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Referral Patterns and Yield of Computed Tomography Pulmonary Angiography for Suspected Pulmonary Embolism In A Resource Limited Environment

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in complete fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology

Johannesburg, 2020

Declaration

I, Thato Sefanyetso, declare that this research report is my own work. It is being submitted for the degree of MMed Rad(Diag) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Thato Sefanyetso

On this 25th day of September 2020.

This project is dedicated to my only son, Lesego Tlotlo Sefanyetso.

For all the nights I couldn't tuck you in because I had to finish this project.

This is to you, my boy.

Publications and presentations

This work has never been published nor presented at any local or international congresses.

Abstract

INTRODUCTION: Pulmonary embolism is a common cause of morbidity and mortality despite advances in the diagnosis and treatment. There is increased utilization of CTPA (Computed Tomography Pulmonary Angiogram) despite the low yield for pulmonary embolism.

AIM: To evaluate referral patterns and the outcome of CTPA in patients with suspected pulmonary embolus in our resource restricted environment in order to develop protocols for imaging practice.

METHOD: The study population that met inclusion criteria was 132 patients. The primary investigator and two radiologists read CTPA images independently., noting the presence and severity of pulmonary embolism. The additional/alternate findings were also recorded. The presenting symptoms were found in the request forms and clinical files. HIV results and D-dimer concentrations were searched for in the NHLS computer system.

RESULTS: Pulmonary embolism was found in 37% of patients and alternate findings seen in 73.8% of those with a negative CTPA result.

CONCLUSIONS: Alternate findings are found in a significant number of patients with suspected pulmonary embolism. Clinical predictive scores and D-dimer levels could preclude the need for CTPA.

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1. Introduction

Pulmonary thromboembolic disease (PTE) is a common and important cause of morbidity and mortality despite advances in the diagnosis and treatment (1). It has been reported that PTE has been identified as the cause or major contributor of death in a significant number of patients in autopsy based studies and that only a third of PTE is diagnosed ante mortem (2). In only about a fifth of cases, there is a genetic predisposition and therefore in the rest of the cases, identification of risk factors is crucial (2, 3). PTE can present clinically as a range between an incidental benign disease and a serious cardiovascular compromise (4). Unfortunately clinical presentation is not specific and there are no pathognomonic signs of the disease, with many other cardio-respiratory conditions being major mimickers (4). The mortality from PTE can be reduced to half if unfractioned / low molecular weight heparin is used as prophylaxis (5).

The diagnosis of PTE can present a challenge mostly due to a non-specific clinical presentation and lack of specificity of some of the diagnostic modalities (4). There are many diagnostic tools available but it remains a challenge to decide which are appropriate and cost effective strategies at each individual clinical setting (4). There is an objective clinical probability assessment stratification recommended by the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) investigators for all patients suspected of having PTE (6). There are also validated clinical algorithms assessing for the presence of PTE such as the modified Wells' score. However, these are not optimally used by the referring clinicians despite recommendation by the expert groups including PIOPED II and Fleischner Society investigators (7).

D-dimer testing in suspected PTE can be essential in excluding the presence of the disease (8). However, the accuracy of D-dimer results depends on the type of assay performed, there being many available, with different sensitivities (8). The use of these clinical assessment strategies combined with the appropriate D-dimer assays can substantially reduce the workload and costs imposed on the imaging departments (9).

The gold standard test for the diagnosis of PTE is conventional pulmonary angiogram. This is however an invasive study that has its own morbidities (1). The available non-invasive tests

are Ventilation/Perfusion (V/Q) lung scan and Computed Tomography Pulmonary Angiography (CTPA) (10). CTPA is a very sensitive study and its use has increased the diagnosis of pulmonary embolism (11). There has been growing evidence that there is overuse of the study and a related low yield of positive PTE (12). In most studies, between 13 and 33% of patients suspected of having PTE were found to be actually positive for the disease, therefore there are concerns regarding whether CTPA is used appropriately to exclude PTE (11).

1.1. Definition of PTE

Pulmonary thromboembolism (PE) is a complication of deep vein thrombosis (DVT) whereby thrombi from the peripheral sites embolise to the pulmonary arteries, occluding them and resulting in serious clinical sequelae (10). Venous thromboembolism (VTE) is a clinical entity that includes both DVT and PE (13). About 70% of patients diagnosed with pulmonary embolism (PE) have evidence of a DVT somewhere and approximately 50% of patients with DVT of the popliteal and more proximal veins go on to develop PE (10). PE is less likely if DVT is confined to the calf veins. Thrombosis of the iliac, renal and upper limb vasculature is rare and thus it is rare for PE to originate from these sites (10). In fact it has been reported that 90% of symptomatic PE originates in the lower limb deep veins (13).

1.2. Epidemiology of PTE

PE is paradoxically both over diagnosed and over investigated (3). Most deaths are a result of failure to diagnose or where the diagnosis is not made timeously (3). Clinicians tend to have a low threshold for investigating for PE due to the dire consequences of missing the diagnosis (3).

Pulmonary embolism is the third most common cardiovascular disease, after coronary artery disease and stroke (14). It is estimated to affect 60-70 per 100 000 people in the general population (1, 15). However, this could be an underestimation as silent PE affects about 40-50% patients with DVT (1). Autopsy studies have shown that only 30-45% of PE is diagnosed before death (1). The incidence of PE increases with age, with the peak seen in individuals between 70 and 80 years, according to the autopsy studies (1). This increase of PE seen with

age is likely due to the presence of other risk factors (13). In the United States, the prevalence of PE in patients less than the age of 40 is 1/10000 and this rate escalates steeply after age of 40 such that at 80 years the prevalence is 5-6/1000 (13).

There are also racial differences with regards to the incidence of PE (16). The Asian population shows a significantly lower incidence in comparison to other race groups (16). In the USA, the African American population have a higher incidence than the Caucasian population (15, 16).

There are many risk factors predisposing to the development of PE and the presence of malignancy is one of the major contributors (17). Of all new cases of PE, 20% are attributed to underlying malignancy (17). Patients with malignancies have a seven times higher relative risk of developing PE as compared to individuals without active cancer (17).

The association between PE and HIV is overwhelming. In 2005 a large population based study showed that the prevalence of venous thromboembolism in HIV positive individuals is about 18% (18). In South Africa, a vast majority of patients with VTE are also HIV positive (18).

1.3. Pathogenesis of VTE

Venous thromboembolism encompasses both deep venous thrombosis and pulmonary embolism. The pathogenesis of VTE is described by Virchow's triad, which consists of factors that predispose to VTE. These factors are: a systemic hypercoagulable state, venous endothelial damage, and venous stasis (10). Usually two of these factors have to be present for the development of VTE (10).

Most DVTs originate in the calf veins, remain localised to this region and are thrombolised by intrinsic processes (10). However, if the factors that caused thrombosis do not resolve, thrombosis in the calf veins can propagate to the larger veins of the lower limb. When the thrombus has extended to the larger proximal veins, the risk of embolism is much greater (10). Presence of DVT is proven in 70% of cases of PE and it is said that in the rest of cases

the whole thrombus is probably not seen as it has already detached and embolised to the pulmonary vasculature (19).

The pulmonary emboli obstruct the pulmonary arteries, resulting in increased alveolar dead space and bronchoconstriction with subsequent increase in pulmonary arterial pressures (10). Pulmonary artery pressures increase to more than 30 - 40mmHg when about 30 – 50% of the pulmonary arterial bed is obstructed (13). It is at this stage when patients will presents with acute symptoms (13). Increased workload on the right ventricle follows the high arterial pressure with subsequent hypoxia secondary to decreased cardiac output (10). The narrowing of the pulmonary arteries by the thrombus together with the vasospasm that ensues result in the ventilation/perfusion mismatch that is seen on V/Q scanning (13). There are multiple factors that will determine the haemodynamic status of a patient with PE (13). These include, the diameter of the affected vessel, the pre PE cardio-pulmonary state, the amount of released neuro-humoral substances from the damaged endothelial/mast cells and platelets (13).

1.4. Risk Factors

The risk factors of PTE are also related to Virchow's triad. These can be hereditary or acquired factors (14). The acquired risk factors are divided into strong, moderate and weak associations. Hip/leg fracture, hip/knee replacement, major general surgery, major trauma, and spinal cord injury are considered strong risk factors with an odds ratio of more that 10; whereas arthroscopic knee surgery, central venous lines, chemotherapy, congestive cardiac failure, hormone replacement therapy, paralytic stroke, malignancies, post partum and previous VTE are said to be moderate risk factors (14). Weaker risk factors include bed rest, prolonged immobility, pregnancy, laparoscopic surgery and presence of varicose veins. (14)

There are many hereditary risk factors associated with VTE and they are also categorised into strong, moderate and weak associations (14). Strong risk factors include deficiency of coagulation inhibitors such as antithrombin and protein C + S; defective anticoagulant pathways and elevated factor VIII level (14).

An important risk factor especially for the South African population for the development of VTE is infection with HIV. According to Veller HIV is recognised as a hypercoagulable state and a large number of patients diagnosed with VTE in South Africa are HIV positive (18). There is evidence to suggest that the presence of HIV infection increases the odds of VTE by 2 to 10 times (20). This significant association between VTE and HIV infection has led to some reporters suggesting that PE should be a differential diagnosis in patients with HIV presenting with unexplained dyspnoea (20). They also suggest that HIV testing should be done in young patients with confirmed PE (20).

There's a higher incidence of PE if there are multiple predisposing factors and in many PE studies one or more predisposing factors are found in 80-90% of cases (2). Fatal PE occurs in about 5% of patients with a strong risk factor such as major abdominal surgery but only one in 10 000 minor elective operations (2). Fortunately, the rate is declining due to extensive pharmacological and physical prophylaxis (14).

Obstetric patients have a higher incidence of VTE, particularly if operative delivery is employed and this risk extends into the early puerperal period. The previously seen higher risk of PE with use of oral contraceptives has decreased with the use of lower dose formulations of oral contraceptives and hormone replacement therapy (2). Upper limb venous thrombosis is far less common than that in lower limbs and far less likely to result in PE. Central line catheters placed for a prolonged period can result in PE, however it is unlikely to be fatal due to the fact that the size of thrombi are usually much smaller (2).

1.5. Clinical Symptoms / Signs

The most common symptoms of pulmonary embolism are dyspnoea, pleuritic chest pain, and haemoptysis (21). PIOPED II investigators found that 44% of patients with pulmonary embolism presented with either haemoptysis or pleuritic chest pain whilst dyspnoea occurred in 36% of these patients (21). It has also been observed that haemoptysis is a symptom seen most commonly in the male patients while chest pain is more frequent in the younger population (22). Circulatory collapse occurs in only 8% of patients with pulmonary embolism and 14% of these have clinical presentation different from the classical symptoms (19). Findings in these patients include tachycardia, tachypnoea and clinical signs of DVT

(21). Presentation also depends on the position of the thrombi within the pulmonary vasculature. A significant number of patients with thrombi in the proximal pulmonary arteries present with acute dyspnoea or tachycardia, with frequencies of 92% and 65% respectively(21). Patients over the age of 70 are seen to present less frequently with dyspnoea and tachycardia in comparison with their younger counterparts. (21).

