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# Imaging of patients suspected of having pulmonary thromboembolic disease; the value of chest x-ray combined with perfusion scan in South Africa

**Teye, Samuel**

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# IMAGING OF PATIENTS SUSPECTED OF HAVING PULMONARY THROMBO-EMBOLIC DISEASE; THE VALUE OF CHEST X-RAY COMBINED WITH PERFUSION SCAN IN SOUTH AFRICA.



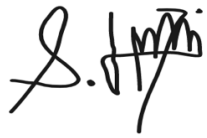

**Dr Samuel Teye**

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine.

Johannesburg February, 2022.

**Declaration**

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



Dr Samuel Teye

23th February, 2022.

**Dedication**

To my family

**Presentation and publication**

This work has never been published. It has never been presented at any congress. However, the intension is to publish it and present it at different conferences to share the findings and knowledge revealed with the scientific community and the general public.

**Acknowledgement**

I give all praise and appreciation to the Almighty God for bringing me this far.

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**Abstract**

**Introduction**: Even with recent technological advancement to improve medical diagnostics, diagnosing individuals suspected of having pulmonary thromboembolism remains difficult in medicine. A complete clinical examination, risk assessment, and imaging, including lung scintigraphy, are all needed to make a diagnosis. To diagnose pulmonary thromboembolism, lung scintigraphy uses a number of interpretation criteria. The PIOPED II criteria, which uses ventilation and perfusion images, the modified PIOPED II criteria, which uses chest x-ray, ventilation, and perfusion images, and the PISAPED criteria, which uses the chest x-ray and perfusion images, are among them. In acute pulmonary embolism, the primary goal of ventilation scanning as an adjunct to perfusion lung scintigraphy is to classify segmental perfusion defects as unmatched, which is widely regarded as proof of pulmonary embolism.

**Aim:** To determine the value of a recent chest x-ray (done within 24 hours of the perfusion scan) combined with perfusion in diagnosing acute pulmonary thromboembolism in clinical settings.

**Method**: Retrospective analysis of 155 consecutive patients clinically suspected with pulmonary thromboembolism between January 2017 and January 2019, who underwent a lung perfusion study.

**Results:** Most of the study participants (75.5%) were Black. The overall population studied had a mean age of 50.09 years (SD 16.78). A recent chest x-ray was found in 40.1% of the projected sample size of 386 people, with 98% of them being of suboptimal quality. The sensitivity and specificity of the PISAPED 1 reader were 96% and 97%, respectively, with an NPV and PPV of 99% and 89%. The sensitivity and specificity of the PISAPED 2 reader were both 96%, with a NPV and PPV of 86%and 99%, respectively. The PIOPED II and the PISAPED 1 had an agreement of 88.39% (Kappa value of 0.7348) while the PIOPED II and the PISAPED 2 had an agreement of 88.39% (Kappa value of 0.7348).

**Conclusion:** Chest x-ray in conjunction with perfusion scintigraphy is accurate and can reliably replace ventilation/perfusion scintigraphy in the diagnosis of pulmonary embolism.

**List and definition of abbreviations**

| | |
|---|---|
| 2D | - Two-dimensional |
| 3D | - Three-dimensional |
| $^{99m}Tc$ | - Metastable technetium 99 |
| COPD | - Chronic obstructive pulmonary disease |
| CT | - Computed tomography |
| CTPA | - Computed tomographic pulmonary angiography |
| DSPA | - Digital subtraction pulmonary angiography |
| DTPA | - Diethylenetriaminepentaacetic acid |
| DVT | - Deep venous thrombosis |
| EANM | - European Association of Nuclear Medicine |
| ECG | - Electrocardiography |
| ECHO | - Echocardiography |
| IAEA | - International Atomic Energy Agency |
| MAA | - Macroaggregates of albumin |
| MBq | - Megabecquerel |
| mCi | - millicurie |
| MDCT | - Multidetector computed tomography |
| mGy | - milligray |
| MRA | - Magnetic resonance angiography |
| PACS | - Picture achieving and communicating system |
| NPV | - Negative predictive value |
| PE | - Pulmonary thrombo-embolism |
| PIOPED | - Prospective investigation of pulmonary embolism diagnosis |
| PISAPED | - Prospective investigative study of acute pulmonary embolism diagnosis |
| PPV | - Positive predictive value |
| SPECT | - Single photon emission computed tomography |
| SPECT/CT | - Single photon emission computed tomography/computed tomography |
| VTE | - Venous thromboembolism |
| V/Q | - Ventilation/perfusion |
| X/Q | - X-ray/perfusion |

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# 1 CHAPTER 1: INTRODUCTION

## 1.1 Background

Even with recent advances in technologies aimed at enhancing medical diagnostics, diagnosing individuals suspected of having pulmonary thromboembolism (PE) remains a challenge in medicine. To arrive at a diagnosis, a thorough clinical examination and risk assessment are required (1–3).

For a definite diagnosis, however, imaging of these patients is essential. A chest x-ray (X) is required as part of the initial evaluation, and lung scintigraphy is frequently performed after that. Similarly, to the chest x-ray, the lung scintigraphy uses ionizing radiation. The lung scintigraphy is made up of two parts, a ventilation study (V) and a perfusion study (Q) component. In nearly a third of all patients suspected of having a PE, normal perfusion scintigraphy usually rules out PE (1,4). However, when there are perfusion abnormalities, ventilation scintigraphy is required to determine whether these defects seen on the perfusion study are matched or unmatched on the ventilation scintigraphy. If these defects are unmatched, the diagnosis of PE is confirmed. However, if these defects are matched, this disproves the diagnosis of PE (2,5).

Although ventilation scintigraphy is an essential tool in this diagnostic strategy, there have been concerns about increased radiation exposure to patients, especially the developing foetus in pregnant women and the lactating breasts (6,7). The study's high cost, non-availability of the tracer, time commitment, and low compliance in patients with respiratory distress are significant limitations in performing ventilation/perfusion (V/Q) studies (5,7).

Several guidelines propose a chest x-ray before referring for lung scintigraphy as part of the diagnostic process (5,6,8). We investigated if a chest x-ray could substitute the ventilation scintigraphy in defining these segmental perfusion defects because the chest x-ray has a similar role in increasing the specificity.

To evaluate the diagnostic accuracy or agreement of the x-ray/perfusion scintigraphy (X/Q) to the ventilation/perfusion scintigraphy (V/Q), we analysed 155 consecutive patients classified by V/Q study and X/Q scintigraphy retrospectively. If their accuracy is comparable, a chest x-ray could potentially replace ventilation scintigraphy in individuals suspected of having PE without compromising PE diagnostic accuracy.

Pulmonary thromboembolism (PE) is the partial or complete obstruction of the lungs' central or peripheral artery by an embolus (9). Acute PE is the 3rd most common cause of death after cardiovascular diseases and malignancies and the 3rd common cause of cardiovascular death after myocardial infarction and stroke (9,10). In South Africa, however, there is a lack of data on the disease prevalence. Both PE and anticoagulation therapy for PE may be detrimental to the health of the patient. There is, therefore, a need for prompt and accurate diagnosis.

Over 650,000 cases of PE are diagnosed annually, with more than 100,000 deaths yearly worldwide (11). The mortality rate is approximately 30% but could be reduced to 3 - 10% if anticoagulation is commenced timeously or inferior vena cava filters, when indicated, are placed in time.

There are several modalities employed in the imaging work-up of PE. This includes chest radiograph, ventilation/perfusion scintigraphy (V/Q), Computed Tomography Pulmonary Angiography (CTPA) and Magnetic Resonance Angiography (MRA) (5,6).

The V/Q scintigraphy was first introduced in 1964 to assess pulmonary blood flow (12). Over the past five decades, it has become an essential modality for assessing PE (12). V/Q scintigraphy is a diagnostic nuclear medicine imaging procedure that compares the pattern of distribution in the lungs of intravenously injected radiopharmaceuticals labelled with metastable technetium 99 with inhalation of inert gases or aerosols. PE affects the pulmonary arterial tree and manifests as a wedge-shaped, pleural-based defect on the perfusion component, which corresponds to a bronchopulmonary segment. The blood supply to the lung parenchyma via a branch of the bronchial artery does not impact ventilation in the afflicted section. A gamma camera is then employed to acquire two-dimensional (2D) or three-dimensional image (3-D) images (13). A conventional V/Q study is performed with planar imaging (2-D).

V/Q scintigraphy is the imaging of choice in the setting of a patient suspected of having PE with a normal chest radiograph. Also, it has an advantage over other PE assessment techniques like CTPA in that it does not require the use of contrast agents. Patients having a history of iodinated contrast allergy and renal impairment will benefit from this property (12). Furthermore, obese patients who cannot fit in the CT gantry or exceed the table's weight limit will also benefit from V/Q scintigraphy (1). Finally, in pregnancy, where reduced radiation

exposure to the breast and developing foetus is desired, V/Q scintigraphy is also the imaging modality of choice.

Although there are several interpretative criteria employed in lung scintigraphy, The Prospective Investigative Analysis of Pulmonary Embolism Diagnosis (PIOPED) and Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISAPED) criteria are the two most widely used protocols in diagnosing acute PE. In PIOPED, a perfusion scan is read in conjunction with a ventilation scan to make a diagnosis. Perfusion lung scanning was enhanced with ventilation imaging to increase specificity, hoping to distinguish pulmonary vascular occlusion due to embolism from perfusion anomalies caused by respiratory disorders. A retrospective review of the PIOPED data base yielded the PIOPED II criteria. In an attempt to reduce the frequency of non-diagnostic interpretations in V/Q studies, the PIOPED II criteria was revised to the modified PIOPED II criteria, which comprises fewer diagnostic categories. Table 2-5 shows these classifications. In diagnosing PE using the PISAPED criteria, the ventilation study is omitted. The perfusion scan is read in conjunction with a recent chest x-ray ( i.e. one done in less than 24 hours) for interpretation (14). The diagnosis made using these criteria could be a positive, negative or indeterminate study.

