, inappropriate evaluation of pre-test probability for PE and D-dimer levels have resulted in an overuse of CTPAs (33, 34).

Chandra et al (2013) conducted an 11-year retrospective study which showed that findings of an alternate diagnosis on CTPA did not rationalise its increased use (33). Similarly, other studies have suggested that the alternate findings in CTPAs negative for pulmonary embolism have made little difference to clinical management (29, 35).

Poor or incorrect use of standardised protocols may contribute to unnecessary scans being ordered which is an important factor to consider given our resource limited setting as CTPAs are costly and encompass radiation exposure as well as risks of adverse contrast reactions and/or effects to the patients (29).

The cost-effectiveness of these studies may be relevant to low and middle-income countries like ours.

2.4. This project in context: Comparison to literature on the topic

Table 2 and 3 below summarise the relevant studies in current literature from which this study will be compared to.

Table 2: Comparison of literature on CTPA findings in suspected PE globally

Study	Chandra(33)	Peralas (29) (36)	Ferreira (16)	Sharma(30, 37)	Anjum(31, 38)
Year	2013	2015	2016	2017	2019
Imaging Modality	CTPA and V/Q scans	CTPA and chest radiographs	CTPA and chest radiographs	CTPA and contrasted CT Chest	CTPA
HIV status	Not included	Not included	Not included	Not included	Not included
Focus of study (PE positive vs. PE negative CTPAs)	Both	PE-negative	PE-negative	PE-positive	PE-negative
Total No. of patients (n)	850 [examined over 3 index years (2000, 2005, 2008)]	641	191	570	1708
Mean age (years)	62	57	59	63	62
Gender (female) [n (%)]	560 (66%)	442 (69%)	63 (33%)	382 (67%)	973 (57%)
No. of PE- positive cases [n (%)]	150 (17.7%)	61 (9.5%)	47 (24.6%)	n (ranged from 12 – 28%) - this study looked at trends	223 (13.1%)
No. of PE-negative cases [n (%)]	700 (82.3%)	580 (90.5%)	144 (75.4%)	N/A	1475 (86.4%)
No. of normal studies [n (%)]	N/A	115 (17.9%)	24 (12.6%)	N/A	N/A

Study (continued)	Chandra(33)	Peralas (29) (36)	Ferreira (16)	Sharma(30, 37)	Anjum(31, 38)
No. of cases with major findings (PE-negative scans) [n (%)]	N/A	16 (2.6%) – categorised as "urgent" – needing immediate attention. 12 (2%) – categorised as non-urgent but "requiring follow-up"	39 (27.1%)	No distinction made between major or minor findings	173 (11.7%)
Commonest major lung finding or diagnosis if given (PE-negative scans)	N/A	Pneumonia (7.07%)	Pneumonia (51.2%) Atelectasis (48,6%), pulmonary nodules (30.6%), consolidation (21.5%), emphysema (21.5%)	Consolidation (25%), emphysema (22%), atelectasis (22%)	Pneumonia (7.6%), pulmonary mass (1.3%)
Commonest major cardiac finding (PE negative scans)	N/A	Pulmonary oedema/heart failure (1.38%)	Decompensated heart failure (20.5%), cardiomegaly (20.1%)	Not mentioned	Cardiomegaly (7.6%) - classified as incidental
Commonest major pleural finding (PE-negative scans)	N/A	Large pleural effusion (0.52%)	Pleural effusion (29.9%)	Pleural effusion (25.8%)	Not mentioned
Other commonest pathological finding(s)	N/A	Recurrence of known malignancy or new metastases (1.21%)	Hiatus Hernia (2.8%), Thyroid nodule (2.1%)	Malignancy < 5%	Mediastinal lymphadenopathy (5.8%), mediastinal masses (4.9%)
Commonest pathological finding overall	N/A	Pulmonary/ parenchymal	Pulmonary/ parenchymal	Pleural effusion	Pulmonary/ parenchymal
Prevalence of PE (%)	17.7%	9.5%	24.6%	20%	13.6%