1.6. Complications of PTE

Pulmonary embolism can result in a number of complications, which include pulmonary infarction, chronic thromboembolic pulmonary hypertension and cardiac ischemia (10). Thrombi can embolise into the small sub segmental pulmonary arteries, causing ischemia and resultant infarction of the parenchyma (10). Patients with pulmonary infarction commonly present with pleuritic chest pain, haemoptysis and peripheral consolidation on chest x-ray (10). Pulmonary infarction is more likely to occur in patients with chronic cardiac failure complicated by pulmonary embolism (10).

Chronic thromboembolism occurs in about 4% of pulmonary embolism patients (10). It is defined as persistently high mean pulmonary artery pressure six months after the acute episode (10). Clinically patients can present with syncope, right heart failure and exertional dyspnoea. Cardiac ischemia follows, with hypotension as a result of the right heart failure and subsequent decreased venous return to the left ventricle. This occurs in a majority of patients with more than 50% obliteration of the pulmonary arterial system(10).

1.7. Diagnostic Tests (Including Imaging)

There are many diagnostic tests that can suggest or even prove the presence of pulmonary embolism. These tests differ in accessibility, risk to patient and cost. It is therefore essential for the clinician to bear that in mind when deciding which modality to choose.

CXR is normal in most cases of pulmonary embolism (2, 10). Findings on CXR may include evidence of pulmonary infarction (2). This is shown as triangular peripheral lung opacity with the base of the triangle along the surface of pleura, known as the Hampton's hump (2). In some cases, oligaemia or hyperlucency can be detected in parts of the lung affected by an

occluded pulmonary artery; this is known as Watermark's sign (2). CXR is also essential to exclude other diseases, which may mimic pulmonary embolism such as pneumothorax and pneumonia (2).
D-dimer is a degradation product of cross-linked fibrin and it indicates the presence of endogenous fibrinolysis. It has a high sensitivity for venous thromboembolism but a low specificity because there are many diseases that can cause elevated D-dimer levels. D-dimer testing can reduce the number of imaging investigations performed because a normal D-dimer value has a high negative predictive value (14).

V/Q scans can also be used to diagnose pulmonary embolism and high probability scans demonstrate presence of PE in 86-92% of cases (10). There are however many other causes of perfusion defects on V/Q scans (10). These include tumours, consolidation, left heart failure and obstructive airways disease (10). It is for this reason that V/Q scanning is not recommended in patients with abnormal CXR (10). The ventilation aspect of the V/Q scan increases the specificity because the perfusion defect is matched with a ventilation defect (10).

CTPA has become the first line investigation for patients with suspected pulmonary embolism throughout the world (1,20). This is mostly due to its accessibility, relatively simple interpretation and rapid acquisition time (1, 23). The advantage of CTPA is that apart from demonstrating the presence or absence of PE, it can also diagnose the presence of other cardiorespiratory diseases (20). Amongst these are pneumonia, pulmonary masses, chronic obstructive pulmonary disease and mediastinal masses (23). The severity of PE can also be assessed on CTPA by assessing the clot burden, which has a high impact on prognosis(24).

There are, however, several disadvantages to CTPA. Contrast induced nephropathy is a well known complication of CTPA and occurs in 6.6-19% patients who have had a CTPA (3). A further disadvantage of CTPA is higher exposure to ionizing radiation as compared to V/Q scanning (23). The radiation risk is an important factor. When doing CTPA the effective patient dose radiation exposure is 10 mSV, which is not insignificant (25). It has been shown amongst the Hiroshima and Nagasaki atomic bomb survivors that there is an increased risk of cancer when the effective dose was between 10 and 100 mSv (25). CTPA is less desirable than V/Q scanning in younger women because it delivers significantly higher effective doses

to breast tissue, which is particularly radiosensitive, and the risk of possible foetal exposure in this group of patients is also of concern. (26). Children are more sensitive to radiation exposure and their chance of developing cancer is raised due to the fact that their cells live longer after the radiation exposure (27). Contrast material induced allergic reactions and extravasation of contrast into the subcutaneous tissues are added potential risks (25). In addition there is a real burden on resources and significant costs attached to performing this investigation (25).

Conventional digital subtraction pulmonary angiography (DSA) has been considered the gold standard for diagnosing PE but the quality of CTPA images have improved over the years such that it has now mostly replaced DSA.(1) The challenges with pulmonary DSA are the invasiveness of the procedure, lack of easy accessibility and lack of expertise (2, 28). There is also a lower inter-observer agreement in comparison to CTPA (2). With all these factors borne in mind, DSA pulmonary angiography should only be considered when the clinical suspicion is high and other investigations failed to show the disease. It should also be available urgently when there is cardiovascular collapse or hypotension is present (2).

Compression ultrasound of the leg veins has been shown to be essential in the diagnosis of DVT. It has the advantage of being a real time investigation with no radiation exposure. It has high accuracy in the femoro-popliteal segments but the iliac and calf vessels can also be evaluated due to the availability of colour flow Doppler (5). A large number of patients with PE have a proximal leg DVT even in the absence of clinical symptoms (5). Therefore if a diagnosis of DVT is made in the presence of clinical suspicion of embolus then it is logical to start treatment even without proof of PE (5).

1.8. Wells score

The Wells' rule was developed by Wells et al in 2000 to guide clinicians in the diagnostic workup of PE. When the Wells score is used with the D-dimer test, it can exclude the need for further investigation with CTPA. (26,27). It consists of seven variables obtained from clinical history and examination. Different points are then assigned to different variables. It is said that PE is likely if the total score is more than 4 and less likely if it is equal or less than 4 (29, 30). A simplified Well's score has also been described (29), where one point is assigned

for each variable and PE is likely if the total score is 2 or more (26). The calculations of the original and the modified Wells scores are summarised in Table 1.1.

Table 1.1. Method of calculating the Wells' score and simplified Wells' score

Condition	Original Wells score	Simplified Wells score
Clinical signs of DVT	3	1
Heart rate> 100/min	1.5	1
Recent surgery or immobilisation	1.5	1
Previous PE/DVT	1	1
Haemoptysis	1	1
Malignancy	3	1
Alternative less likely than PE	3	1
TOTAL (maximum score)	14	7
PE unlikely	≤ 4	≤ 1

1.9. Qanadli score

The Qanadli obstruction score has been designed as a PE severity index based on images obtained by CTPA scanning. According to Yi, the Qanadli score is calculated as follows: "The arterial tree of each lung is regarded as having 10 segmental pulmonary arteries i.e. three to the upper lobes, two to the middle lobe or lingula and five to the lower lobes. Presence of embolus in a segmental PA is scored as 1 point and emboli at the most proximal arterial level are scored a value equal to the number of segmental PA's arising distally. Weighting factor is used for each value: 0 for no defect; 1 for partial occlusion; and 2 for complete occlusion. A sub-segmental embolus is considered a partially occluded artery therefore given a value of 1. The maximum CT obstruction index is 40. Patient's score is divided by 40, which is the maximum score one can get and converted to a percentage" (31). There is an association between pulmonary artery clot burden and prognosis of patients

with PE (32). A clot burden of more than 60% is associated with 85% mortality rate, whereas if the clot burden is less than 60%, mortality decreases to 2% (32).

1.10. Recommendations of international societies

There is a global consensus with regards to the strategies of diagnostic work up in patients with suspected pulmonary embolism. The Fleischner society, American thoracic society and the British thoracic society all recommend clinical probability testing as the initial assessment before laboratory or imaging investigations are considered (33-35). D-dimer testing should only be done if the clinical probability is low or intermediate. If D-dimer concentration is below 0.5mg/L and clinical probability is low, then PE can be reliably excluded (33-35). Patients with high clinical probability should not have D-dimer testing because it doesn't preclude the need for imaging(33-35). CTPA is the initial imaging modality of choice with high sensitivity and specificity(33-35). V/Q scanning can also be used as initial imaging in the diagnosis of pulmonary embolism however this test is only reliable if the CXR is normal (33-35).

CTPA and venography is recommended if PE cannot be excluded on clinical and D-dimer testing grounds. Most of these investigators recommend V/Q scanning as the first line modality in pregnant women (6). There is no place for D-dimer testing in pregnant patients suspected of PE and this is because the levels may be elevated by pregnancy (34). The initial imaging of choice in pregnant patients is venous ultrasound of the legs. This test will preclude the need for radiation exposure to pregnant patients and the foetus if the result is positive (34) . If ultrasound is negative, perfusion scintigraphy without the ventilation part is recommended as this delivers less radiation dose to the foetus than when both V and Q are done (34) . It also delivers much less radiation exposure to the foetus when compared to CTPA (34) . The use of iodinated contrast material is not contraindicated in pregnancy however it must be noted that it can cause hypothyroidism in the neonate (34) .

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

Several studies have found the yield of CTPA for suspected PE to be quite low. The PIOPED II, Christopher and the Swiss/French studies had higher frequency of positive CTPA compared with most studies as seen in table 1.2. below (7).

Table 1.2. Comparison of studies that showed the use of CTPA to diagnose PE

	Number of patients	Well's score in patients with PE	D-dimer	Wells' score + D-dimer level	Positive CTPA
Costa (2014) Canada (7)	3571	Not assessed	97,9% sensitivity; 98% NPV	Not assessed	15.4%
Stefan Walen (2013) Netherlands (36)	974	Only 13% documented	Documented in 61%	Could not be interpreted due to low numbers	23%
Shuujat (2013) New York City (3)	231	42% Moderate; 100% high clinical probability	Documented in 54%	Not assessed	20.7%
Mittadodla (2013) Pennsylvania (11)	185	66% Moderate; 23% high clinical probability	Done in only 16%	Not interpreted	16.2
Soo Hoo (2011) Carlifornia (37)	261	5.5 +/- 2.4 (unknown number documented)	Documented in 67%	72% positive D-dimer+ high clinical probability had PE	16.5%
Donohoo (2008) Rhode Island (38)	2620	N/A	N/A	N/A	6.7%
Van Belle (2006) Netherlands (39)	2199	Pulmonary embolism likely – 37%	N/A	Only 0.5% with negative D-dimer and low clinical probability had PE	20.4%
Perrier (2005) France (40)	756	95% in high clinical probability	N/A	N/A	26%
Wells (2001) Canada (41)	930	40.6% hih clinical probability pos for PE	72% PE pos D-dimer	Neg D-dimer + clinical prediction score < 2 excluded PE in 47%	16.9%

The reason for this is that these studies were multi centre; cohort, prospective studies and the patients were evaluated with the clinical probability scores before CTPA studies were performed. (7). There is no agreement regarding an ideal CTPA yield rate, however it has

been shown that a rate of 10% or less renders CTPA a screening tool rather than an investigation modality (7). The Christopher study by van Belle et al mentioned that several management studies have shown that PE can be safely excluded in patients with low clinical probability and low D- dimer test without the need for imaging (39).

The problem with many of the studies is that they are retrospective with uncertainty of the reliability of data, missing or undocumented test results such as D-dimers and undocumented Wells score as can be seen in Table 2 (36).