In a number of studies to compare the modified PIOPED II and the PISAPED parameters, statistics showed that the sensitivity and specificity were not significantly different (84.9% and 92.7%, respectively, for modified PIOPED II and 80.5% and 96.6%, respectively, for PISAPED) (15,16). Furthermore, Miniati et al. (1996) and Watanabe et al. (2015), in their studies, suggested that using the PISAPED criteria reduces the percentage of patients with indeterminate findings that will require an additional test to arrive at a diagnosis of positive or negative study for PE (16,17).

## 1.2 Problem statement

Pulmonary thromboembolism (PE) is responsible for 10% of all hospital mortality in South Africa (18). Patients with medical illnesses account for almost three-quarters of all deaths. Despite the fact that PE was revealed to be the third most common cause of natural death in females in an autopsy series conducted in an adult population in Cape Town between 2001 and 2005, the true incidence of PE in South Africa is unknown (18).

About 474 patients suspected of having PE are referred to the Charlotte Maxeke Johannesburg Hospital's Nuclear Medicine department for diagnostic testing annually. According to the relevant diagnostic methodology, patients should have a chest x-ray as the first means of assessing their chest signs and symptoms. The patients are exposed to about 0.07msv of ionizing radiation during this chest x-ray. They are then sent for ventilation and perfusion scintigraphy, which exposes them to an additional 2msv of ionizing radiation (14). These procedures increase the patient's exposure to radiation, take more time, cost more money, and put more work on health care institutions.

In Nuclear Medicine, the diagnosis of PE is obtained by comparing ventilation/perfusion studies (V/Q) or a recent chest x-ray to a perfusion study (X/Q). According to numerous published research, both approaches are equally accurate in determining the intended diagnosis (1,5,19,20). However, to the best of our knowledge, no such investigations have been conducted in South Africa. We decided to test if the X/Q method is reliable in diagnosing PE in our environment; therefore, we will compare the two methods. Suppose the X/Q approach is proved to be an accurate tool. In that case, the perfusion scan will be compared to the recent chest x-ray for diagnosis, avoiding the use of ventilation scintigraphy for patients who have already undergone a recent chest x-ray as part of their diagnostic work-up.

In an era where less radiation exposure to the general public and health personnel is advocated, the direct implication of this study will be lower radiation dosage to the patient, particularly in pregnant and breastfeeding mothers. Also, in a resource-constrained country like South Africa, it might help with cost-cutting and timesaving, which would help with service delivery.

### 1.3 Justification

In Nuclear Medicine, there are several diagnostic criteria used in the assessment of PE. Available criteria include ventilation/perfusion single-photon emission computer tomography (V/Q SPECT), Prospective investigation of pulmonary embolism diagnosis II (PIOPED II), Modified PIOPED II and the prospective investigative study of acute pulmonary embolism diagnosis (PISAPED) criteria. The PISAPED criteria use a perfusion only study and a recent chest radiograph (21). Various studies have shown that this combination gives a reliable interpretation of detecting or excluding PE with a sensitivity of 80% to 85% and a specificity of 93% to 97% (Sostman et al., 2008), and this was comparable to the diagnostic accuracy of V/Q scintigraphy in the PIOPED II study. The main reason for ventilation scintigraphy is to

increase the specificity of the study for PE diagnosis, thus, enable the identification of other pathologies (5).

In South Africa, patients referred for assessment for acute PE usually have undergone a radiological chest x-ray examination to assist in identifying the cause of the patients' chest symptoms.

This study compares the ventilation and perfusion scan findings using the modified PIOPED II criteria and the perfusion chest x-ray combination using the PISAPED criteria. If the results are similar, then, if already performed, the chest x-ray can replace the ventilation scintigraphy in selected investigations.

The direct consequences of this study will be reduced radiation dose to the patient, the developing foetus and breasts of pregnant women and lactating mothers, respectively. It may also assist in cost reduction and save time, thus assisting in service delivery. Finally, because the ventilation component of the study is an aerosol generating technique, eliminating it in this era of COVID-19 pandemic will lower the risk of corona virus transmission to nuclear medicine staff.

### 1.4 Aim

To determine the value of a recent chest x-ray (done within 24 hours of the perfusion scan) combined with perfusion in diagnosing acute pulmonary thromboembolism in clinical settings.

### 1.5 Specific objectives

1. To describe the demographic characteristics and risk factors for pulmonary thromboembolism.
2. To assess the diagnostic accuracy of chest x-ray/perfusion in the patients suspected of pulmonary thromboembolism.
3. To assess the degree of interobserver agreement between readers of ventilation/perfusion scintigraphy and chest x-ray/perfusion scans.

# 2 CHAPTER 2: LITERATURE REVIEW

## 2.1 Introduction

The respiratory system and pulmonary embolism are covered in this chapter. It also discusses the latest literature in diagnostic accuracy of chest x-ray/perfusion imaging in a patient suspected of having pulmonary embolism and the interobserver variabilities, and the demographic characteristics and risk factors for PE in patients.

## 2.2 The respiratory system

The pulmonary system consists of the lungs, airways, pulmonary and bronchial circulation, and chest wall (2,22).

The lungs consist of lobes, three in the right (upper, middle, and lower) and two in the left lung (upper and lower). Each lobe is again divided into segments and lobules. The airway network consists of upper airways (nasopharynx and oropharynx) and lower airways (trachea, bronchi, bronchioles, and alveolar ducts) linked by the larynx (2).

Bronchopulmonary segments are found in the lobes of the lungs. The bronchopulmonary segments provide the segments their independence and allow them to be resected. Each bronchovascular section consists of a terminal respiratory unit. An alveolus has an average diameter of 150μm. An adult human has about 700 million alveoli with a surface area of 80m2. Apart from the direct pathway, air can get to the alveoli through indirect channels such as the pores of Kohn and the canals of Lambert. Such indirect routes enable collateral ventilation and avoid the collapse of an obstructed section or parts of the bronchopulmonary segment or segments(2,5).

Two separate blood circulations are provided to the lungs: pulmonary circulation and bronchial circulation. The pulmonary circulation contains the vast majority of pulmonary blood and is a low pressure, low resistant mechanism through which oxygen enters, and carbon dioxide exists. The pulmonary circulation arises from the pulmonary arteries, which branches out into two pulmonary arteries into each lung. They then divide progressively into smaller branches following the bronchial tree into pre-capillaries and then to the capillary network of the alveoli. The pre-capillary arterioles are approximately 35 μm in diameter and number about 300 million in adults. The capillaries are about 7–10 μm in diameter and number 300 billion in adults. The

more proximal terminal arterioles have a diameter of approximately 100 µm. The bronchial circulation carries about 5% of the blood coming to the lungs and is part of the systemic circulation. The bronchial circulation does not engage in gaseous exchange as opposed to the pulmonary circulation. However, it delivers oxygenated blood to the tracheobronchial tree, large pulmonary vessels, and other structures of the lungs, including the pleurae(2,5,22).

The lungs are lined on the outside by a visceral membrane while the thoracic cavity is bordered on the inside by a parietal layer forming the pleural cavity in between, containing serous fluid – a lubricant during breathing.

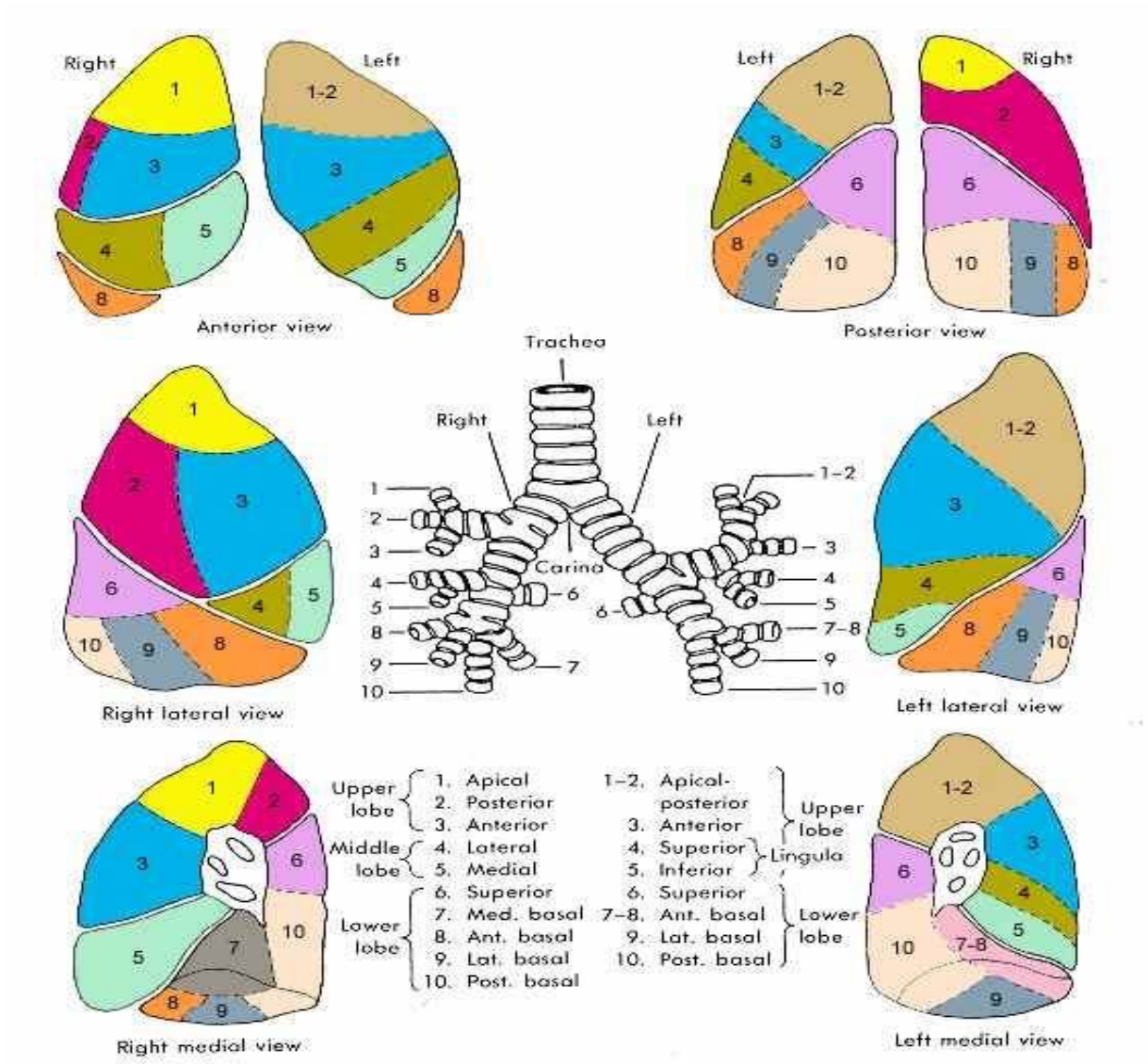


Figure 2-1: Bronchopulmonary segments of the lungs

Source: (23)