Table 3: Comparison of literature on CTPAs for suspected PE in Africa

Study	Ogeng'o (27)	Goldstein (19)	Meels (4)	Ramlakhan (17)	Bulajic (9)
Year	2011	2017	2018	2017	2019
Imaging Modality	Multi-modality (US, Contrasted CT Chest, CTPA)	CTPA, ultrasound (US)	CTPAs	CTPA	CTPA
HIV status	Included (10.9% HIV positive)	Included (50% HIV positive)	Included (40% HIV positive)	Included (49% HIV positive)	Included (43% HIV positive)
Focus of study (PE positive vs. PE negative CTPAs)	PE-positive	VTE positive (including DVT and PE)	PE-positive	PE-positive	PE-positive
Total No. of patients (n)	128	74	147	164	127
Mean age (years)	40.8	40 overall (< 50 in 85.7% of the HIV positive group)	46.8 overall (24 in the HIV positive group)	45	43 overall (45 in the PE positive group)
Gender (female) [n (%)]	68 (53%)	49 (66%)	115 (78.2%)	115 (70.1%)	120 (94%)
No. of PE- positive cases [n (%)]	N/A (all patients included had PE)	18 (24%) (rest had DVT only)	60 (40.8%)	43 (26%)	41 (32%)

Study (continued)	Ogeng'o (27)	Goldstein (19)	Meels (4)	Ramlakhan (17)	Bulajic (9)
Most affected lung lobes (HIV positive group)	N/A	N/A	N/A	Right lower lobe (82%) and Left lower lobe (86%) in HIV positive group. The Left lower lobe (91%) was the most common in the HIV negative group. The Qanadli score revealed highest clot burden in the right middle lobe.	N/A
Pulmonary complications (HIV positive group)	N/A	N/A	N/A	Ground-glass opacity (48%), Wedge-shaped opacity (18%). These were higher than the HIV negative group but determined not to be statistically significant	N/A
Pleural complication (HIV positive group)	N/A	N/A	N/A	Pleural effusion (45%) No statistically significant difference vs. the HIV negative group	N/A

Cardiac complications (features of right heart strain)	N/A	N/A	N/A	No statistically significant difference vs. the HIV negative group	N/A
Incidental findings:	N/A	N/A	N/A	Consolidation (68%), Atelectasis (5.2%)	N/A
Prevalence of PE	N/A	N/A	30% overall, 40% in the HIV positive group	26% overall, 67% in the HIV positive group	32% overall, of which 37% were HIV positive

South Africa differs considerably to the rest of the world in terms of its HIV/TB burden. There is limited data on VTE in Africa and given our setting where a few studies have already demonstrated a high association between VTE and HIV positive patients (see Table 3 above), and thus further research in this area is warranted.

Of interest, no study has been done looking specifically at alternative or incidental findings on CTPA in HIV positive patients referred for suspected pulmonary embolism which are negative for PE which makes this project unique.

ART initiation in sub-Saharan Africa occurs late in the course of infection (22) and so a wider range of pathology can be expected in our setting. This project will be an opportunity to explore whether alternate/incidental findings in this population group may differ comparably to other studies done on HIV negative populations (see Table 2 above).

The radiological findings (whether PE-positive or PE-negative) in this study may give some insight into the appropriateness of CTPA referrals by clinicians and prompt further research into this area which is an important factor to consider given our resource limited setting.

This project will also provide further information on the radiological findings of PE in HIV positive patients in Gauteng, as the only other similar study documenting CTPA findings in this population group was done in the Western Cape (17). This study will differ from the study done by Ramlakhan et al (2017) in that it will have three readers instead of one, it will not include HIV negative patients and it will include CT findings in PE-negative CTPAs in HIV positive patients. Our study will also mention incidental findings noted in the PE-positive group which is not described in detail in the study done by Ramlakhan et al (2017).

3. Aim

To document the CT findings in HIV positive patients referred for CTPA for suspected pulmonary thromboembolic disease in a Johannesburg-based academic hospital.

4. Study Objectives

Primary objective:

To document the CT findings in HIV positive patients referred for CTPA for suspected PE.

Secondary objective:

To determine the CTPA prevalence of PE in HIV positive patients referred for suspected PE.

5. Methods

5.1. Research paradigm

The research paradigm is a retrospective, descriptive, cross-sectional study based at a tertiary referral hospital in Johannesburg, South Africa.

5.2. Sample

The study population will comprise of documented HIV positive individuals who underwent CPTA for suspected pulmonary embolism for a one-year period spanning from 1st January 2018 to 31st December 2018 at Helen Joseph Hospital, a tertiary referral hospital in Johannesburg.

5.2.1. Inclusion criteria

All adult HIV positive patients who have undergone a CTPA for suspected pulmonary thromboembolism during the study period will be considered for inclusion in the study.

5.2.2. Exclusion criteria

CTPA records without images on PACS.