With regards to the large multi centre prospective trials, CTPA reports were used and no second reading was done to improve accuracy. However, this effect is most likely small as large sample groups were used (7).

In a resource-constrained environment like ours one has to be sure that the indications for CTPA are optimised, to minimise unnecessary investigations with the accompanying burden on staff, equipment, time and consumables.

1.12. Study aims and objectives

1.12.1. Study aim

This study aims to evaluate referral patterns and outcome of CTPA in patients with suspected pulmonary embolus in a resource restricted environment in order to develop protocols for imaging practice.

1.12.2. Study objectives

The objectives are:

1. To document the symptoms and clinical findings of patients referred for CTPA and calculate the clinical score (Wells score) for these patients.
2. To document the frequency of the presence of PE in patients who underwent CTPA for suspected PE; to calculate the pulmonary artery obstruction index according to a recognised scoring system (Qanadli score); as well as to describe additional lung pathology identified on CTPA.

3. To compare the Wells and Qanadli scores to see if there is an association between the clinical and radiological severity scores.

4. To compare CTPA findings in subgroups of HIV positive and negative patients.

5. To determine interobserver agreement for three readers interpreting the CTPA scans.

2. Materials and Methods

2.1. Research paradigm

A retrospective quantitative descriptive cross sectional study was performed.

2.2. Sample

The study population is all patients who underwent CTPA for suspected pulmonary embolism at Helen Joseph hospital during the period between 1st March 2012 and 28th February 2013.

2.2.1. Inclusion criteria

All adult patients (> 18yrs) that underwent CTPA at Helen Joseph hospital in the specified time period are included in the study.

CTPA should have been done only for the suspicion of pulmonary embolic disease

2.2.2. Exclusion criteria

Patients with absent clinical information.

Patients with incomplete or corrupt CT data.

2.3. Materials and Methods

An existing database of patients clinically suspected of having pulmonary embolism was used. Dr M Chohan, a physician at Helen Joseph Hospital collected this data over a period of one year (March 2012 to Feb 2013) at Helen Joseph hospital. The database consists of 219 patients. The request forms were retrieved from the CT department filing room. Clinical data noted on the request forms was collected onto a data sheet (Appendix B). The clinical notes were collected from the hospital filing room and the clinical symptoms and signs noted in the files were entered onto the data-collecting sheet. The laboratory data was accessed via the NHLS computer results system for collection onto the data sheet.

The CTPAs of all the patients that met the inclusion criteria were retrieved from the erasable optical discs (EOD) imaging archives. The patients that had corrupt or missing CT data were excluded from the study. The patients that had absent clinical information were also excluded from the study. The CTPA studies were done on a 16-slice multi detector computerized tomography, Phillips medical system. Contrast material used was iodinated contrast, Omnipaque at iodine concentration of 300mg per millilitre. Contrast was injected at a rate of 3 – 4ml/s with no bolus tracking. The region of interest is applied at the centre of the pulmonary trunk. A tube voltage of 120kV with a tube current of 240mAs, pitch of 1.1 and detector collimation of 1.0mm was used. The CTPA studies were saved onto DVDs then transferred onto a hard drive. Two qualified radiologists and the primary investigator downloaded the images from the hard drive into their personal computers to read the images independently. The readers analysed the scans for the presence of filling defects in the pulmonary trunk, main pulmonary arteries, lobar, segmental and sub-segmental pulmonary arteries. They also had to document the presence of associated findings, complications and alternate pulmonary parenchymal findings. The scans that had poor contrast enhancement or were unreadable due to motion artefact were excluded from the study population. The readers were blinded to the clinical notes and the previous assessment of the scans. All the readers used Osirix software to view the scans so as to standardise the viewing platform. The readers were allowed to use any post processing tools they deemed necessary for interpretation of the images. Readers documented their findings on the CT data collection sheet (Appendix B). The primary investigator made the final decision regarding the presence of PE by majority rule i.e. 2 out of 3 readers agree.

2.4. Data collection and calculations

Clinical and laboratory data was collected according to the attached data sheet (Appendix B). These included age, risk factors, and other relevant data, e.g. RVD status and D-dimer assay level.

The simplified Wells score (see Table 1.1.) was either extracted from the patient's records, or calculated by the primary investigator for all the patients that the relevant information was available. The simplified Wells score was used for the purposes of this study, because it has been shown to have similar validity as the original Wells score and may increase its applicability (29).

The three readers documented their CTPA findings on a CT data-collecting sheet (appendix C). The readers were blinded to the clinical findings.

A Qanadli score was calculated on the basis of CTPA result final decision. The calculations were done according to the method described by Qanadli (31) and categorised in increments of 10.

2.5. Reliability and validity

Three readers read all the scans: two qualified radiologists and the primary investigator (a registrar in the third year of radiology training), improving the reliability of the results. CTPA is considered a very sensitive and specific imaging modality for the diagnosis of PTED (1).

2.6. Bias

There is bias present as all the readers know that the study is assessing for PE therefore the readers will have a high index of suspicion for the presence of a pulmonary embolism. However, the readers did not have access to any clinical information that could give an indication of the risk of PE for individual patients.

2.7. Statistical analysis

1. Results were expressed as frequencies and percentages for categorical variables
2. Pearson's correlation was used to assess the association between Wells' score and Qanadli index, as well as between D-dimers and Qanadli index
3. Inter observer agreements were assessed using Randolph's Kappa.

3. Results

3.1. Constitution of study population

In the period between March 2012 and Feb 2013, 219 CTPA studies were performed at the diagnostic radiology department of Helen Joseph Hospital, fulfilling the inclusion criteria for this study. There were 146 scans found in the archives. Of these 146 scans, six were excluded, as they were non-diagnostic because of technical factors. A further eight patients were excluded as they lacked both clinical files and CTPA request forms.

The final number of patients that were included as the study population was 132 as depicted in figure 3.1 below.

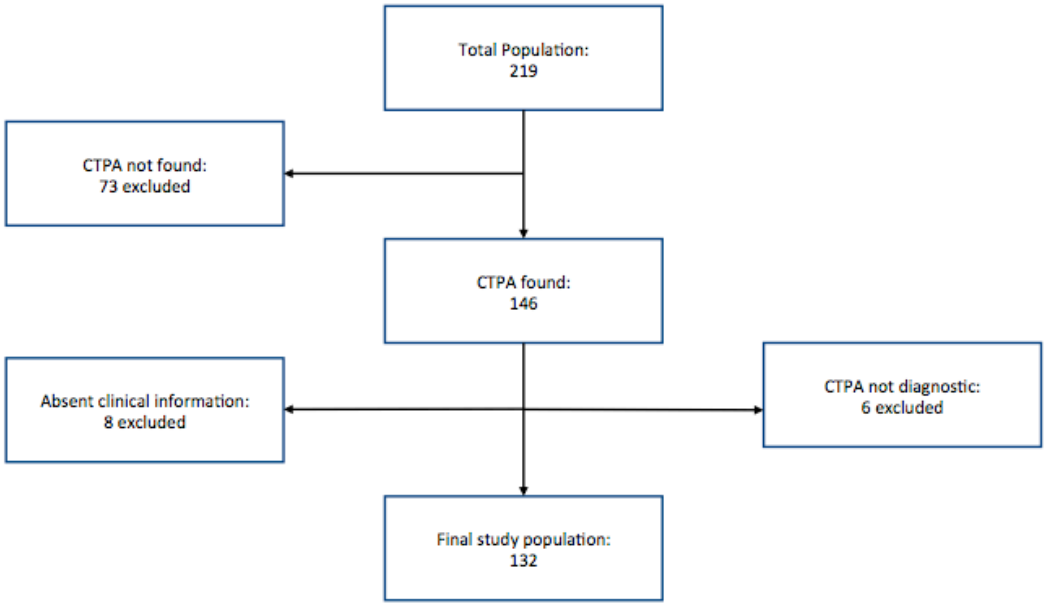


Figure 3.1. Flow diagram of the constitution of final study population

3.2. Demographics

A total of 132 patients were included in the study. The male to female ratio was 1:2.

The age ranged from 19 to 77 with a mean age of 48 and a median of 48. The majority of patients belonged to the 31 to 50 year old group.

3.3. Clinical factors in patients that underwent CTPA for suspected PE

3.3.1 Presenting symptoms in all patients

The most common presenting symptom was dyspnoea, with 75 (66%) of patients presenting in this way. It was common in patients with positive CTPAs as well as those that were negative. It was shown that there was no significant statistical difference between patients with a positive and a negative CTPA in presenting with dyspnoea. P-value = 0.99.

Presentation with chest pain was less common compared to dyspnoea, constituting 29 (25.6%) of all the patients in the study.

The least common symptom was haemoptysis and only 9 patients (7.9%) had this presentation.

Table 3.1. Comparison of CTPA findings in patients with different presenting symptoms

Presenting symptoms	CTPA positive N=49 (%)	CTPA negative N= 83 (%)	All patients N=132 (%)
Dyspnoea	33 (67.3%)	42 (50.6%)	75 (56.8%)
Chest pain	10 (20.4%)	19 (22.9%)	29 (22%)
Haemoptysis	3 (6.1%)	6 (7.2%)	9 (6.8%)
Other	10 (20.4%)	22 (26.5%)	32 (24.2%)
Not documented	4 (8.2%)	11 (13.2%)	15 (11.4%)

Note: Percentages don't add up to 100%, as some patients had more than 1 symptom

There was no statistically significant association between any of the symptoms and the presence of a positive CTPA. The odds ratio of presenting with dyspnoea (p=0.1), chest pain (p=0.61) or haemoptysis (p=0.73) did not show any statistically significant association with having pulmonary embolism. Table 3.2 demonstrates the odds ratios and p values of the presenting symptoms in association with presence of pulmonary embolism.

Table 3.2. Odds ratio of a positive CTPA when associated with a specific presenting symptom

Clinical factor	OR (95% CI) p-value
Dyspnoea	1.96 (0.87 – 4.41) 0.10
Chest pain	0.80 (0.33 – 1.92) 0.61
Haemoptysis	0.77 (0.18 – 3.26) 0.73

There were no significant differences between males and females with regards to presentation with dyspnoea as presented in Table 3.3. The percentage of males and females with dyspnoea was 60.6% and 68.8% respectively.

There were no significant differences between males and females with regards to presentation with chest pain, with 27.2% of males and 25% of females presenting this way.

Haemoptysis was seen in twice as many males as in females. Male patients had 12.1% rate of haemoptysis while females had 6.2%. This result was however, not statistically significant (p-value=0.3).

Table 3.3. Relation of gender to presenting symptoms

Symptom	Male n = 33(%)	Female n = 80 (%)	p-values
Dyspnoea	20 (60.6%)	55 (68.8%)	0.30
Chest pain	9 (27.2%)	20 (25.0%)	0.75
Haemoptysis	4 (12.1%)	5 (6.2%)	0.30
Total	43 (100%)	89 (100%)	

3.3.2. Wells score

3.3.2.1. Documentation of Wells score

In our sample cases, Wells score was poorly documented. It was either not documented or lacked the variables to be calculated from the patients' records in a large number of patients

(83 patients, 62.9%). The required information was present in only 49 (37.1%) of patients. There was no difference in the documentation of the Wells score between the patients with and without a positive CTPA. These findings are summarised in table 3.5. below.