## 2.3 Epidemiology of pulmonary thromboembolism

Pulmonary thromboembolism (PE) is a common disorder, with more than 650,000 cases identified each year and more than 100,000 deaths globally (11). Dentan et al. (2014) conducted research in the United States to investigate the specific venous thromboembolism (VTE) risk associated with tuberculosis. The prevalence of VTE/PE was determined to be 2.07% in this retrospective multivariate analysis of 27,659,947 admissions utilizing the Premier Perspective database (95% CI, 1.62%-2.59%). Males were shown to be at a higher risk of acquiring PE, with the median age of onset being 53. Despite the vast sample size, most patients were Black, and several studies have shown that this demographic is more likely to have tuberculosis, a hypercoagulable disease (24,25). However, in a study of 889 patients, Sostman et al. (2008) discovered a prevalence of PE of 19% (21). This was somewhat higher than the study by Dentan et al (2014).

Despite the high frequency of PE, there is currently a lack of data on the disease's prevalence in Africa. Therefore, Danwang et al. (2014) conducted a comprehensive review to determine the prevalence, incidence, and mortality of PE in Africa. Their study of 21 different articles estimated the prevalence of deep vein thrombosis (DVT) to be 2.4% -9.6% post-surgery and the rate of PE to be 0.14% -61.5%. Even though their conclusions are based on a small sample size of 21 studies, they conclude that PE has a mortality rate of 40% to 69.5%, highlighting the need for early detection and anticoagulant therapy (10). Their study also suggested an increased risk of PE in people of African descent and an age of above 50 years (10,26).

Pulmonary thromboembolism was also observed in 17.5% of 131 patients with severe acute exacerbation of chronic obstructive pulmonary disease (COPD) in the intensive care unit of a Tunisian hospital in retrospective research by Bahloul (2015). However, this may not accurately reflect the true incidence of PE because the patients in the research already had lung disease and were immobilized in hospital settings, both of which enhance their risk of developing VTE, including PE (27).

In a prospective research in a Cameroonian hospital in Bamenda, Abah et al. (2016) discovered that PE was present in 0.96% of 1,445 hospitalized patients, contrary to other studies conducted in hospital settings that increased the likelihood of patients developing PE (28,29).

Statistical data from 2014 in South Africa revealed that 2,415 persons died due to pulmonary circulation illnesses (132). Although this figure includes disease-related mortality, it grossly

underestimates the disease's severity (24). Pulmonary thromboembolism is challenging to diagnose and frequently ignored. Still, a two-year retrospective record analysis in a district hospital in Cape Town, South Africa, revealed that the prevalence of PE was 32% in a small group of 127 patients. This statistic appears to be relatively high and could be attributable to the high prevalence of HIV and tuberculosis in their research sample, both of which are considered hypercoagulable states (24).

## 2.4 Pathophysiology

The primary source of PE is thromboembolic arising from the deep veins. Other less critical causes are fat, air and tumour emboli (2). The classical risk triad known as the Virchow's triad contributes to the development of PE. This triad includes venous stasis, intimal injury and coagulation alteration (2).

When a thrombus is acutely formed, it is usually soft and thus prone to embolization. The thrombolytic system inherent in the human body generally works to dissolve the thrombus. The dynamic battle between fibrinolysis and thrombus formation occurs over a 7–10 day period (2).

If this system fails, there may be one of two outcomes. First, the thrombus may integrate into the venous wall, leading to contraction and scarring. This may result in some degree of occlusion of the vessel, as well as damage to the lower limb vasculature (30). Then, collateral veins can develop to bypass the occluded region resulting in chronic DVT (30). The other consequences are that the thrombus may dislodge from the vessel wall and become an embolus in the systemic circulation. It then travels through the right-sided chambers of the heart to enter the pulmonary vasculature, where it may completely obstruct a major vessel, culminating in the most feared complication, i.e. fatal pulmonary embolus (31–33).

The risk of PE depends on the location of the thrombus. If the thrombus is in the small calf veins, the risk of PE is low (30). However, if the thrombus occurs in the more prominent veins, such as the popliteal, femoral or iliac veins, the possibility of breaking off to form PE progressively increases (30). This is valid for both the initial PE as well as any recurrent episodes. PE can recur in up to half of the patients, although, in treated PIOPED patients, the incidence was only 8.3 % (2,30).

Many risk factors have been shown to increase PE, including long-distance travels, obesity, smoking, use of oral contraceptives, postmenopausal hormone replacement, pregnancy, surgery, trauma and medical conditions such as antiphospholipid antibody syndrome, malignancy, systemic arterial hypertension and chronic obstructive pulmonary disease (34).

## 2.5 Haemodynamic effect of PE

Ventilation of areas without blood supply can result in increased dead space (5). It is one of the explanations for why dyspnoea occurs. Many pathways cause hypoxia, frequently seen in significant PE. Haemorrhage, pleuritic pain, pleural effusion and atelectasis can result from emboli occluding pulmonary end arteries. The lung has no pain fibres. Pain with PE indicates the involvement of parietal pleura (5,35).

Furthermore, acute right-sided heart failure due to increased pulmonary vascular resistance has been identified as the primary cause of death in PE. Increased pulmonary vascular resistance can lead to right ventricle strain and failure, electromechanical dissociation, syncope of hypotension and sudden death. An increase in right atrial pressure via a patent foramen ovale leading to hypoxaemia may lead to a right to left heart shunt. The shunt can also contribute to paradoxical emboli, which means that a thrombus of venous origin induces infarctions in the central circulation, usually the brain (35).

## 2.6 Natural history of pulmonary thromboembolism

The degree of blockage and the hemodynamic repercussion of PE determines the prognosis. For example, massive PE has a 25-65% mortality rate, submassive PE has a 3-15% mortality rate, and low-risk PE with good cardiac function has a 1% mortality rate with anticoagulation (36).

The resolution of PE is variable. There is a rapid resolution of a massive PE within hours of the onset of heparin therapy (2,36). It is noted complete restoration of lung perfusion in patients with PE within one week of diagnosis and that majority of patients who have unresolved PE at six months from diagnosis are unlikely to have a resolution of their PE (2,37). Due to the

rapidly changing patterns of perfusion in PE, Kearon (2014) recommended that imaging studies be performed very early, preferable within 24 hours of onset symptoms (38).

## 2.7 Clinical presentation of pulmonary thromboembolism

The clinical presentation of PE varies. Small emboli can be asymptomatic and seen only incidentally while a large PE may be life-threatening. Smaller thrombi appear to penetrate deep into the lungs due to their small size, thus occluding the vessels at the periphery of the lungs. A large enough thrombus to cause an infarction may create an inflammatory response at the parietal pleura. That leads to pleuritic chest pain (32,33).

Over time, multiple PE can contribute to the development of chronic thromboembolic pulmonary hypertension (CTEPH) and cor pulmonale. Clinically, these manifest as raised jugular veins, systemic hypotension and a loud P2 on pulmonary auscultation (31–33). Several studies suggest that for severe pulmonary hypertension to occur, the affected region of the pulmonary vascular bed must be decreased by a minimum of 60%. Those patients can then progress to right ventricular failure, which presents with a gallop rhythm and peripheral oedema (31–33).

The typical symptoms of PE include dyspnoea, pleuritic chest pain, cough and haemoptysis (39). Other symptoms may include tachycardia and tachypnoea. However, a patient without pulmonary infarction will usually present with non-specific symptoms. For example, their chest pain may be difficult to distinguish from the chest pain seen in myocardial infarction. Thus, a high index of suspicion will direct the performance of appropriate diagnostic studies. Extensive thrombus can compromise a patient's haemodynamics. This can result in hypotension and then cardiogenic shock. Patient with cardiogenic shock presents with impaired consciousness, oliguria, and cold extremities. In severe cases, nearly a third of patients may die (40–42). PE is, therefore, a medical emergency where urgent treatment is needed (43).

## 2.8 Diagnosis of pulmonary thromboembolism

The clinical diagnosis of PE is complicated and unreliable. This results from the non-specificity of the clinical features and the findings on laboratory investigations and imaging modalities

(32). Furthermore, the clinical signs and symptoms are not typical in the elderly compared to the younger age groups.

Many authors have reported PE in about 24% of antemortem cases (38). The mortality of untreated PE is about 30%. In patients diagnosed with PE, the mortality was about 2.5-8% if treatment was started promptly (2). As a result, once PE is clinically suspected, the patient must be investigated expediently. Available modalities that increase the likelihood of making a diagnosis of PE includes history and physical examinations, blood analysis, electrocardiogram (ECG), conventional imaging (Chest x-ray, USG, CTPA and MRA) and functional imaging.

## 2.9 Risk stratification of patients

In patients with suspected PE, a tentative diagnosis is mandatory to identify those who require anticoagulant therapy. However, the clinical signs and symptoms of PE are non-specific (44). Therefore, CTPA and V/Q imaging are necessary to assist in confirming the diagnosis. However, the cost, exposure to ionizing radiation, risk of contrast-induced nephropathy and the potential for over-diagnosing make CTPA less desirable as a first-line test (45).