Request forms with illegible documentation, such that the HIV status and/or other reason for which the request cannot be interpreted.

5.3. Materials and Methods

The CTPA hard-copy reports done between 01 January 2018 to 31 December 2018 will be accessed via the radiology CT records filing room of Helen Joseph Hospital.

These reports which meet the inclusion and exclusion criteria will be selected/retrieved and soft-copy records will be made via CAM-SCANNER app on an android phone for a printed copy to be made and kept by the primary investigator.

Patient's in the study have been scanned on a Phillips 16 slice CT scanner at Helen Joseph Hospital. 100ml Omnipaque 350 was injected via 18G or 20G intravenous cannulas in the antecubital fossa, using an automated pressure injector at a rate of 4mls per second followed immediately by 50mls saline bolus chaser.

The selected CTPA studies will be retrieved on PACS using their hospital numbers/names on the CTPA request forms and the CT DICOM images will be copied onto DVDs.

The patient's personal data such as name and hospital number will not be used and each study will be assigned a code for identification to be kept by the primary investigator (PI) and supervisors to maintain patient anonymity.

Evaluation of the studies will be performed by three readers (R1, R2, R3), who are consultant radiologists with at least four years post graduate experience. The PI will not be involved in the interpretation of the studies to limit bias.

The scans will be viewed on Apple computers, via standardised DICOM-viewing software. They will each complete a prescribed data collecting tick-sheet for each study (see appendix 1). The readers will be blinded to the presenting symptoms and to each other.

The tick-sheets will be completed electronically using Research Electronic Data Capture (REDCap).

REDCap is a web-based application whereby an applicant may capture and store data for clinical research purposes on a secure electronic platform. The data is captured and stored safely on the REDCap site and can be accessed only by the primary investigator and exported into statistical programs for data analysis.

Uniform instructions on how to complete the tick-sheet on REDCap and how to use OsiriX will be given to each reader prior to reading the studies. Once completed, these tick-sheets will automatically be stored on REDCap and used for data interpretation and statistical analysis.

5.4. Data collection

Patient demographics and presenting symptoms will be obtained from the CT request form. The National Health Laboratory Service (NHLS) will be accessed for CD4 counts done within a six-month period of the requested scan (see Appendix D).

Information to be collected from the CTPA DICOM images can be viewed in Appendix A.

CTPAs will be classified as PE-positive or PE-negative based on the presence or absence of filling defects within the pulmonary artery and/or any of its branches respectively. A study will be regarded as PE-positive if two out of the three readers interpret it as positive.

Studies having significant motion/breathing artefact or suboptimal opacification of the pulmonary arterial system rendering interpretation impossible will be classified as 'Non-diagnostic for PE'.

"Parenchymal" findings will be findings limited to the lung parenchyma, excluding the pulmonary vessels and lymph nodes. "Pleural" findings will be findings limited to the parietal and visceral pleura. "Cardiac" findings will be findings limited to the heart and pericardium. "Extra-thoracic" findings will include soft tissue, visceral, bone and nodal findings above the thoracic inlet or below the diaphragm. Chest wall abnormalities will also fall under this group. "Other Intra-thoracic" findings will include abnormalities of mediastinal/hilar lymph nodes, oesophagus, bronchial arteries and anterior mediastinum.

5.5. Reliability and validity

Reliability of the study has been optimised by using 3 readers blinded to each other and to the clinical presentation, by using a standard DICOM-viewing software, and by giving uniform instructions to all the readers. Reporting is also standardised by using a tick sheet.

5.6. Bias

To eliminate experimenter/researcher bias, the CTPA studies will be analysed by three independent radiologists (readers) who will not be given patient history or details. The readers will also be blinded to each other.

Sampling bias is inherent in this study due to:

- Sample being a hospital-based population (pathology encountered is likely to be more severe than the general population).
- Readers knowing that the study involves HIV positive patients.

6. Data Analysis and statistics

A study number will be allocated to each CTPA in this research. A datasheet only available to the PI and supervisors will be used to correlate the study numbers with the patient's names/details. All data captured from the tick sheet will be recorded on REDCap and transferred into Excel spreadsheets and data analysis software for analysis by the PI.

All CTPA findings and nominal data will be recorded as frequencies and percentages.

Period prevalence of PE positive scans will be reported as a percentage for the time period of this study (12 months).

Inter-reader agreement will be calculated using Free-Marginal Multi-rater Kappa (Randolph's Kappa).