Table 3.4. Prevalence of Wells score documentation

	CTPA positive n (%)	CTPA negative n (%)	Total n (%)
Wells calculated n=49	18 (37%)	31 (63%)	49/132 (37.1%)
Wells not calculated n=83	31 (37%)	52 (63%)	83/132 (62.9%)

3.3.2.2. Impact of Wells score on CTPA findings

The simplified Wells score was calculated according to the method described in Table 1.1. The results are shown in Table 3.5 below. We did not show any association between simplified Wells score and the presence or absence of a pulmonary embolism (p=0.93)

Table 3.5. Frequencies of simplified Wells scores in patients that underwent CTPA studies

Simplified Wells score	CTPA positive n = 18 (%)	CTPA negative n = 31(%)	All patients n = 49 (%)
1	5 (28%)	9 (29%)	14 (29%)
2 or more	13 (72%)	22 (71%)	35 (71%)
Total	18 (100)	31 (100)	49 (100%)

3.3.2.3. D-dimers

D-dimer values were recorded on the NHLS system for 87 patients (65.9%) Figure 3.2 demonstrates the different categories of D-dimer values in this study. The majority of patients had D-dimer values in the 0.5 to 1.99 mg/L (25 patients, 25/87 = 28.7%) and 2.0 to 4.99 mg/L categories (32 patients, 32/87 = 36.7%). Only 13 patients (13/87 = 14.9%) had D-dimer values less than 0.5mg/L and 17 (17/87 = 19.5%) had D-dimer levels above 5mg/L.

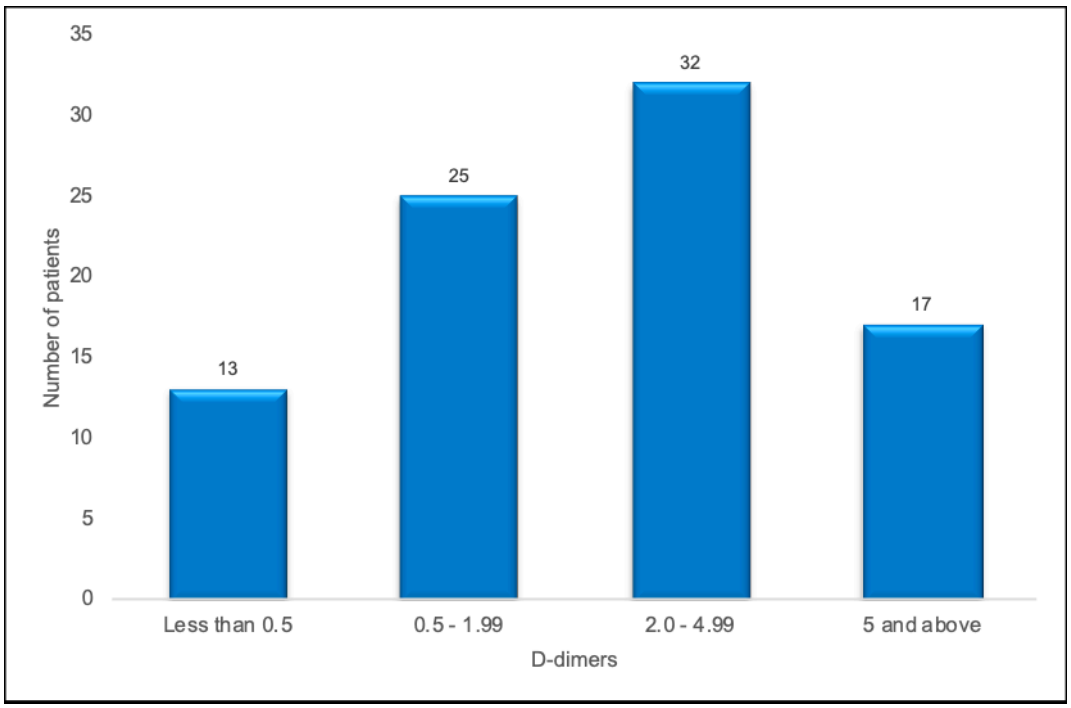


Figure 3.2. Frequency of D-dimer values in patients that underwent CTPA for suspected PE

Table 3.6 shows that the patients with a positive CTPA had D-dimer concentration in range of 0 to 17.6 mg/L with a median value of 2.65 mg/L. Those patients with a negative CTPA had D-dimer concentration that ranged between 0 to 11.1 mg/L and a median value of 1.73 mg/L.

The percentage of patients with D-dimer concentration above 0.5mg/L and positive CTPA was 91.2%. Three patients (8.8%) had pulmonary embolism and a negative D-dimer assay. A high percentage of patients had a positive D-dimer assay even though CTPA was negative for pulmonary embolism. Ten patients had a negative D-dimer level with a negative CTPA result.

Table 3.6. D-dimer values in patients that underwent CTPA for suspected PE

	Positive CTPA n (%)	Negative CTPA n (%)	All patients n (%)
D dimer available	34 (39%)	53 (69%)	87 (100)%
D dimer	0 – 17.6 mg/L	0 – 11.1 mg/L	0 – 17.6 mg/L
D dimer median	2.65 mg/L	1.73 mg/L	2.06mg/L
D dimer positive (> 0.5 mg/L)	31 (91.2%)	43 (81.1%)	74 (100%)
D dimer negative (< 0.5 mg/L)	3 (8.8%)	10 (18.9%)	13 (100%)

The odds of having a positive CTPA result increased with increasing concentration of D-dimer. The odds ratio of having pulmonary embolism when D-dimer was positive was 1.25 times higher than when D-dimer was negative. Patients with D-dimer concentration of 5mg/L and above had 6.11 times odds of having pulmonary embolism. This result was found to be statistically significant.

Table 3.7. Odds ratio of pulmonary embolism with increasing D-dimer level

D dimer	Positive CTPA n (%)	Negative CTPA n (%)	Odds Ratio OR (95% CI) p
Under 0.5	3 (23.1%)	10 (76.9%)	reference
0.5 – 1.99	6 (24%)	19 (76%)	1.05 (0.22 – 5.13) 0.95
2.0 – 4.99	14 (44%)	18 (56%)	2.59 (0.60 – 11.24) 0.20
5 and above	11 (65%)	6 (35%)	6.11 (1.19 – 31.16) 0.03
Any positive D-dimer	34 (39%)	53 (61%)	2.4 (0.61 – 9.46) 0.21

Table 3.8. Sensitivity, specificity, PPV and NPV of D-dimer test

	CTPA positive	CTPA negative	
D-dimer positive	31	43	PPV 41.9%
D-dimer negative	3	10	NPV 77%
	Sensitivity 91.2%	Specificity 18.9%	

Sensitivity of D-dimer test was found to be high at 91.2%, however specificity was low (18.9%) as presented in Table 3.8..

3.4. Findings on CTPA

3.4.1. Frequency of CTPA between males and females

There were more females than males in the study, with a male to female ratio of 1:2. Comparing the frequency of pulmonary emboli in the male and female groups, it was shown that there was no significant difference between the two genders. (P-value = 0.99) This is shown in table 3.9. below.

Table 3.9. Frequency of PE in patients that underwent CTPA for suspected PE by gender

	Male N=43	Female N=89	All patients
CTPA positive n (%)	16 (37.2%)	33 (37.1%)	49 (37%)
CTPA negative n (%)	27 (62.8%)	56 (62.9%)	83 (63%)
Total n (%)	43 (100%)	89 (100%)	132

3.4.2. Severity of PTED (Qanadli Index)

The Qanadli Index was calculated and categorised for patients with positive CTPA to assess the severity of the PTED according to the method described in section 2.4. Figure 3.3. shows that most patients had Qanadli scores between 10% and 20%. Patient numbers decreased with increasing Qanadli score.

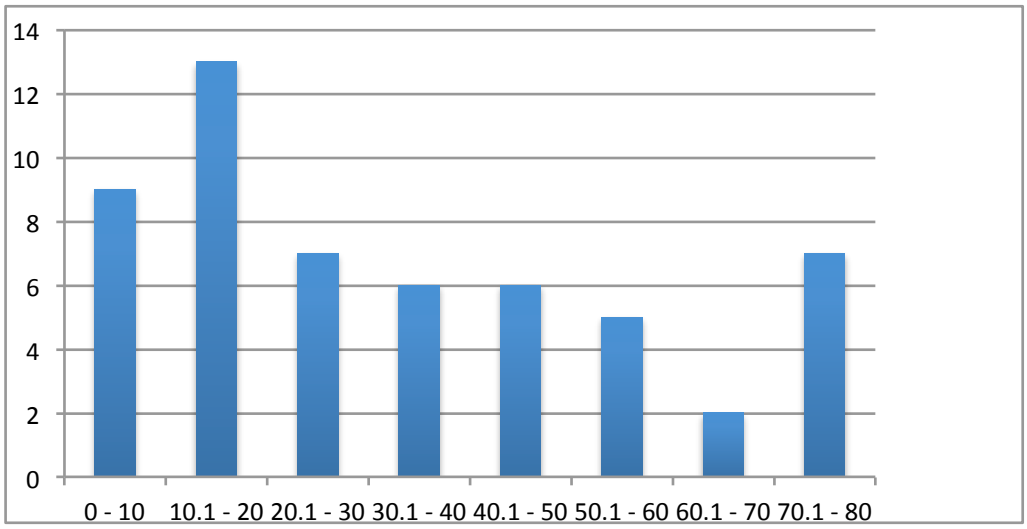


Figure 3.3. Frequency of Qanadli scores in this study population

3.4.3. Additional findings on CTPA

CTPA was able to diagnose some of the complications of PTED, such as pulmonary infarction, cardiomegaly or pulmonary hypertension. There was no significant difference between the CTPA positive and CTPA negative groups in the incidence of finding pulmonary hypertension or cardiomegaly. These two variables can occur as complications of pulmonary embolism however they are not specific for pulmonary embolism and they can be seen in a host of other conditions.

More patients with a positive CTPA (59%) showed reflux of contrast into the IVC compared to those with a negative CTPA (41%). This result was statistically significant (p = 0.001). Pulmonary infarction exclusively occurred in CTPA positive patients. These findings are shown in Table 3.10.

Table 3.10. Associated PE findings found on CTPA done for suspected PE

	CTPA positive N = 49	CTPA negative N = 83	OR (95% CI) p	Total
Pulmonary hypertension	22 (51%)	21 (49%)	2.40 (1.14 – 5.09) 0.02	43 (100)
Cardiomegaly	30 (48%)	32 (52%)	2.51 (1.22 – 5.20) 0.01	62 (100)
Reflux into IVC	24 (59%)	17 (41%)	3.72 (1.72 – 8.08) 0.001	41 (100)
Pulmonary infarction	13 (100%)	0 (0%)	1	13 (100)
Pleural Effusion	19 (44%)	24 (56%)	1.56 (0.74 -3.28) 0.24	43 (100)

Table 3.11. Alternate findings on CTPA

	CTPA positive N = 49	CTPA negative N = 83	OR (95% CI) p	Total
Consolidation	15 (33%)	31 (67%)	0.74 (0.34-1.57) 0.43	46 (100)
Pneumothorax	0	3 (100%)	1	3 (100)
Pulmonary / mediastinal mass	1 (17%)	5 (83%)	0.33 (0.04-2.87) 0.31	6 (100)
Emphysema	4 (24%)	13 (76%)	0.48 (0.15-1.56) 0.22	17 (100)
Any	17 (27%)	46 (73%)	0.42 (0.21 – 0.89) 0.02	63 (49%)
No alternate findings	32 (46%)	37(54%)	N/A	69/132 (53%)

There were numerous findings on CTPA that were not directly related to PTED, but could account for the presenting symptoms like dyspnoea, haemoptysis or chest pain. This includes consolidation, pneumothorax, masses and emphysema. These findings are shown in Table 3.11.