According to the principles of Bayes' theorem's, it is essential to understand the test used to diagnose PE since the accuracy of any test depends on its sensitivity, specificity, and pre-test probability (46,47). This theorem emphasizes that a positive test result is more likely to be a true positive if pre-test suspicion is high. However, the likelihood drastically drops if suspicion is low. Therefore referring physicians should perform patient risk stratification to assess the overall probability of PE before ordering an extensive workup (2,48,49).

There are several methods available to predict the likelihood of PE clinically. These include the Wells score and the Geneva score. Phillip Steven Well, in 1995, developed an algorithm to predict the risk of PE. This rule was revised in 1998 and again in 2000 (45,50). The Wells score objectively assign points based on patient history, symptoms, and physical findings (51).

Table 2-1: Criteria for assessment of pre-test probability for pulmonary embolism

| Criteria | Points |
|---|---|
| Suspected DVT | 3 |
| Alternative diagnosis less likely than PE (by history, physical examination, CXR, ECG and blood results) | 3 |
| Heart rate >100 beats/min | 1.5 |
| Recent immobilization or surgery | 1.5 |
| Previous DVT/PE | 1.5 |
| Haemoptysis | 1 |
| Malignancy (on treatment or treated in the past six months) | 1 |

Source: Wells et al., 2000

Table 2-2: Clinical risk assessment

| Risk | Total score (Points) |
|---|---|
| High | >6 |
| Moderate | 2-6 |
| Low | <2 |

Sources: Wells et al., 2000

Table 2-1 shows the parameters involved in calculating the Wells score, and table 2-2 shows the risk of having a PE for the estimated Wells score.

Stein and co-workers (2007), in a prospective multicentre study among 824 participants comparing the accuracy of multidetector computer tomography angiography alone and combined with venous-phase imaging found that a Wells score of < 2 was associated 15% risk of PE, a score between 2-6 was associated with 29% risk of PE and lastly, a score of > 6 was associated with a 59% risk of PE (52). Also, PE was found to be 8%, 28% and 74% in patients with low risk, moderate risk, and high risk, respectively, according to Le Gal et al. (2006), who constructed a simple score based entirely on clinical variables and independent from physicians implicit judgement at three university hospitals in Europe (48,53). The drawback, however, in their study was that they didn't study the interobserver agreement for the score items.

An alternate interpretation of the Wells score has been suggested as follows ("Effectiveness of Managing Suspected Pulmonary Embolism Using an Algorithm Combining Clinical Probability, D-dimer Testing, and Computed Tomography," 2013; Ruiz-Artacho et al., 2015; Wells et al., 2000). In this algorithm, a Score > 4 signifies that PE likely and diagnostic imaging should be considered. A score ≤ 4, on the other hand, predicts that PE was unlikely, and that D-dimer testing should be considered to rule it out completely.

Some of the other scores that have been used include the Geneva score and its sequel, the revised Geneva score.

Table 2-3: Revised Geneva score

| Criteria | Points |
|---|---|
| Age > 65 years | 1 |
| Previous PE or DVT | 3 |
| Recent surgery or fracture of lower limbs | 2 |
| Active malignant condition | 2 |
| Unilateral lower limb pain | 3 |
| Haemoptysis | 2 |
| Tachycardia (beats/min) | |
| • 75-94 | 3 |
| • >94 | 5 |
| Pain on palpation of the lower limb and unilateral oedema | 4 |

Source: Le Gall et al., 2006

Table 2-4: Interpretation of revised Geneva score

| **Interpretation of risk** | **Score range (points)** |
|---|---|
| High risk | >10 |
| Moderate risk | 4-10 |
| Low risk | <4 |

Source: Le Gall et al., 2006

Pre-test probabilities have been used to augment the use of diagnostic imaging. For example, imaging can be safely withheld in about 28% of patients classified as 'PE unlikely' by the Wells rule and have a D-dimer result below 0.5mg/ml (53).

The positive predictive value of 87% for a high probability lung scan in the PIOPED study increased to 96% positive predictive value after taking into account a high pre-test probability (20). Similarly, the positive predictive value of 14% for a low probability lung scan in the PIOPED study decreased to a mere 4% after considering a low pre-test probability ( 20).

In a prospective cohort study in 807 patients, Douman et al. (2011) concluded that the various Wells rule, the simplified Wells score, the Geneva score and the revised Geneva's score had a similar performance in predicting the likelihood of PE occurrence (46,55). However, despite the recommendation to use a well-validated algorithm in the diagnostic workup of PE, the threshold for performing imaging appears to have been lowered over the years, probably because of the fear of missing a potentially fatal diagnosis and facilitated by the readily and widespread availability of computed tomography at emergency departments. It is also possible that a clinical decision score, such as the Wells score, may be perceived as too complicated for use at the bedside, as seven clinical items have to be remembered, assessed, assigned different weights, and then summed to reach this score (32,44,47,48,56,57).

In South Africa, Adams et al. (2013) in their structured record review in 3500 consecutive patients referred for CTPA in 2 urban hospitals also noticed that the recommendation to risk stratify patients before with pre-test algorithm (Well’s score or revised Geneva score) were overlooked with less than 50% of referral for CTPA following these guidelines. CTPA was performed in 1908 patients with a revised Geneva score <10, without D-dimer or after a negative D-dimer test result. In their study, the overall PE rate was 9.7% and a potential false-positive diagnosis occurring in 2 out of 3 patients with a revised Geneva score of <10 and a negative D-dimer test result (58,59).

## 2.10 D-dimers

D-dimer has been an important initial screening method in diagnosing in emergency settings since its introduction in the 1990s (48,60). D-dimer is a specific degradation product of cross-

linked fibrin in blood clots. So it is elevated in the blood and immediately after PE or DVT (61–63).

D-dimers are identified by immunoassays using monoclonal antibodies specific for the cross-linked D-dimer domain in fibrinogen. Commercially available assays include latex agglutination, immunoturbidimetry, and enzyme-linked immunosorbent assay (ELISA) (64). The NPV and sensitivity of developed central laboratory ELISA D-dimer and rapid quantitative full blood D-dimer tests were 100%. In spite of this, the rapid whole-blood test had higher specificity for VTE disease (73.3% vs 67.9%), and the positive predictive value for both tests was low (65). The Innovance D-dimer assay is an extremely sensitive test, and it has positive results for almost all patients with reported DVT or PE (66,67). The high sensitivity of the D-dimer ELISA, as well as it's exceptional high NPV, has led to the consensus that the risk of PE is minimal in the settings of a negative test and that further diagnostic investigation is generally superfluous (68–70). There is nevertheless a question as to whether D-dimer testing alone is sufficiently reliable to validate or exclude PE (60,71,72). An elevated D-dimer assay, however, is non-specific, as these may occur under certain physiological conditions such as pregnancy and puerperium, increasing age (>65 years) and African American ancestry (64). Non-physiological causes of elevated D-dimer includes sepsis, pneumonia, various malignancies, smoking, recent trauma, post-operative period, cardiovascular diseases and even different inflammatory conditions (60–63,73).

However, the recent ADJUST-PE research by Righini et al. in a multicentre, multinational prospective study in 3346 patient over a three month period has shown that PE can be safely excluded in a more significant number of patients, particularly the elderly, by using the age-adjusted D-dimer levels (74). Using the age-adjusted cut-off values in patients over the age of 75, the diagnostic yield increased by a factor of 5 (from 6.4% to 29.7%) (74). Therefore, PE may quickly be ruled out without the need for additional imaging in a large number of elderly patients. However, the drawback of their study was that two different pre-test probability assessment tools and six different commercial D-dimer assays were used; therefore, not all the patients included in their study used the same diagnostic tool (74).

According to the EANM guideline, a negative D-dimer test has a very high NPV of VTE (75). This guideline stated that the risk of developing PE in patients with a low clinical likelihood who are left untreated after a negative D-dimer test is 1% three months after the initial assessment, according to the results of outcome studies (71,75,76). A positive quantitative D-

dimer test, on the other hand, does not change the pre-test likelihood and is therefore clinically useless due to its low predictive value (62,75). On the other hand, recent data indicate that extremely high D-dimer levels are linked to a fourfold increase in the risk of PE (48,67,77). Thus, it may be useful in determining the severity of thromboembolic disease and may have prognostic value (77,78).

According to a study conducted by Schols et al. (2019) in 470 patients from 47 general practices in the Netherlands, many of the patients (72.3%) had a D-dimer test performed based on the prescribing physician's clinical suspicion of VTE. A positive test was found in 330 (97.1%) of the patients, and 15 out of 340 (4.4%) of them were diagnosed with VTE, with 19 (5.6%) of them having a PE (79). However, data on the association of D-dimer and VTE in South Africa are rare.

### 2.11 Arterial Blood Gas (ABG)

The PIOPED and PISAPED trials identified hypoxaemia and respiratory alkalosis in patients with PE. Nevertheless, in about 75% of patients who did not have PE, the PISAPED analysis acknowledged these symptoms (17). As a result of its rather low sensitivity and specificity, the measurement of ABG's role is limited to assessing the severity of PE (80,81)

However, in a recent study, Egermayer and colleagues (1998) assessed the safety and clinical utility of the D-dimer test, arterial oxygen tension and respiratory rate measurement for excluding PE in 517 consecutive medical inpatients. They concluded that it was safe to exclude PE with a negative D-dimer test result and a $Pa_{O2} \geqslant 80$ mm Hg (82).

### 2.12 Electrocardiograph

Electrocardiogram (ECG) has a limited role in the diagnosis of PE. The classic ECG finding is $S_1Q_3T_3$ (83). This is a sign of acute cor pulmonale and represents right ventricular strain (83). However, these ECG findings are present in only 15 to 25% of patients eventually diagnosed with PE (84). Any cause of acute cor pulmonale may result in the $S_1Q_3T_3$ findings on ECG, including PE, acute bronchospasms, pneumothorax, and other severe lung disorders.