This study is estimated to have a sample size of around 50 patients based on the numbers found during the feasibility assessment for this project.

7. Ethics

Submitted to HREC – pending approval.

7.1. Consent forms

Patient consent forms will not be required for this study, due to its retrospective nature.

Reader consent forms and information sheets will be distributed to each participating reader (see Appendix B and C).

7.2. Data safety

Each patient's data will be anonymised and coded before distribution to the three readers. Only the PI and supervisors will have the key to access these codes.

8. Budget

DVDs	R400
Printing	R400
Travel to congress to present findings	R200
Total	**R1000**

All costs listed above will be covered by the primary investigator and will involve no costs to Helen Joseph Hospital or the University of Witwatersrand.

9. Anticipated limitations

Patient records may be incomplete or not retrievable.

Initially, progress of the study will be limited by the readers.

10. Timing

Month of the Year	**1**	**2**	**3**	**4**	**5-7**	**8-10**	**11-15**	**16**	**17,18**
Literature search									
Reading literature									
Summarising literature									
Preparing Protocol									
Protocol Assessment									
Ethics application									
Collecting data									
Data analysis									
Writing up thesis									
Submit: marking									
Writing up paper									

Appendix A – Ticksheet

Confidential

Reader Tick Sheet

Study Number:	_____ (Note: This is the assigned study number provided and does not correlate with the patient's hospital ID record number)
Please indicate your Reader number:	◯ Reader 1 ◯ Reader 2 ◯ Reader 3
Please rate the diagnostic sensitivity:	◯ Sensitive for both central and peripheral PE, ◯ Sensitive for central but not peripheral PE, ◯ Non-diagnostic for either central or peripheral PE
Is the study PE-positive or PE-negative?	◯ PE-positive ◯ PE-negative
What pattern of involvement is noted?	◯ Central ◯ Peripheral ◯ Mixed (Please specify the location of disease: Central = pulmonary trunk to lobar artery; Peripheral (segmental, subsegmental, peripheral); Mixed (both central and peripheral))
Which Lobe(s) of the Lung is/are involved?	☐ RUL ☐ RML ☐ RLL ☐ LUL ☐ LLL ☐ All (Saddle Embolus) (Saddle is defined as extending across the pulmonary trunk in the right and left pulmonary arteries)
Is there a pleural effusion?	◯ Yes ◯ No
Which of the following features of right heart strain are present?	☐ Contrast reflux into IVC/hepatic veins ☐ RV:LV ratio > 1 ☐ None (Select all relevant. Right Ventricle: Left Ventricle (RV:LV) ratio is measured on axial planes. The RV short-axis diameter is measure at the level of the tricuspid valve from inner wall to inner wall at its widest portion. The LV short-axis diameter is measured at the level of the mitral valve from inner wall to inner wall at its widest portion. Note that RV and LV short axis measurements may be on different axial levels.)

Which of the following parenchymal changes are present?	☐ Pulmonary infarcts (peripheral wedge-shaped consolidations) ☐ Linear atelectasis ☐ Focal ground-glass attenuation ☐ Mosaic attenuation ☐ Bronchial artery dilatation ☐ None above (Select all that apply, Note: bronchial artery diameter exceeding 2mm is considered dilated*)
Is there evidence of pulmonary arterial hypertension?	◯ Yes ◯ No (PAH defined as MPA: AA > 1.1)
Which of the following incidental parenchymal changes are present?	☐ No abnormalities ☐ Non wedge-shaped consolidation ☐ Tree-in-bud-nodules ☐ Solid pulmonary nodules (> 3 mm) ☐ Sub-solid pulmonary nodules (> 6mm) ☐ Pulmonary masses ☐ Bronchiectasis ☐ Emphysematous changes ☐ Lung cavity/cavities ☐ Lung cyst/s ☐ Honey-combing ☐ Ground-glass opacities ☐ Interlobular septal thickening ☐ subpleural reticulations (Pulmonary nodule < 3cm; Pulmonary mass > 3cm)
Which of the following incidental pleural findings are present?	☐ Nil abnormalities ☐ Pleural effusion in the absence of PE ☐ Empyema ☐ Pleural calcifications ☐ Apical pleural thickening ☐ Non-apical pleural thickening ☐ Pneumothorax
Which of the following incidental cardiac findings are present?	☐ Nil abnormalities ☐ Cardiomegaly ☐ Pericardial effusion ☐ Aortic dissection ☐ Aortic aneurysm (Cardiomegaly is defined as a cardiothoracic ratio > 50%. Tubular aortic aneurysm defined as > 45 mm)
Which of the following other intra-thoracic findings are present?	☐ Enlarged mediastinal/hilar nodes with significant mass effect causing bronchial or vascular obstruction ☐ Enlarged mediastinal/hilar nodes without significant mass effect ☐ Anterior mediastinal mass suspicious for neoplasm ☐ Esophageal mass or abnormal thickening ☐ Esophageal dilation/ Achalasia ☐ Rasmussen aneurysm ☐ Pulmonary vascular malformation ☐ None of the above (Enlarged nodes are lymph nodes with short axis diameter > or = 1cm.)