Half the patients in the whole study population were found to have alternate findings on CTPA. Most of these patients were CTPA negative with a frequency of 73.0%. The most common alternate finding was consolidation followed by pleural effusion and emphysema. There were 6 patients found to have a pulmonary/mediastinal mass and 3 patients had a pneumothorax..

In the CTPA was negative group, 67% were found to have consolidation. CTPA was completely normal in 28% of the patients with a negative CTPA.

The odds of having pulmonary embolus increased 1.25 times if D-dimers were elevated and there were even higher odds when D-dimers were equal or higher than 5. This increased the odds by 6.11. Amongst the presenting signs, it was only dyspnoea that had a statistically significant association with pulmonary embolism, increasing the odds by 5.62 in the multivariate analysis. Pulmonary hypertension, cardiomegaly, reflux of contrast into IVC and pulmonary infarction had a statistically significant association with pulmonary embolism with the odds of having a positive CTPA increasing by 2.40, 2.51, 3.72 and 29.6 for the respective variables.

There was no association between having pulmonary embolus and consolidation, pleural effusion, pulmonary/mediastinal mass.

3.5. Comparison of clinical and radiological severity scores

3.5.1. QI and Wells score

Comparison between the CTPA obstruction index (Qanadli Index) and the simplified Wells score was done. As can be seen in the scatter plot below, fig 3.4, there was no linear relationship between the two scores. The chi square test demonstrated no correlation at a value of 0.56 ($p = 0.015$).

The Kruskal-Wallis test was also performed and showed no relationship between the two scores ($p=0.2$).

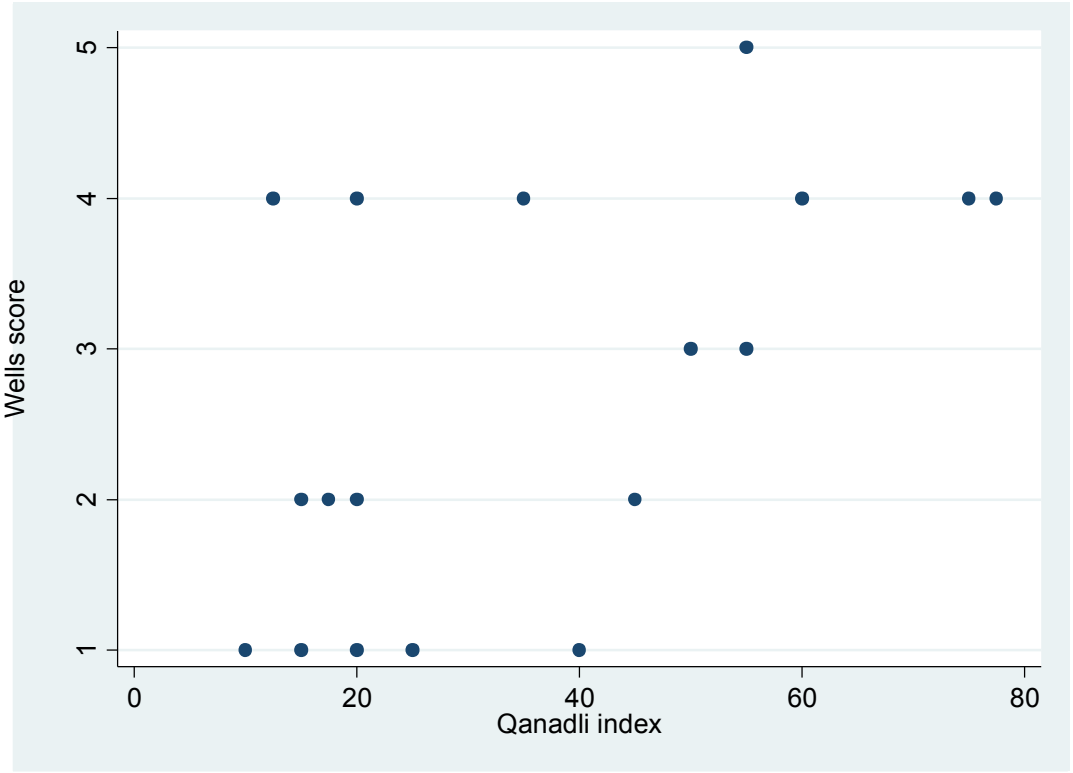


Figure 3.4. Scatter plot correlating Wells score and Qanadli index

3.5.2. Correlation of QI and D-dimers

Correlation between the Qanadli index and D-dimer level was calculated using Pearson's Correlation and found to be 0.05 (p = 0.78). This result demonstrates no correlation between the two variables and this can be seen in the scatter plot below (figure 3.5) that there is no relationship.

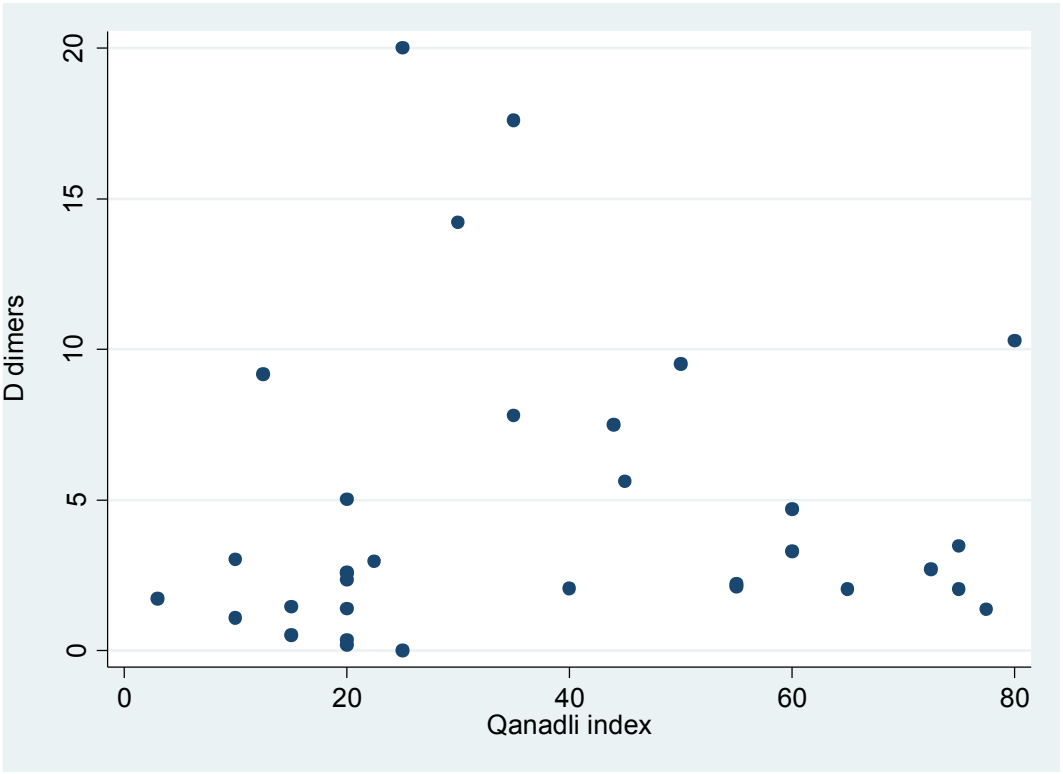


Figure 3.5. Scatter plot correlating D-dimer level and Qanadli index

3.6. Influence of HIV status on CTPA findings

3.6.1. HIV and presence of pulmonary embolism

The HIV status was recorded on the NHLS system for 108 patients (108 / 132 = 81.8%) and 24 (24 / 132 = 18.2%) patients did not have results available. Of the 108 patients that had documentation of their HIV status, 50 patients (50 / 108 = 46.3%) were found to be HIV positive while 58 (58 / 108 = 53.7%) were HIV negative. The HIV status of the patients that underwent CTPA for suspected pulmonary embolism is documented in Table 3.12. below. Odds ratio of patients with HIV for the presence of PE was 2.84 and this result was statistically significant with a p value of 0.01.

Univariable and multivariable analysis demonstrated statistically significant increase in the odds of having pulmonary embolus when HIV positive, when there's dyspnoea as presentation and when D-dimer is elevated. The odds of having pulmonary embolus increased 2.84 times in HIV positive patients.

Table 3.12. HIV status of patients that underwent CTPA for suspected PE

	CTPA positive (%) N=49	CTPA negative (%) N=83	Odds Ratio (CI) P	All patients (%) N=132
HIV positive	26 (53.1%)	24 (28.9%)	2.84 (1.28 – 6.33) 0.01	50 (37.9%)
HIV negative	16 (32.7%)	42 (50.6%)	Reference	58 (43.9%)
HIV unknown	7 (14.3%)	17 (20.5%)	1.08 (0.38 – 3.09) 0.89	24 (18.2%)
Total	49 (100%)	83 (100%)		132 (100%)

3.6.2. Parenchymal findings in HIV positive patients

The parenchymal findings of patients with and without HIV were similar. These findings are shown in Table 3.13. below.

Table 3.13. Comparison of HIV positive and negative patients with presence of parenchymal findings on CTPA

	HIV positive N = 50 (%)	HIV negative N = 58 (%)	HIV unknown N = 24 (%)	p-value	All patients N = 132 (%)
Pulmonary hypertension	19 (44%)	19 (44%)	5 (12%)	0.34	43 (100%)
Cardiomegaly	26 (40%)	25 (42%)	11 (18%)	0.64	62 (100%)
Reflux into IVC	16 (39%)	19 (46%)	6 (15%)	0.76	41 (100%)
Pulmonary infarction	8 (61%)	4 (31.%)	1 (8%)	0.17	13 (100%)
Consolidation	19 (41%)	18 (39%)	9 (20%)	0.72	46 (100%)
Pleural Effusion	17 (40%)	17 (40%)	9 (20%)	0.74	43 (100%)
Pneumothorax	0 (0%)	2 (67%)	1 (33%)	0.39	3 (100%)
Pulmonary / mediastinal mass	2 (33%)	4 (67%)	0 (0%)	0.38	6 (100%)
Emphysema	4 (24%)	9 (53%)	4 (23%)	0.42	17(100%)

3.7. Interobserver agreement on CTPA findings

Table 3.14. Demonstrates the CTPA results as read by the different radiologists in our study. The frequency of finding a positive CTPA was concluded to be 37%.