Other ECG findings noted during the acute phase of a PE include a new right bundle branch block (complete or incomplete), the rightward shift of the QRS axis, ST-segment elevation in $V_1$ and aVR, generalized low amplitude QRS complexes, atrial premature contractions, sinus tachycardia, atrial fibrillation/flutter, and T wave inversions in leads $V_1$-$V_4$ (84,85). The ECG use in a patient with suspected PE is to rule out the specific life-threatening diagnosis (e.g., acute myocardial infarction) (83,85). However, ECG abnormalities are common among patients with massive acute PE and may serve as a prognostic indicator.

## 2.13 Imaging

There are several modalities employed in the imaging workup of PE. This includes chest radiographs, ventilation/perfusion scintigraphy (V/Q), computed tomography pulmonary angiography (CTPA) and magnetic resonance angiography (MRA).

## 2.14 Chest radiograph

The chest x-ray is the first test in the initial cardiopulmonary disease evaluation and has the benefit of being non-invasive (86). When assessing potential critical PE, the chest x-ray obtained from the acquired in the posterior-anterior and lateral view is the baseline examination (87). While there are no definitive findings indicative of PE, the American College of Radiology recommends the chest x-ray as the most appropriate study for ruling out other causes of chest pain in patients suspected of PE. These other causes are pneumothorax, pulmonary oedema, malignancy, or pneumonia (88–90).

The chest x-ray's extra utility is in the patient triage in the emergency room. So, as well as being able to show other causes of chest pain, the x-ray of the chest also plays a part in determining which imaging modality is favoured. If the chest x-ray is normal or near-normal, these patients are referred for V/Q studies (91). A normal x-ray of the chest, especially with an abnormal alveolar-arterial gradient, is highly suggestive of PE. CTPA is favoured when the chest x-ray is abnormal.

A chest x-ray done within 24 hours of scintigraphy is appropriate for patients with no signs or symptom changes (93). A more recent chest x-ray, preferably within 1 hour, is needed in patients with symptoms and signs that alter (93). Nonetheless, a report by de Groot et al. (2000)

in 389 patients showed that about 83% of patients referred for PE evaluation had a chest x-ray done within 48 hours. Despite the fact this these chest x-ray were deemed outdated in standard practice, about 12-30% confirmed PE had a nearly normal chest radiograph (1,52,93).

If there are significant chest x-ray anomalies, these patients should then be referred for a CTPA instead, because the risks of non-diagnostic results in this sub-group are high (70,91,94). This is because in the presence of extensive parenchymal lung changes, lung scintigraphy has a poorer sensitivity and specificity in identifying PE resulting in more non-diagnostic findings. Radiological signs that might indicate a chest x-ray diagnosis of PE include Fleischner's sign – *(*dilatation of the proximal pulmonary artery); Hampton's hump – (pleural based infiltrates); and Westermark's *sign* – (decreased vascularity ipsilateral to the affected area affected by PE) (86).

The original PIOPED study had a very high number of inpatients who made up 68% of the overall population. However, in the PIOPED II study, only about 11% of the population were in-patients. In-patients are far more likely to have chest x-ray anomalies that would potentially conflict with optimal V/Q scan interpretation. Therefore, chest x-ray screening has dramatically decreased the number of intermediate or non-diagnostic interpretations in V/Q studies (19,52).

Currently, some published evidence contradicts the relationship between chest x-ray results in subjects examined for PE and the findings on V/Q scan. While PIOPED data analysis did not imply an association, other studies indicate that chest x-ray findings may be significant.

Khan et al. (2009) in a review of 1,063 patients suspected of having PE concluded that, only 12% of cases confirmed with PE had a normal chest x-ray (95,96). Also, the International cooperative study of PE registry (ICOPER, 2000) reported 24% out of a total of 2,452 patients having acute PE and a normal chest x-ray in their prospective study in 52 hospitals in 7 different countries (87,96). Zubairi et al. (2007) also found that in 50 patients, 18% had normal chest x-ray findings (86). With all this information, Shawn et al. (2018) estimated that 80% of patients referred for PE assessment had chest x-ray changes (96). Also, in the PIOPED study, the chest radiographs of most patients (88%) were considered abnormal (39). Data identifying radiographic findings associated with PE diagnosis are minimal (87). However, Zubairi et al. (2007) revealed that the most common radiographic abnormality associated with acute PE is cardiomegaly (38%). Others are pulmonary infiltrates (34%), atelectasis (26%), pleural

effusion (24%) and pulmonary congestion (24%) (87). These findings were similar to the ICOPER study (2000) (86,87).

Even though chest x-rays are often used for investigations, the accurate analysis of the resulting film is relatively difficult (70,97). The most common x-ray to be misinterpreted by observers is the chest x-ray, according to reports. Even when experienced chest radiologists perform radiograph evaluation involves subjectivity, variability, and ambiguity, and interobserver variability is difficult to resolve even among senior radiologists (98,99). Gatt (2003) conducted a prospective study on 507 patients who were discharged from the emergency room daily. These patients initially presented with cough, chest pain, and dyspnoea, among other symptoms. Emergency medicine physicians recorded 557 findings in this research, while a senior radiologist identified 647 of the chest x-rays examined. He concluded that emergency medicine physicians and the senior radiologist had moderate to poor interobserver reliability (Kappa 0.40 CI 0.35-0.46) (100). On the other hand, a survey of emergency medicine physicians and radiologists by Tranovich et al. (2019) found 1,044 inconsistencies out of 16,111, suggesting 93.5% agreement. These discrepancies were deemed minor, and the discrepancies were attributed to a minor disagreement in results between the emergency medicine physicians and the radiologist. They came to the conclusion that emergency medicine physicians would view simple radiographs with a very low incidence of clinical discrepancies (101).

## 2.15 Pulmonary angiography

For many years, pulmonary angiography (PA) has remained the 'gold standard' for the diagnosis or excluding of PE. However, it is now performed to a lesser extent, as less-invasive computed tomography pulmonary angiography (CTPA) provides comparable diagnostic precision (102). Pulmonary angiography is a technique for accurately visualizing the pulmonary arteries to detect PE directly.

In PA, PE is diagnosed based on direct evidence of a thrombus in two projections, either as a filling defect or amputation of a pulmonary arterial branch (102). A positive PA of the pulmonary system excludes all further examinations. However, a negative PA has an exceptionally high negative predictive value if the entire pulmonary vasculature of both lungs is visualized. However, this is not always possible because arterial branches smaller than third-

order branches are not generally visualised (103,104). In addition, indirect signs of PE, such as sluggish contrast flow, regional hypoperfusion, and delayed or reduced venous pulmonary flow, are not validated and thus non-diagnostic (105).

Problems associated with PA include the fact that it is an invasive procedure, patients may be allergic to the iodine contrast material used, and lastly, experience in this technique appears to be diminishing (94,103). With PA, procedure-related mortality was 0.5%, with a major non-fatal complication occurring in 1% and minor complications occurring in 5% of cases. There is also a significant death rate in patients who are not haemodynamically stable or respiratory failure (106). In addition, the risk of complication of bleeding associated with access is increased if thrombolysis is attempted in patients with PE (20,106,107).

Given its limitations, PA remains a useful investigation when CTPA is not possible or cannot be performed for various reasons.

## 2.16 Computed tomography pulmonary angiography (CTPA)

Since its introduction in the early 1990s, computed tomography pulmonary angiography's (CTPA) has become the modality of choice for imaging the pulmonary vasculature in patients with suspected PE (108–110). It allows the pulmonary arteries to be adequate visualization down to at least the level of the segmental arteries.

Computed tomography pulmonary angiography studies using multislice techniques demonstrated high sensitivity and specificity and replaced pulmonary angiography as a reference tool for diagnosing acute PE (111). This attributed to its improved availability and greater familiarity with CT by the radiologist (112). American College of Radiology (ACR) has also recommended CTPA as the standard of care in the diagnosis of PE (113,114).

Computed tomography pulmonary angiography's sensitivity has increased dramatically, from 73% to 83%, due to technological advancement (109,110,115). However, the sensitivity is still on the lower side for more distally positioned PE (115–117). The PIOPED II research, on the other hand, showed that CTPA has a high specificity of around 96% (115).

Computed tomography pulmonary angiography's 's key benefit over V/Q scintigraphy, in particular, is its ability to detect alternative disease processes which may clinically present similarly to PE (91,115). CTPA offers an alternative diagnosis in 30-60% of patients suspected of PE (Huda and Vance, 2007). Also, the usage of CTPA is more common because of the lower indeterminate readings than other modalities. This because of its simplified reading (PE positive or PE negative) as compared to the probabilistic studies of V/Q scan (low, intermediate or high probability) (30,115). Finally, CTPA is also readily available and quickly yields reliable results (118).

Computed tomography pulmonary angiography's disadvantages include iodinated-contrast issues in allergy individuals (91,110,115). This is especially important for pregnant women and those with impaired kidney function. Significant side effects are less common in patients (less than 1%). If these patients have severe kidney disease, this number might rise to over 50% (115). Also, congenital hypothyroidism can develop in neonates exposed to iodinated contrast in the womb (115). Another issue with CTPA is that it exposes the patient, as well as the growing fetus in the case of pregnant women, to a lot of ionizing radiation. According to the International Commission on Radiation Protection (ICRP), the average effective dosage for 4–16-detector multi detector computed tomography (MDCT) is 5.4 mSv. This level of exposure should be especially concerning for pregnant women and breastfeeding mothers. During the first trimester, the absorbed fetal dose was 0.24– 0.66 mGy, with a modest increase later in pregnancy. The amount of radiation received by the breasts is believed to be between 35 and 42 mGy. According to Pahade et al. (2009), the whole-body effective dose in CTPA is nearly five times higher than V/Q imaging. The dose to the female breast, in particular, is 20-40 times higher (8). There, CTPA is ineffective in patient follow-up due to the high level of radiation (75,119). Despite these drawbacks of CTPA, the findings of the PIOPED II study, according to Freeman, "do not explicitly support the superiority of CT angiography over ventilation/perfusion scanning for the diagnosis of PE." (75,120).