Which of the following extra-thoracic findings are present?	☐ Intra-abdominal nodal masses ☐ Massive ascites ☐ Hiatus Hernia ☐ Abdominal visceral lesions suspicious for neoplasm or metastases ☐ Benign abdominal visceral lesions (eg. simple renal cysts, simple hepatic cysts, uncomplicated cholelithiasis, adrenal adenoma, splenic granuloma) ☐ Acute severe abdominal pathology (e.g; pancreatitis, cholecystitis, perinephric abscesses, pneumoperitoneum) ☐ Vertebral or rib fractures ☐ Vertebral or rib lesions suspicious for metastases ☐ Breast mass suspicious for neoplasm ☐ Chest wall mass suspicious for neoplasm ☐ Significant but discrete axillary or supraclavicular nodes ☐ Enlarged thyroid gland ☐ None of the above (Significant lymph nodes measure > or = 1cm on short axis diameter)
Are there findings in this study other than PE severe enough to cause respiratory distress that would warrant immediate/urgent medical attention?	◯ Yes ◯ No (Examples of emergent findings: pneumothorax, massive pleural effusion, empyema, extensive consolidation, end-stage interstitial lung disease, cardiac failure, significant pericardial effusion, aortic dissection, haemorrhaging aneurysm, massive ascites, severe abdominal disease, tracheal or central bronchial obstruction (e.g by mass or mucous plug), advanced metastatic disease)
What is your overall assessment/impression of this study?	☐ Normal study ☐ Findings related to presence of PE ☐ Pulmonary findings not related to PE ☐ Cardiac findings not related to PE ☐ Other significant Intrathoracic findings (mediastinal/nodal/esophageal) not related to PE ☐ Extrathoracic significant findings

Appendix B – Reader information sheet

INFORMATION DOCUMENT FOR READERS

Study title: CTPA Findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease

Greetings,

I, Diane Wiese (MMED candidate), along with my supervisors (Dr. Susan Lucas and Dr. Leisha Rajkumar) are doing research to look at CTPA findings in HIV positive patients referred for suspected pulmonary thrombo-embolic disease at Helen Joseph Hospital. Our study aims to determine the prevalence of PE in this population group and document the CT findings in both PE-positive and PE-negative studies.

We are inviting you to partake in this research as a Reader. This study will have a total of three readers.

The research paradigm is a retrospective, descriptive, cross-sectional study. CPTA records of HIV positive patients referred for suspected PE for the period of 1st January – 31st December 2018 will be retrieved from filing and their DICOM images will be copied onto portable discs for viewing on OsiriX-DICOM viewing software.

These studies will be made available to you for viewing and the data collection will be done with the use of electronic (online) data-collecting tick sheets created and stored on REDCap for which you will be provided access to. As a reader, you will be asked to answer a series of simple set questions on a prescribed online tick sheet based on your interpretation of these CTPA studies. The information will be automatically stored onto the REDCap database.

This study involves no risks or direct benefits to you.

Participation is voluntary and you may discontinue participation at any time.

For any further information or queries you may have (e.g. regarding the reporting of studies, REDCap use, etc.) you may contact me telephonically (0766548657) or via email (dianewiese1122@gmail.com).

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Appendix C – Reader consent form

READER CONSENT FORM

I _____ hereby agree to review 40 CTPA scans and enter the information of the provided data collection sheets (i.e. Appendix A) on REDCap for the MMed research of Dr D. Wiese.

I understand that my participation will be limited to reviewing and I have no expectation of monetary compensation on the abovementioned project.

_____ _____

Name Date

_____

Signature

Appendix D – Data collection sheet (for use by primary investigator only)

Study Date	Study No.	Age	Gender	CD4 (u/L)	Presenting Symptoms	Other information	R1	R2	R3

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