Table 3.14. Differences between readers and final CTPA result

	Reader 1 n (%)	Reader 2 n (%)	Reader 3 n (%)	CTPA Result n (%)
CTPA negative	84 (64%)	94 (71%)	80 (61%)	83 (63%)
CTPA positive	48 (36%)	38 (29%)	52 (39%)	49 (37%)

The interobserver agreement was calculated using Randolph's kappa. This is shown in Table 3.16. below. The interobserver agreement for the presence of PE was moderate (K = 0.60). There was substantial agreement (kappa values of more or equal to 0.7) between the readers when evaluating findings other than pulmonary embolus on CT.
Interobserver levels of agreement are described in Table 3.15. below.

Table 3.15. Kappa Agreement

Kappa	**Agreement**
<0	Less than chance agreement
0.01 – 0.20	Slight agreement
0.21 – 0.40	Fair agreement
0.41 – 0.60	Moderate agreement
0.61 – 0.80	Substantial agreement
0.81 – 0.99	Almost perfect agreement

Table 3.16. Randolph Kappa agreement for all variables

Variable	Frequency	Randolph's	Kappa agreement

		Kappa	
CTPA result	49%	0.60	Moderate
Pulmonary hypertension	32.6%	0.70	Substantial
Cardiomegaly	47.0%	0.73	Substantial
Pleural Effusion	32.6%	1.0	Perfect
Consolidation	34.8%	1.0	Perfect
Pneumothorax	2.3%	1.0	Perfect
Pulmonary / Mediastinal mass	4.5%	1.0	Perfect
Emphysema	12.9%	1.0	Perfect

4. Discussion

There is an increasing trend for the utilisation of CTPA in recent years. This may be attributed to the wide availability of the study, its sensitivity for detecting the presence of pulmonary embolism and the ability to detect findings other than PE, which may explain patient symptoms. The problem arises if the detection rate is not high enough to justify the cost and exposure to radiation. There are clinical predictive scores that have proven to correlate well with the presence of pulmonary embolism. However, these are often not used. If the clinical guidelines were to be strictly utilised, then the yield of CTPA for presence of pulmonary embolism would rise and the cost burden be ameliorated.

4.1. Demographics

The male to female ratio of the patients included in our study was 1:2, but the percentage of positive scans was the same in both genders. This is in contrast to other studies, which reported M:F ratios ranging from 1:1.6 to 1:1 (42, 43). Chen et al found that there are more requests for CTPA for female patients than male patients with no significant differences in the yield (44). This was found to be true in our study as well, with 67% of our study population being female, but with no difference in rates of positive PE between the genders.

4.2. Clinical symptoms

We found that 72% of patients with positive CTPAs presented with dyspnoea. Chest pain and haemoptysis were less common. This is comparable to the PIOPED study (45) that found that dyspnoea was present in 75% of patients with PE. They found the most common presenting symptom to be dyspnoea, or a combination of dyspnoea and pleuritic chest pain with a smaller number presenting with haemoptysis or other symptoms (21). Donnamaria et al showed that pulmonary embolism was very unlikely without dyspnoea, tachypnoea, pleuritic chest pain or signs of DVT (22). Dyspnoea was seen in 92% of patients with pulmonary embolism in the proximal pulmonary arteries (22). Although we showed that 50% more males presented with haemoptysis, this was not statistically significant in our small study population. The much larger study carried out by Donnamaria did demonstrate that this difference is statistically significant (22).

4.3. D-dimer concentration

The cut off level used for a positive D-dimer in our setting is 0.5mg/L, which is also used in many laboratories worldwide. It has been shown that if the cut off for D-dimers was adjusted for age, many CTPA would be avoided as D-dimer levels tend to rise with age (46).

In our study D-dimer levels in patients with **positive** CTPA had a median value of 2.65 and those that were **negative** had median value of 1.73. Our study also showed that the odds of having a positive CTPA increased by at least 1.25 for any level of D-dimer above 0.5mg/L. There was a very high odds ratio (6.11) when D dimer was above or equal to 5mg/L. These results showed statistical significance.

The mean D-dimer level found in both the pulmonary embolus positive and negative groups was lower than the mean level found in the literature. In a study by Shah et al in 2013 it was shown the mean D-dimer for the positive CTPA group was 4.9mg/L and that for the CTPA negative group was 2.01mg/L (47). They also demonstrated that if the D-dimer level increases, so is the likelihood of having pulmonary embolism with odds ratio of 1.17 and a markedly elevated D-dimer of more than 20mg/L, had a positive predictive value of pulmonary embolism of 45% (48)(49). In addition they also suggested that there might also be association between severity of pulmonary embolism and the rising level of D-dimers (48)(49). Hoo et al showed similar findings: that D-dimer elevation beyond 3mg/L is associated with a very high odds ratio of 6.69 of having pulmonary embolus (37).

In our study, 3 (8%) patients were found to have D-dimer levels lower that 0.5mg/L and a positive CTPA. This shows a very good negative predictive value (77%) of a negative D-dimer and it was confirmed by the literature.

The negative predictive value of D-dimer test ranges between 91 and 100% according to a number of studies (48-51). In our study, 23% of patients with a negative D-dimer (less than 0.5 mg/L) were found to have pulmonary embolus, therefore resulting in a negative predictive value of 77%. This result is lower than that reported in the literature and most likely influenced by the smaller sample size of our study as the absolute number of patients with a negative D-dimer and a positive CTPA were only 3.

We found a high frequency (81%) of patients to have negative CTPA and a high D-dimer level. The specificity of D-dimer test in our study was found to be 18.9%. This finding is in correlation with what is already known about the D-dimer test, that it has a low specificity. The specificity of D-dimer test in the literature is in the region of 39% (50, 52).

Several studies show that the sensitivity of D-dimer for the presence of pulmonary embolism ranges between 89% and 96.4% (49, 50, 52). Our study confirmed this, with a sensitivity of 91.2%.

Even though D-dimer test has a good negative predictive value, there were 3 patients that we found to have pulmonary embolus with a negative D-dimer (NPV = 77%). There is a study that had similar results with 5.6% of patients with pulmonary embolism and negative D-dimers (52). In our study 9.0% of patients had positive CTPA with negative D-dimers. According to Parent et al, D-dimer accuracy also depends on the location of the embolus, with better accuracy seen in the larger and segmental artery emboli than in sub-segmental vessels (54, Goy J). In another study, only 0.3% of patients had positive CTPA with negative D-dimer (51). This study was large with 1106 patients analysed for presence of PE and level of D-dimer (51). They found that despite finding 24% of patients with normal D-dimers, imaging was still done which could have been avoided, considering the high sensitivity of the test, which was 96.4% in that study (51).

4.4. Wells score documentation

Calculating the Wells score has clinical significance. Shujaat et al found that high clinical probability score yields PE in 100% of patients, moderate clinical probability score yields PE in 72% and low clinical probability score yields PE only in 7.3% of patients (3). When there is a high clinical probability for PE as calculated by a well-recognized probability score, the yield of CTPA increases significantly.

In our study only 25% of patients had enough information to calculate the Wells score. This frequency was higher than that found in the literature, but it was still too low to yield results of any statistically significant value. A number of studies also showed poor documentation of Wells score, making it difficult for them to assess the relationship between the findings of CTPA and the Wells score. Walen et al study was unable to assess this relationship as only

13% of patients had Wells score documented (36). In a 2013 CTPA study of 4000 patients Hedner et al found the information needed to calculate Wells score in only 0,4% of patients (53).

4.5. CTPA findings

The positive yield of CTPA for PE ranges 15 – 38.9% in most studies in the literature (3, 7, 36, 44, 54, 55).

Our study found the frequency of pulmonary embolism to be 37%, which is at the high end of the range found in most studies. A possible reason for the higher yield in our study is the significant incidence of HIV infection. HIV infection leads to a 2 – 10 fold increase in the frequency of venous thrombosis (20). Thus our population is likely to have a higher frequency of venous thrombosis and therefore pulmonary embolism. The studies mentioned above did not investigate the impact of HIV infection on the outcome of CTPA.

Shujaat showed that a combination of a D-dimer level above 3.0mg/L and Wells score of more than 4 were even better predictors of having a positive CTPA with odds ratio of 6.69 (3). This was difficult to assess in our study as there were a limited number of patients found to have Wells score documented and very few with both Wells score and D-dimers documented. It is well known that as D-dimer concentration increases, the likelihood of having pulmonary embolism also increases (48). The same problem was faced by Walen et al where they could not interpret the association of Wells score and CTPA yield due poor documentation of Wells score by the clinicians (36). Only 10% of patients in the Whalen study had both D-dimers and Wells score documented (36). They showed a CTPA yield of 23% and they attributed the high yield to advancing technology in scanning, leading to visualisation of small sub segmental emboli, however they also continue to say that the clinical relevance of these emboli is still controversial (36).

4.5.1. D-dimer correlated with pulmonary artery obstruction index

Our study did not show any correlation between the level of D-dimer and the pulmonary artery obstruction severity index (Qanadli score). This is in contrast to a number of studies that showed a significant correlation between the two variables. Ji quoted a few studies that have shown that with increasing level of D-dimer value, the pulmonary artery obstruction

severity index (PAOI) also increases (31). This relationship between increasing D-dimer value and the PAOI was shown using different clot burden scores. It was also shown that patients with a high clot burden have higher D-dimer levels, using the Miller score (31).
This relationship was also demonstrated by Ghanima using Qanadli score (56). According to Ji Y et al, the PAOI of more than 21.3 is associated with a higher D-dimer level and mentioned that this association could be because the higher the clot burden, the higher will be the degradation products, thereby increasing the D-dimer level (31).

Significant Pearson correlation of between 0.36 and 0.5 was found in a few studies, also indicating significant linear association (32, 56, 57). This relationship is important because some have suggested that a D-dimer level can predict the severity of pulmonary embolism and therefore it can be used as an easy test to predict mortality or prognosis (32).

Kucher et al used the Miller index and divided the patients into three categories of clot burden (58). Patients with index of less than 30%, 30 – 80% and more than 80% had average D-dimer concentration of 1960, 2885 and 6638 ng/ml respectively. The small number of patients found to have recorded D-dimers could explain the lack of association in our study. The low numbers made it difficult to interpret the influence of D-dimer on the severity index.

4.5.2. Alternate diagnosis on CTPA

Alternative findings were found in 63 patients in our study. Of these, 46 (73%) did not have pulmonary embolus. These results are comparable with those found in a study by van Es et al where they found alternate diagnosis in 43% of patients (59). They also reported that an alternative diagnosis is seen in 25 – 52% in most studies (59).

Consolidation and atelectasis are the most common findings followed by pleural effusion and pulmonary nodules in a number of studies (12, 59-63). It is known that pleural effusion can complicate pulmonary embolism however when associated with PE it is usually unilateral and too small for diagnostic thoracentesis (62). The presence of pleural effusion is not associated with clot burden as mentioned in one study (62).

There is a large study that ran between the years 2000 to 2010 with more than 12000 patients in the study population, that proved that the diagnosis of alternate finding is not a good enough reason for the increase in the use of CTPA (12). They found that 47% of patients had an alternate diagnosis that was seen on CXR but CTPA was ordered anyway (12).