### 2.17 Lung scintigraphy (Ventilation / perfusion scintigraphy)

Ventilation (V) and perfusion (Q) scan are most often called a V/Q scan. The perfusion scan refers to the blood flow to the lung. The V/Q was first introduced in 1964 to assess pulmonary blood flow (12). Over the past five decades, it has become an essential modality for assessing

PE (12). V/Q scintigraphy is a diagnostic nuclear medicine imaging study that makes use of limited capillary blockage with radiopharmaceuticals labelled with metastable technetium 99 as well inhalation of inert gases or aerosols and comparing their pattern of distribution in the lungs with the aid of a gamma camera either by a two -dimensional image (2-D) acquisition or a three dimensional image (3-D) acquisition (13). A conventional V/Q study is performed with planar imaging (2-D).

V/Q scintigraphy is the imaging of choice in the setting of a patient suspected of having PE with a normal chest radiograph. It is also advantageous over other modalities to assess PE, such as CTPA, because it does not require contrast agents. It is also utilized in patients with a history of iodinated contrast allergy and renal impairment (12,110). Obese patients who cannot fit in the CT gantry or exceed the table's weight limit also benefit from V/Q (1). Finally, in pregnancy, where reduced radiation exposure to the breast and developing foetus is desired, V/Q scintigraphy is the imaging modality of choice (121).

Inert gases were the first ventilation agents to be used in V/Q imaging. These included 133 Xenon and 81-m Krypton (9). Their physical properties enable them to be washed out of the lungs rapidly, thereby reducing the radiation dose to the patients. Radioaerosols were later introduced. These include diethylene-triamine pentaacetic acid (DTPA). Technegas was later introduced. Technegas consist of metastable 99-Technetium labelled solid graphite particles with a submicron diameter of approximately 100nm in argon carrier gas (9,122).

Perfusion imaging, on the other hand, is usually done with radioactive technetium labelled macro-aggregated albumin (99m Tc- MAA). This which comes is in the form of particles ranging in size from 5-30μm is injected into the patient's veins (5,9). Between 200,000 and 500,000 particles are injected. After peripheral intravenous injection, it moves rapidly through smaller vessels and either filtered out or trapped throughout the pulmonary bed. When perfusion is decreased or absent, it appears as a "cold" region or a defect of perfusion scintigraphy (75,122). A minimum of 6 views of ventilation and perfusion is performed to adequately assess the various segments of the lungs in different views. In a lung that is perfused normally, there is a homogeneous distribution of radiotracer. Therefore, the diagnostic feature of pulmonary embolism in a V/Q lung scan is a perfusion defect in a region of the normally ventilated lung, the so called mismatched perfusion defect.

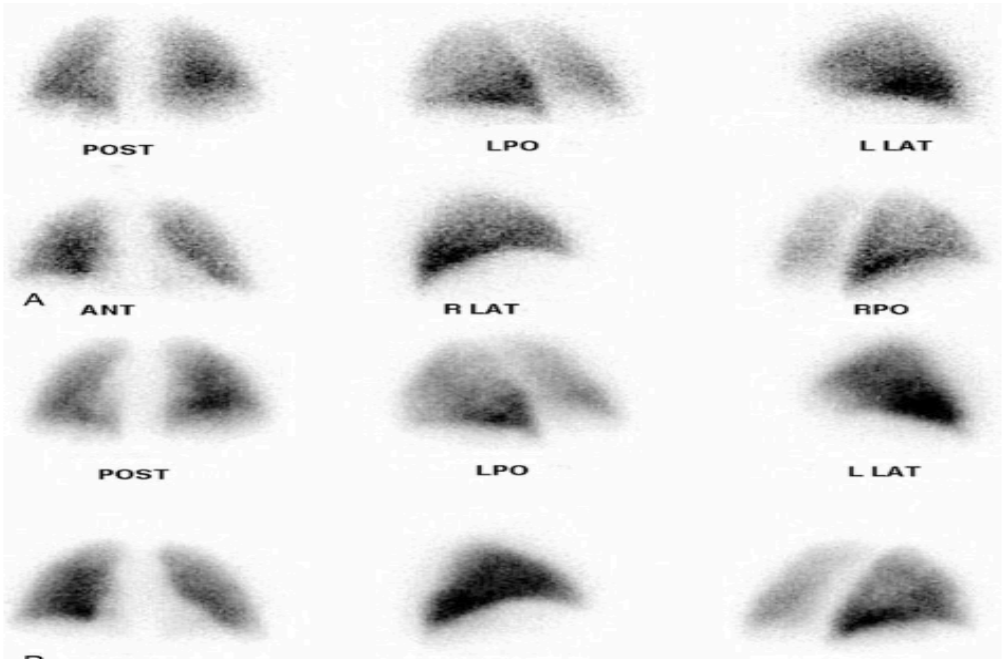


Figure 2-2: Normal lungs scintigraphy.

Ventilation Tc-99m diethylenetriaminepentaacetic acid (DTPA) and (B) Perfusion Tc-99m macroaggregated albumin (MAA) lung scan images show homogeneous distribution and the normal gradient of increasing activity in the bases relative to the apices.

Source: (123)

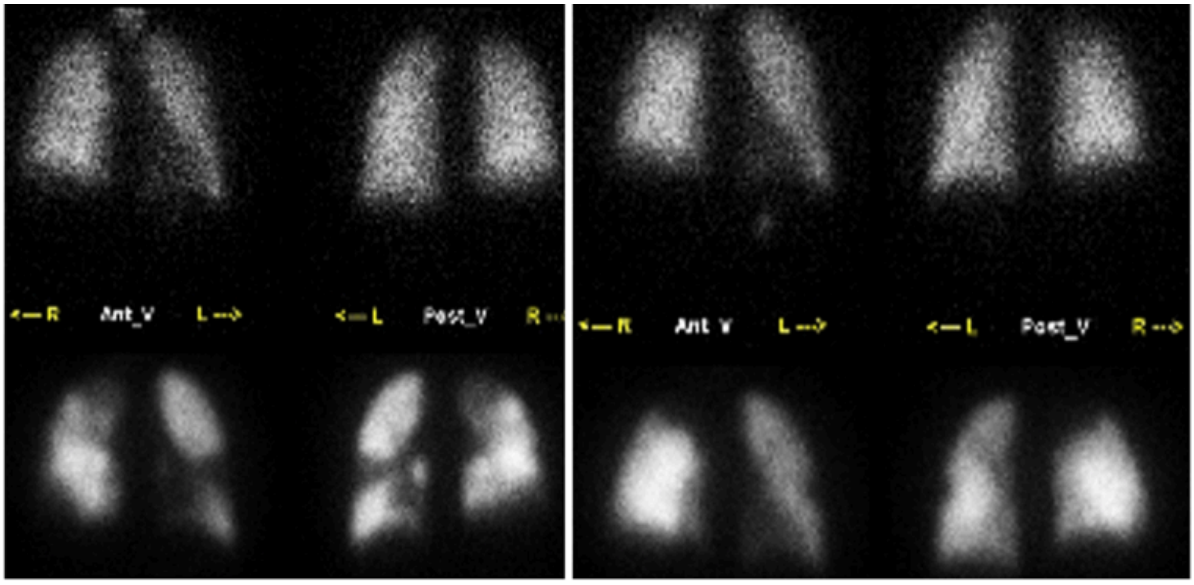


Figure 2-3:Planar images from a lung scintigraphy in pulmonary embolism.

Ventilation images in the upper row and perfusion images in the lower row. Left panel shows multiple bilateral mismatched defects.

Source: (124)

V/Q scan is relatively safe, with low radiation exposure and has very few contraindications (122,125). It has a sensitivity of over 90%. However, specificity varies from 58% - 90% (9,126).

## 2.18 Diagnostic criteria in lung scintigraphy

Various criteria are utilized in lung scintigraphy for assessing PE. These include the PIOPED, modified PIOPED II, PISAPED and the V/Q SPECT/CT using the EANM guidelines. However, the PIOPED II and the PISAPED criteria are the two most widely used protocols in diagnosing acute PE (127).

Table 2-5: Ventilation, perfusion, and radiographic interpretive criteria for pulmonary embolism

| PIOPED | Modified PIOPED II | Perfusion-only modified PIOPED II | Perfusion-only PISAPED |
|---|---|---|---|
| High LR | High LR | PE present | PE present |
| >2 large mismatched (V:Q) segmental defects* | ≥2 large mismatched (V:Q) segmental defects* | ≥2 large mismatched (Q:CXR) segmental defects* | ≥1 wedge-shaped Q defects |
| Borderline high LR | | | |
| 2 large mismatched (V:Q) segmental defects* | | | |
| Intermediate LR | Nondiagnostic | Nondiagnostic | Nondiagnostic |
| 2 moderate or 1 large mismatched (V:Q) defect* | All other findings | All other findings | Cannot classify as PE-present or PE-absent |
| Difficult to categorize as high or low | | | |
| Borderline low LR | | | |
| 1 matched (V:Q) defect, CXR-negative | | | |
| Low LR | | | |
| Nonsegmental perfusion defects† | | | |
| Q defect substantially < CXR defect | | | |
| Matched (V:Q) defects, CXR-negative | | | |
| Any number of small Q defects* | | | |
| Normal | Very low LR | PE absent | PE absent |
| No Q defects | Nonsegmental† | Very low probability | Non–wedge-shaped Q defect |
| | Q defect < CXR lesion | Nonsegmental† | Contour defect caused by enlarged heart, mediastinum, or diaphragm |
| | 1–3 small segmental* defects | Q defect < CXR lesion | Near-normal Q |
| | Solitary matched (V:Q:CXR) defect (≤1 segment) in mid or upper lung | 1–3 small segmental* defects | Normal Q |
| | Stripe sign‡ | Solitary matched (Q:CXR) defect (≤1 segment) in mid or upper lung | |
| | Solitary large pleural effusion§ | Stripe sign‡ | |
| | ≥2 matched (V:Q) defects, regionally normal CXR | Solitary large pleural effusion§ | |
| | Normal | | |
| | No Q defects | | |

Source: (128)

The PIOPED study began in the late 1980s, intending to determine accuracy, optimizing interpretation, and standardizing result reporting. Out of 1493 patients, 933 were randomly selected for this prospective trial, with 931 having a V/Q and 755 having a PA. PE was found to be prevalent in 33% of the participants in this investigation. Almost every PE patient had an abnormal study. One hundred and two (88%) of the 116 patients with high-probability scans and definitive angiograms had a PE, but only a minority with PE had high probability scans (sensitivity: 41% and specificity: 97%). A high probability study's PPV was 90%, and a normal examination nearly ruled out PE (129). The key flaw in this study was the unacceptably high rate of intermediate interpretation (44%). The modified PIOPED research of 1993 attempted to address the PIOPED group's issues by reclassifying small segment mismatched segmental abnormalities as intermediate defects and creating a very low probability group with a 10% likelihood of PE (15). This dramatically reduced the non-diagnosis of patients suspected of having PE, necessitating medical surveillance (123). The modified PIOPED II study was then presented. A total of 824 patients were evaluated in the PIOPED II research, with V/Q scintigraphy, lower extremity doppler sonography for deep venous thrombosis (DVT), Well's score, and pulmonary digital subtraction angiography (where available) serving as the composite reference standard for the diagnosis of PE. The reported sensitivity and specificity of the V/Q scan was 83% and 96%, respectively (52). As a result, V/Q imaging may provide a definitive diagnosis in the vast majority of cases.