4.4. HIV status

The frequency of HIV positive patients in the study population was 37.8%, in contrast to the frequency of HIV in the general adult population in South Africa in 2013 of 18.5% in the adult population, according to Statistics South Africa (64). The possible reasons for this high incidence are that the hospital where the study was conducted has a large HIV/AIDS clinic. The other possible reason is that HIV infected individuals are more likely to present with respiratory symptoms due to the higher risk of opportunistic infections. They are therefore more likely to be in the study population because even when they have opportunistic infections they can still present with clinical symptoms similar to pulmonary embolism. They are also more likely to present with venous thrombosis (18, 20).

Of those with pulmonary embolism, 61.9% were HIV infected. Of the HIV negative patients, 63.6% were CTPA negative. The frequency of pulmonary embolism in the HIV infected population was 52%, which is higher than other comparable studies (20, 65). The main studies looking at the incidence of venous thromboembolism in HIV infected individuals reported a range between 0.19 to 7.63% per year (20, 65). Most of these studies were in the pre HAART era and they were conducted in the western countries where the prevalence of HIV is much lower than in South Africa. A more recent study done in the Danish population showed an incidence of 8 to 15% of venous thromboembolism in HIV infected persons (6). This study was done in the period 1995 – 2007 (20).

The studies that were done between 1991 and 2007 concluded that there is a 2 to 10 fold higher risk of venous thromboembolism in chronic HIV infection, compared to the general population (20). There are studies which also showed that HAART may also have a role in increasing the incidence of thromboembolic disease, however there is still controversy about this matter with some studies suggesting multifactorial cause for the association of venous thrombosis and HAART (20) This increase in incidence post HAART era was also seen in a

study done between 1990 to 2005 which showed an increase of venous thrombosis post initiation of HAART with relative risk rising from 1.23 to 1.43 (66).

Shah reported that there is an increase of 43% of developing pulmonary embolism in HIV infection with the odds ratio of 1.43 (47). A higher odds ratio of 1.58 was found in the 21 – 50 age group (47).

In our study the odds ratio of pulmonary embolism associated with HIV was found to be 2.84 and this result was statistically significant.

4.5. Interobserver agreement

CTPA is a gold standard imaging modality for diagnosing pulmonary embolism and it has a reliable interobserver agreement in the international literature. The interobserver agreement in CTPA findings ranges between a Kappa of 0.75 – 0.93 in most studies (67-71). It was also found that the agreement between the on call radiology registrars and the consultant radiologist is also very good (68, 70-72).

Randolph's Kappa was used to calculate the interobserver agreement between the 3 readers in this study. This showed a moderate agreement on the presence of a PE (kappa = 0.60). This was slightly lower than in other studies (67-71). A possible reason for the lower agreement could be that pulmonary embolism in the small sub-segmental vessels can be difficult to diagnose and a substantial number of patients in our study had only peripheral pulmonary emboli. Furthermore, our CTPA examinations were done on a 16-slice scanner, which is a lot more susceptible to partial volume artefacts, contributing to the fact that agreement was only moderate. The interobserver agreement was substantial to perfect for all other findings on the CTPA scans in our study.

4.6. Current applications/Recommendations

It has been shown in this study that there is a very poor documentation of the Wells score in patients suspected of having pulmonary embolism. International societies recommend the use of the clinical probability scores before further tests are done. It should be stressed to the referring clinicians to document Wells score before CTPA study is requested. This might

enforce the application of these scores in assessing patients for the possibility of pulmonary embolism.

Our study also confirms that a high D-dimer level is sensitive for the presence of pulmonary embolism and therefore CTPA need not be done if the D-dimer is negative and should be included in the protocol for investigation of pulmonary embolus.

A very high percentage of alternative findings were found in patients without pulmonary embolism. This means that there is a possibility that CTPA could have been avoided in these patients if these findings were diagnosed by other means. Most of these findings were likely to have been seen on plain CXR. We can therefore apply this result by requesting to see the CXR before CTPA is done in the protocols, however, also noting that the presence of plain film findings would not exclude pulmonary embolus.

4.7. Limitations of the current study

This was a retrospective study with all the limitations that comes with a study of this nature. There was incomplete documentation of clinical findings, missing files and reader bias. Reader bias was addressed by having three readers read the images, but the readers knew that the patients had suspected PE.

4.8. Future applications

A prospective study with documentation of the Wells score should be done to correlate this clinical probability score with frequency of positive CTPA.

A study population with a bigger sample might be able to show correlation of D-dimer level with Qanadli score which might help in the future for predicting the severity of pulmonary embolism without the need to calculate the severity score and tailor treatment accordingly.

The influence of HIV on pulmonary embolism should be explored further in our setting to assess the usefulness of D-dimer testing in HIV infected patients with suspicion of pulmonary embolism. The possibility of a modified Wells score for HIV infected patients should be explored.

5. Conclusion

A significant number of patients with pulmonary embolism present with dyspnoea, however this symptom is not specific for presence of PE as it is seen in equal numbers in patients without PE and those with other cardiopulmonary conditions.

In our setting, patients are referred to radiology for CTPA without assessment of the clinical probability scores for pulmonary embolism despite this being a recommendation by various international expert societies. A high number of these patients are found to have alternate findings on CTPA studies which in retrospect most likely could have been diagnosed on CXR, which is less costly and delivers much less radiation to the patients.

In a resource-limited environment like our setting, strict international guidelines should be adhered to so as to limit inappropriate usage of CTPA studies, reducing the financial burden imposed onto our health care system. D-dimer levels should also be sought as we showed that even in our setting this test is very sensitive to the presence of pulmonary embolism and its use can avoid unnecessary performance of CTPA studies.

HIV increases the risk of having venous thromboembolism and as there is a high prevalence of this disease in our population, perhaps our criteria for accepting CTPA requests should include HIV status.

6. References

(1) Belohlavek J, Dytrych V, Linhart A. 2013. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Experimental and clinical cardiology*, 18(2):129-38.

(2) 1997. Suspected acute pulmonary embolism: a practical approach. British Thoracic Society, Standards of Care Committee. *Thorax*, 52 Suppl 4:S1-24.

(3) Shujaat A, Shapiro JM, Eden E. 2013. Utilization of CT Pulmonary Angiography in Suspected Pulmonary Embolism in a Major Urban Emergency Department. *Pulmonary medicine*, 2013:915213.

(4) Duriseti RS, Brandeau ML. 2010. Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms. *Annals of emergency medicine*, 56(4):321-32 e10.

(5) Pforte A. 2004. Epidemiology, diagnosis, and therapy of pulmonary embolism. *European journal of medical research*, 9(4):171-9.

(6) Stein PD, Woodard PK, Weg JG*, et al.* 2007. Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II Investigators. *Radiology*, 242(1):15-21.

(7) Costa AF, Basseri H, Sheikh A*, et al.* 2014. The yield of CT pulmonary angiograms to exclude acute pulmonary embolism. *Emergency radiology*, 21(2):133-41.

(8) Langan CJ, Weingart S. 2006. New diagnostic and treatment modalities for pulmonary embolism: one path through the confusion. *The Mount Sinai journal of medicine, New York*, 73(2):528-41.

(9) Tick LW, Nijkeuter M, Kramer MH*, et al.* 2008. High D-dimer levels increase the likelihood of pulmonary embolism. *Journal of internal medicine*, 264(2):195-200.

(10) Riedel M. 2004. Diagnosing pulmonary embolism. *Postgraduate medical journal*, 80(944):309-19.

(11) Mittadodla PS, Kumar S, Smith E*, et al.* 2013. CT pulmonary angiography: an over-utilized imaging modality in hospitalized patients with suspected pulmonary embolism. *Journal of community hospital internal medicine perspectives*, 3(1).

(12) Chandra S, Sarkar PK, Chandra D*, et al.* 2013. Finding an alternative diagnosis does not justify increased use of CT-pulmonary angiography. *BMC pulmonary medicine*, 13:9.

(13) Yucel I, Akar M, Durukan A*, et al.* 2005. The effect of the menstrual cycle on the optic nerve head analysis of migrainous women. *Current eye research*, 30(3):163-9.

(14) Moheimani F, Jackson DE. 2011. Venous thromboembolism: classification, risk factors, diagnosis, and management. *ISRN hematology*, 2011:124610.

(15) Hwang HG, Schulman S. 2013. Respiratory Review of 2013: Pulmonary Thromboembolism. *Tuberculosis and respiratory diseases*, 75(3):89-94.

(16) White RH, Keenan CR. 2009. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thrombosis research*, 123 Suppl 4:S11-7.

(17) Wun T, White RH. 2009. Epidemiology of cancer-related venous thromboembolism. *Best practice & research Clinical haematology*, 22(1):9-23.

(18) Veller M, Pillai J. 2009. Deep-vein thrombosis and pulmonary embolism coexist to cause significant morbidity and mortality. *CME*, 27(7):306-11.

(19) Riedel M. 2001. Acute pulmonary embolism 1: pathophysiology, clinical presentation, and diagnosis. *Heart*, 85(2):229-40.

(20) Bibas M, Biava G, Antinori A. 2011. HIV-Associated Venous Thromboembolism. *Mediterranean journal of hematology and infectious diseases*, 3(1):e2011030.

(21) Stein PD, Beemath A, Matta F*, et al.* 2007. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. *The American journal of medicine*, 120(10):871-9.

(22) Donnamaria V, Palla A, Giuntini C. 1994. Gender, age and clinical signs in patients suspected of pulmonary embolism. *Respiration; international review of thoracic diseases*, 61(1):1-7.

(23) Yin F, Wilson T, Della Fave A*, et al.* 2012. Inappropriate use of D-dimer assay and pulmonary CT angiography in the evaluation of suspected acute pulmonary embolism. *American journal of medical quality : the official journal of the American College of Medical Quality*, 27(1):74-9.

(24) Furlan A, Aghayev A, Chang CC*, et al.* 2012. Short-term mortality in acute pulmonary embolism: clot burden and signs of right heart dysfunction at CT pulmonary angiography. *Radiology*, 265(1):283-93.

(25) Crichlow A, Cuker A, Mills AM. 2012. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*, 19(11):1219-26.

(26) Schembri GP, Miller AE, Smart R. 2010. Radiation dosimetry and safety issues in the investigation of pulmonary embolism. *Seminars in nuclear medicine*, 40(6):442-54.

(27) Dijk FN, Curtin J, Lord D*, et al.* 2012. Pulmonary embolism in children. *Paediatric respiratory reviews*, 13(2):112-22.

(28) Roy PM, Colombet I, Durieux P*, et al.* 2005. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. *Bmj*, 331(7511):259.

(29) Douma RA, Gibson NS, Gerdes VE*, et al.* 2009. Validity and clinical utility of the simplified Wells rule for assessing clinical probability for the exclusion of pulmonary embolism. *Thrombosis and haemostasis*, 101(1):197-200.

(30) Wells PS, Anderson DR, Rodger M*, et al.* 2000. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thrombosis and haemostasis*, 83(3):416-20.

(31) Ji Y, Sun B, Juggessur-Mungur KS*, et al.* 2014. Correlation of D-dimer level with the radiological severity indexes of pulmonary embolism on computed tomography pulmonary angiography. *Chinese medical journal*, 127(11):2025-9.

(32) Jeebun V, Doe SJ, Singh L*, et al.* 2010. Are clinical parameters and biomarkers predictive of severity of acute pulmonary emboli on CTPA? *QJM : monthly journal of the Association of Physicians*, 103(2):91-7.

(33) Group BTSSoCCPEGD. 2003. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax*, 58(6):470-83.

(34) Leung AN, Bull TM, Jaeschke R*, et al.* 2012. American Thoracic Society documents: an official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline--Evaluation of Suspected Pulmonary Embolism in Pregnancy. *Radiology*, 262(2):635-46.

(35) Remy-Jardin M, Pistolesi M, Goodman LR*, et al.* 2007. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. *Radiology*, 245(2):315-29.

(36) Walen S, Leijstra MA, Uil SM*, et al.* 2014. Diagnostic yield of CT thorax angiography in patients suspected of pulmonary embolism: independent predictors and protocol adherence. *Insights into imaging*.

(37) Hoo GW, Wu CC, Vazirani S*, et al.* 2011. Does a clinical decision rule using D-dimer level improve the yield of pulmonary CT angiography? *AJR American journal of roentgenology*, 196(5):1059-64.

(38) Donohoo JH, Mayo-Smith WW, Pezzullo JA*, et al.* 2008. Utilization patterns and diagnostic yield of 3421 consecutive multidetector row computed tomography pulmonary angiograms in a busy emergency department. *Journal of computer assisted tomography*, 32(3):421-5.

(39) van Belle A, Buller HR, Huisman MV*, et al.* 2006. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA : the journal of the American Medical Association*, 295(2):172-9.

(40) Perrier A, Roy PM, Sanchez O*, et al.* 2005. Multidetector-row computed tomography in suspected pulmonary embolism. *The New England journal of medicine*, 352(17):1760-8.

(41) Wells PS, Anderson DR, Rodger M*, et al.* 2001. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Annals of internal medicine*, 135(2):98-107.

(42) Keenan CR, White RH. 2007. The effects of race/ethnicity and sex on the risk of venous thromboembolism. *Current opinion in pulmonary medicine*, 13(5):377-83.

(43) Groth M, Henes FO, Mayer U*, et al.* 2012. Age-related incidence of pulmonary embolism and additional pathologic findings detected by computed tomography pulmonary angiography. *European journal of radiology*, 81(8):1913-6.

(44) Chen YA, Gray BG, Bandiera G*, et al.* 2015. Variation in the utilization and positivity rates of CT pulmonary angiography among emergency physicians at a tertiary academic emergency department. *Emergency radiology*, 22(3):221-9.

(45) Stein PD, Henry JW. 1997. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. *Chest*, 112(4):974-9.

(46) Altmann MM, Wrede CE, Peetz D*, et al.* 2015. Age-Dependent D-dimer Cut-off to Avoid Unnecessary CT-Exams for Ruling-out Pulmonary Embolism. *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin*, 187(9):795-800.

(47) Shah K, Quaas J, Rolston D*, et al.* 2013. Magnitude of D-dimer matters for diagnosing pulmonary embolus. *The American journal of emergency medicine*, 31(6):942-5.

(48) Deonarine P, de Wet C, McGhee A. 2012. Computed tomographic pulmonary angiography and pulmonary embolism: predictive value of a d-dimer assay. *BMC research notes*, 5:104.

(49) Dunn KL, Wolf JP, Dorfman DM*, et al.* 2002. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. *Journal of the American College of Cardiology*, 40(8):1475-8.

(50) Froehling DA, Elkin PL, Swensen SJ*, et al.* 2004. Sensitivity and specificity of the semiquantitative latex agglutination D-dimer assay for the diagnosis of acute pulmonary embolism as defined by computed tomographic angiography. *Mayo Clinic proceedings*, 79(2):164-8.

(51) Huckins DS, Price LL, Gilley K. 2012. Utilization and yield of chest computed tomographic angiography associated with low positive D-dimer levels. *The Journal of emergency medicine*, 43(2):211-20.

(52) Parent F, Maitre S, Meyer G*, et al.* 2007. Diagnostic value of D-dimer in patients with suspected pulmonary embolism: results from a multicentre outcome study. *Thrombosis research*, 120(2):195-200.

(53) Hedner C, Sundgren PC, Kelly AM. 2013. Associations between presence of relevant information in referrals to radiology and prevalence rates in patients with suspected pulmonary embolism. *Academic radiology*, 20(9):1115-21.

(54) Goy J, Lee J, Levine O*, et al.* 2015. Sub-segmental pulmonary embolism in three academic teaching hospitals: a review of management and outcomes. *Journal of thrombosis and haemostasis : JTH*, 13(2):214-8.

(55) Kurcz J, Garcarek J, Guzinski M*, et al.* 2013. Multislice computed tomography angiography as an imaging modality of choice in patients with suspicion of pulmonary embolism - own experiences and modern imaging techniques. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University*, 22(5):705-13.

(56) Ghanima W, Abdelnoor M, Holmen LO*, et al.* 2007. D-dimer level is associated with the extent of pulmonary embolism. *Thrombosis research*, 120(2):281-8.

(57) Goldin Y, Berliner S, Rogowski O*, et al.* 2008. Correlated expression of D-dimer concentrations with thrombotic burden in acute pulmonary embolism. *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis*, 19(2):153-8.

(58) Kucher N, Rossi E, De Rosa M*, et al.* 2006. Massive pulmonary embolism. *Circulation*, 113(4):577-82.

(59) van Es J, Douma RA, Schreuder SM*, et al.* 2013. Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism. *Chest*, 144(6):1893-9.

(60) Green DB, Raptis CA, Alvaro Huete Garin I*, et al.* 2015. Negative Computed Tomography for Acute Pulmonary Embolism: Important Differential Diagnosis Considerations for Acute Dyspnea. *Radiologic clinics of North America*, 53(4):789-99, ix.

(61) Lin YT, Tsai IC, Tsai WL*, et al.* 2010. Comprehensive evaluation of CT pulmonary angiography for patients suspected of having pulmonary embolism. *The international journal of cardiovascular imaging*, 26 Suppl 1:111-20.

(62) Liu M, Cui A, Zhai ZG*, et al.* 2015. Incidence of pleural effusion in patients with pulmonary embolism. *Chinese medical journal*, 128(8):1032-6.

(63) Moriarty JM, Bolster F, O'Connor C*, et al.* 2015. Frequency of nonthromboembolic imaging abnormalities in pregnant women referred for computed tomography pulmonary arteriography. *Canadian Association of Radiologists journal = Journal l'Association canadienne des radiologistes*, 66(1):24-9.

(64) Statistics South Africa. 2015. Mid-year Population Estimates. Available: https://http://www.statssa.gov.za/publications/P0302/P03022015.pdf [Accessed on 13/05/2017].

(65) Rasmussen LD, Dybdal M, Gerstoft J*, et al.* 2011. HIV and risk of venous thromboembolism: a Danish nationwide population-based cohort study. *HIV medicine*, 12(4):202-10.

(66) Malek J, Rogers R, Kufera J*, et al.* 2011. Venous thromboembolic disease in the HIV-infected patient. *The American journal of emergency medicine*, 29(3):278-82.

(67) Courtney DM, Kline JA, Kabrhel C*, et al.* 2010. Clinical features from the history and physical examination that predict the presence or absence of pulmonary embolism in symptomatic emergency department patients: results of a prospective, multicenter study. *Annals of emergency medicine*, 55(4):307-15 e1.

(68) Hochhegger B, Alves GR, Chaves M*, et al.* 2014. Interobserver agreement between radiologists and radiology residents and emergency physicians in the detection of PE using CTPA. *Clinical imaging*, 38(4):445-7.

(69) Jakanani GC, Botchu R, Gupta S*, et al.* 2012. Out of hours multidetector computed tomography pulmonary angiography: are specialist resident reports reliable? *Academic radiology*, 19(2):191-5.

(70) Tamjeedi B, Correa J, Semionov A*, et al.* 2015. Interobserver Agreement between On-Call Radiology Resident and General Radiologist Interpretations of CT Pulmonary Angiograms and CT Venograms. *PloS one*, 10(5):e0126116.

(71) Verweij JW, Hofstee HM, Golding RP*, et al.* 2009. Interobserver agreement between on-call radiology residents and radiology specialists in the diagnosis of pulmonary embolism using computed tomography pulmonary angiography. *Journal of computer assisted tomography*, 33(6):952-5.

(72) Courtney DM, Miller C, Smithline H*, et al.* 2010. Prospective multicenter assessment of interobserver agreement for radiologist interpretation of multidetector computerized tomographic angiography for pulmonary embolism. *Journal of thrombosis and haemostasis : JTH*, 8(3):533-9.

Appendix A: Ethics Clearance

M140244

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140244

NAME: (Principal Investigator)	Dr Thato Sefanyetso and Dr Mohammed Chohan
DEPARTMENT:	Diagnostic Radiology Helen Joseph Hospital
PROJECT TITLE:	Referral Patterns and Yield of Computerised Tomography Pulmonary Angiography for Suspected Pulmonary Embolism in a Resource Constrained Enviroment
DATE CONSIDERED:	28/02/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Susan Lucas
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 11/06/2014

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 Secretary in Room 10004, 10th floor, Senate House, University.

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**.

Principal Investigator Signature M140244Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B. Data Collection Sheet – Clinical Findings

DATA COLLECTING SHEET (Clinical Findings)
Patient number _____

Age	
Gender	

HIV Status	

Symptoms on request card	
Dyspnoea	
Chest pain	
Haemoptysis	

Symptoms in clinical file	
Dyspnoea	
Chest pain	
Haemoptysis	

Wells Clinical Variables	Presence/Absence	Original Wells	Modified Wells
Clinical signs of DVT			
Heart rate> 100/min			
Recent surgery or immobilization			
Previous PE/DVT			
Haemoptysis			
Malignancy			
Alternative less likely than PE			
TOTAL SCORE			

D- dimers	

Appendix C: Data Collection Sheet – Radiological Findings

DATA COLLECTING SHEET (Radiological Findings)
Patient number _____

CTPA Result	

Site of PE

Pulmonary Trunk			
R Main PA		L Main PA	
R 1st seg PA		L 1st seg PA	
R 2nd seg PA		L 2nd seg PA	
R 3rd seg PA		L 3rd seg PA	
R 4rth seg PA		L 4rth seg PA	

Qanadli Score	

Complications of PE	
Pulmonary HPT	
Cardiomegally	
Reflux into IVC	
Pulmonary Infarction	

Incidental Findings	
Consolidation	
Pleural Effusion	
Pneumothorax	
Pulmonary/mediastinal mass	

Appendix D: Note on referencing style

Please note that the referencing in this thesis is a modification of the Vancouver Referencing style, done according to the Faculty of Health Sciences Style Guide as set out by the Wits Health Sciences Library.

The information on this WHSL Vancouver Citation Style Guide for Theses, Dissertations and Research Reports is available from http://libguides.wits.ac.za/whsl-vancouver updated on 30 January 2017.