The investigators of the PISAPED in the evaluation of a patient suspected with PE, took a different approach by removing the ventilation scan and replacing it with objective clinical evaluation and probability assessment parameters, as well as a recent chest radiograph for perfusion scan interpretation (14,16). The original PISAPED analysis prospectively evaluated 890 consecutive patients suspected of having PE. This study relied on physician judgment (gestalt), followed by perfusion scanning in all cases. Before imaging, patients were classified as PE likely, PE possible and PE unlikely. Patients with abnormal scans were followed with pulmonary angiography (PA) within 24 hours, where a definitive diagnosis was made in 563 (84%) of patients. The limitation of this study was that PA was not done in patients with renal failure, contrast allergy and pregnancy. With the PISAPED protocol (X/Q) application, the prevalence of PE was 39% in their study population. This study had a good sensitivity of 92% and a specificity of 87%. The PPV in PE likely and PE unlikely was 99% and 92%, respectively, while the NPV 97% (16). This high diagnostic accuracy restricted the need for invasive PA in patients.

Many authors compared the modified PIOPED II and the PISAPED parameters and concluded that both methods had similar sensitivity and specificity (84.9% and 92.7% respectively, for modified PIOPED II and 80.5% and 96.6%, respectively, for PISAPED) (15,16).

In the PIOPED study, 70% of scintigrams indicated low or intermediate probability (130). Although new diagnostic requirements can reduce the number of subjects who fall into these categories, those whose scintigrams fall into these categories need additional radiological investigation, which adds time and expense to their hospital stay (130,131). Of particular interest was the fact that the Modified PIOPED II interpretations revealed substantially more indeterminate readings (20.6%) than the PISAPED interpretations (0%). The PPVs of the adjusted PIOPED perfusion, PISAPED perfusion, and CTPA were 72.4%, 84.7% and 85.7%, respectively, while the NPVs were 96.5%, 95.5%, and 94.8% (16).

Sostman and colleagues (2008) used data from 889 perfusion scans to equate the PISAPED and PIOPED II criteria with CTPA. They discovered that the PISAPED parameters had a sensitivity of 83.3% (95% CI, 76.0-88.7%) and a specificity of 97% (95% CI, 95.5-98%) for patients under 50 years, compared to CTPA. The PPV and NPV, respectively, were 96% and 95%. There were no patients in this group who had an indeterminate scan. In this same review, the PISAPED parameters were retrospectively checked in scans using the PIOPED II protocol. There was a significant interobserver agreement with Kappa values of 0.765 and 0.774 in their two readers, respectively (19) .

In another retrospective analysis by J vans Es et al. (2015), comparing the diagnostic accuracy of PE using CTPA and the PISAPED criteria in 78 patients, the sensitivity and specificity using the PISAPED parameters (X/Q scan) were around to be 60% (95%CI 41-77%) and 86% (95% CI 74-93%), respectively. The interobserver agreement was extremely strong (K=0.89). After consensus reading, 21 patients (28%, 95% CI 19-38%) were classified as having 'PE present' with X/Q, 53 patients (70%, 95% CI 64-84%) as having 'PE absent,' and the two scan was classified as indeterminate (2.6%, 95% CI 0.8-9.0%). In 59 of 76 patients, there was an overall agreement between the CTPA and the X/Q-scan for the diagnosis of PE (78%, 95% CI 67-86%). The PPV and NPV of X/Q were 71.4% (95% CI 50-86%) and 83% (95% CI 71-91%), respectively. In 9 patients, CTPA was positive, whereas the PISAPED criteria read negative. On the other hand, the PISAPED criteria read a positive PE in 6 patients while the CPTA reported a negative scan (7).

# 3 CHAPTER 3: METHODOLOGY

## 3.1 Study design, site and study population

This retrospective cross-sectional analysis focused on secondary data obtained at the Charlotte Maxeke Academic Hospital's Nuclear Medicine Department. The Charlotte Maxeke Academic Hospital in Johannesburg, South Africa, is a tertiary referral hospital that receives and treats patients from all over Gauteng province. Patients with suspected PE who visited the Nuclear Medicine department for two years (from January 2017 to January 2019) were included in the study.

## 3.2 Inclusion criteria

Patients above 18 years referred for a V/Q scan. Patients with chest x-ray done within 24 hours before lung scintigraphy.

## 3.3 Exclusion criteria

Uninterpretable chest x-ray.

## 3.4 Sample size and sampling methods

The total number of eligible patients for the period under review is 974. The estimated sample size for this analysis was 389, based on a power of 95%, an effect size of 0.2, and an alpha of 0.05. Only 155 of the 389 participants were examined to reflect the appropriate referral pattern of patients who required a chest x-ray in less than 24 hours.

## 3.5 Randomization

Consecutive patients with clinically suspected PE between January 2017 and January 2019 who underwent perfusion lung scintigraphy were analysed using the inclusion and exclusion criteria.

### 3.6 Equipment

Images were retrieved from the hospital's picture achieving and communicating system (PACS) for analysis. The GE Infinia Hawkeye GP3 (2006, W1, USA) gamma camera and the GE Optima 649 (2014, W1 USA) gamma cameras were used to acquire these images. Both cameras were dual-head gamma cameras with similar workstations and processing units. In addition, images obtained using x-ray devices by Philips Medical System powered by Optimus 50 high-frequency generator were also utilised.

### 3.7 Data management

Data were extracted from the hospital database, recorded and saved in excel format. Data extracted included patients' demographics such as age, gender, and clinical information. Patients' identities were then coded and entered anonymously. Data cleaning was done to check for missing data and errors. Patients' laboratory results such as D-dimer and kidney function were retrieved from the National Health Laboratory System (NHLS). Patients' chest radiograph and images from ventilation/perfusion and their reports were retrieved from the hospital database. Data analysis was limited to patients with chest x-ray done within 24 hours before lung scintigraphy. All patients' clinical characteristics and risk factors for pulmonary embolism were recorded from the request forms/report.

The chest x-ray (posteroanterior and lateral view) was read by a different nuclear medicine physician who was unaware of the findings of the V/Q scan. Any abnormalities, such as pleural effusion, atelectasis, tumour or consolidation was labelled as abnormal. The perfusion scan was subsequently compared with the chest x-ray, and the findings were classified based on the interpretation using the PISAPED criteria. The readers interpreted the X/Q scans according to the PISAPED criteria (Table 2-5).

Overall agreement between the modified PIOPED II and PISAPED results and the positive predictive value of the X/Q scan was determined. The positive predictive value was defined as the proportion of all patients with mismatched X/Q scan findings who had pulmonary embolism as defined by a mismatched V/Q scan.

### 3.8 Statistical technique

Different statistical analysis was performed for various specific objectives to address the aim of the study outcome. The research was restricted to patients who have had a recent chest x-ray as well as perfusion and ventilation scan.

### 3.9 Descriptive statistics

A descriptive statistic reporting on frequencies and proportions was computed to describe study participants' demographic characteristics to address objective one, as shown in 3-1.

### 3.10 Cohen's Kappa statistics

Cohen Kappa statistics was employed to achieve objective two as stated on page 5 of the report. This statistical method assesses and determines the overall agreement between two different reviewers or evaluates the performance of a classification model (132,133). In diagnosis and interpretation of examination, the accuracy and reliability of a clinicians rating are essential. The Cohen Kappa statistics similar to other correlational statistics; the Kappa rates range from -1 to +1 and accounts for chance agreement (132,133). The table 3-1 below interprets the kappa.

Table 3-1: Interpretation of Cohen kappa statistical

| **Cohen kappa statistic (k)** | **Strength of agreement** | **Percentage oof data that are reliable** |
|---|---|---|
| <0.00 | Poor | 0 – 4% |
| 0.00 – 0.20 | Slight | – 15% |
| 0.20 – 0.40 | Fair | 15 – 35 % |
| 0.41 – 0.60 | Moderate | 35 – 63% |
| 0.61 – 0.80 | Substantial | 64 – 81% |
| 0.81 – 1.00 | Almost perfect | 81 – 100% |

Source: (132)

This study utilised two experienced nuclear medicine physicians who were unaware of the results of the V/Q scan. They read only the perfusion images against the chest x-ray. These nuclear medicine physicians were coded as P1SAPED 1 and PISAPED 2, respectively. An experienced radiologist (with more than ten years of working experience) also reviews the same chest x-rays to determine the accuracy of the two nuclear medicine physicians' interpretation and to measure interobserver readers' variabilities. A cross-tabulation was performed to assess the agreement in diagnosis by comparing PIOPED II read by an independent experienced nuclear medicine physician to PISAPED 1 and PISAPED 2 and their outcomes. This was followed with Cohen Kappa statistics to assess percentage agreement between PIOPED II (the gold standard) and PISAPED 1 and PISAPED 2 reviewers.

### 3.11 Sensitivity and reliability test

Sensitivity and specificity tests, as well as positive and negative predictive values tests with their corresponding proportions, were also computed, demonstrating true positives and negative cases by nuclear medicine physicians in comparison to the interpretation given by the PIOPED II criteria. The data were analysed using STATA statistical software (version 15). The findings were presented using graphs and tables.

### 3.12 Ethical clearance

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC), with ethic clearance number MP191138. Permission was also received from the CMJAH CEO's office and the Head of CMJAH's Nuclear Medicine department.

### 3.13 Confidentiality

Study participants were coded during the data collection process, and thus their identity will be kept confidential.

### 3.14 Limitations

Several issues regarding the design of our study should be addressed. Due to time restrictions and strict inclusion and exclusion criteria, the study's sample size was limited. The study was only able to include about 60% of our initial population. This was because some patients had

a chest x-ray older than 24 hours before the V/Q scan. If these patients' clinical indications and symptoms had not altered since their previous chest x-ray, they might have been included in the study.

The investigation only took a small sample of the patient's biochemistry. If we had more information about the patient's risk profile, we could better understand how PIOPED II and PISAPED correlate with the other indicators. Although pulmonary angiography is the gold standard for PE diagnosis, we purposefully compared X/Q (PISAPED), and V/Q (PIOPED II) scans instead of pulmonary angiography (PA). Given the sensitivity and specificity of V/Q (PIOPED II) studies as compared to PA, we believe our findings are valid. Finally, advanced image-processing alternatives such as V/Q SPECT and SPECT/CT were not investigated. It is still unknown if such strategies would have enhanced the value of our interpretation.

# 4 CHAPTER 4: RESULTS

## 4.1 Introduction

The findings of this investigation are summarized in this chapter. Tables and figures are used to describe the results of the statistical analysis test. Participants' demographic characteristics and risk factors for pulmonary thromboembolism are described in the first objective. The second objective evaluates the diagnostic accuracy of chest x-ray/perfusion in patients with pulmonary thromboembolism.

Descriptive statistics using frequencies and proportions were computed to describe the demographic characteristics of all study participants.

Table 4-1: Demographic characteristics of study participants

| Indicators | Frequencies (n=155) | Percentage (%) |
|---|---|---|
| **Race of participants** | | |
| Black | 117 | 75.5 |
| Mixed-race | 9 | 5.8 |
| Indian | 2 | 1.3 |
| Caucasians | 27 | 17.4 |
| **Gender of participants** | | |
| Male | 51 | 33 |
| Female | 104 | 67 |
| **Age group (years)** | Mean= 50.09 | Std= 16.78 |
| 18-29 | 24 | 15 |
| 30-39 | 27 | 17 |
| 40-49 | 16 | 10 |
| 50-59 | 35 | 23 |
| 60-69 | 34 | 22 |
| Above 70 years | 19 | 13 |

The majority of the study participants (75%) were Black, followed by Caucasians (17%), mixed-race (6%) and Indians (1%), respectively, as seen in Table 4-1 above. Females made up around two-thirds of the total eligible participants (67%). The two dominant age groups identified in the study were 50 – 59 and 60 – 69 and constituted 23% (35 participants) and 22% (35 participants), respectively, of the total participants. Surprisingly, more patients were in the 30-39 age group (17%) than in the 70+ age group (13%). The mean age of the total population investigated was 50.09 with a standard deviation of 16.78.

Table 4-2: Hospital profile of participants

| Variable | Frequencies | Percentage (%) |
|---|---|---|
| **Status** | | |
| In-patient | 78 | 50.3 |
| Outpatient | 77 | 49.7 |
| **Well score** | | |
| Normal | 2 | 1 |
| High | 6 | 4 |
| Not done | 147 | 95 |
| **D-dimer** | | |
| Normal | 17 | 12 |
| High | 75 | 48 |
| Not done | 63 | 40 |
| **Kidney function** | | |
| Normal | 79 | 51 |
| Abnormal | 71 | 46 |
| Not done | 5 | 3 |

Table 4-2 above shows the participants' status and hospital characteristics of patients included in the study. About half of the participants (50.3%) were hospitalized patients, while the other half were outpatients.

It also demonstrates that around 95% of patients did not have their Wells score calculated before being referred to the Nuclear Medicine department. Only 6 (constituting 4%) of those who had their Wells score calculated had a high Wells score, while only 2 (1%) had a low Wells score.

As seen in Table 4-2, over half of the patients were referred for a D-dimer test before referral. However, out of the 92 patients referred for a D-dimer examination, 41% had high D-dimer levels, while just 12% had normal D-dimer levels.

Furthermore, the data revealed that the vast majority of the research participants (97 %) had a kidney function test before referral. Seventy-nine (constituting 51%) of those tested had normal kidney function, whereas 71 (representing 46%) of total participants had an abnormal renal function.

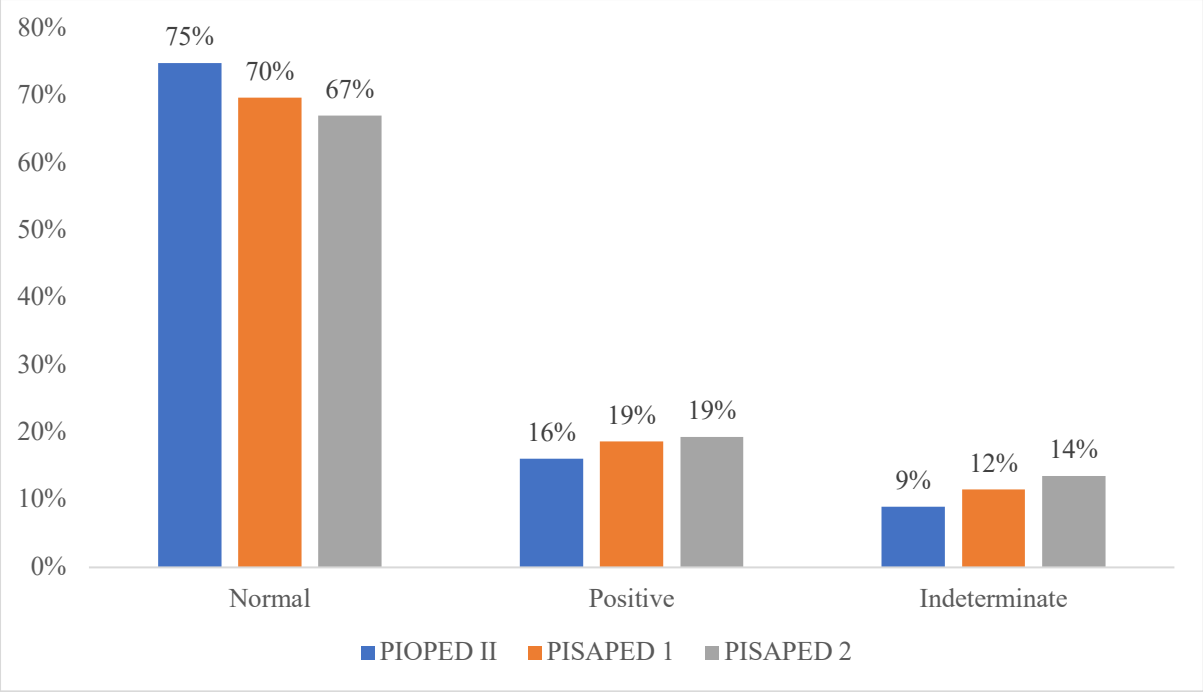


Figure 4-1: Percentage score for diagnostic accuracy comparing PIOPED II with PISAPED 1 and PISAPED 2 readers

A comparison of PIOPED II with the two PISAPED readers is shown in Figure 4-1 above. It reveals that they have essentially similar readings. In PIOPED II, 116 (74.8%) of the patients had a normal study, 25 (16.1%) had scans positive for PE, and 14 (9.1%) had indeterminate studies. In the PISAPED 1 group, 108 people (69.7%) had a normal study, 29 (18.7%) patients had a positive study, and 18 (11.6%) patients had an indeterminate study. Finally, the PISAPED 2 reader saw 104 (67%) normal studies, 30 (19%) positive scans, and 21 (14%) indeterminate studies.

## 4.2 Cohen's Kappa Statistics

Cohen Kappa statistics were also computed to assess percentage agreement between the PIOPED II (Gold standard) and the two (2) other reviewers. The outcome is presented in Table 4-3 below.

Table 4-3: Comparing modified PIOPED II (Gold standard) versus PISAPED 1 (reviewer 1)

| | Modified PIOPED II | | | |
|---|---|---|---|---|
| | **Category** | **Normal** | **Positive** | **Indeterminate** | **Total** |
| **PISAPED 1** | Normal | **104** | 1 | 3 | **108** |
| | Positive | 3 | **24** | 2 | **29** |
| | Indeterminate | 9 | 0 | **9** | **18** |
| | **Total** | **116** | **25** | **14** | **155** |

| **Agreement** | **Expected Agreement** | **Kappa** | **StdErr** | **Z** | **p-value** |
|---|---|---|---|---|---|
| 88.39% | 56.21% | 0.7348 | 0.0613 | 11.98 | < 0.000 |

Out of the 155 instances, 137 agreements between modified PIOPED II and PISAPED 1 were established, as shown in Table 4-3. One hundred and four (104) instances were classified as normal, 24 as positive, and 14 as indeterminate using modified PIOPED II and PISAPED 1. Between modified PIOPED II and PISAPED 1, the observed agreement rate is 88.39%. The Kappa value of 0.7348 suggests that modified PIOPED II and PISAPED1 are strongly correlated and that the observed agreement is not due to chance.

Table 4-4: Comparing modified PIOPED II (Gold standard) versus PISAPED 2 (reviewer 2)

| | Modified PIOPED II | | | |
|---|---|---|---|---|
| | **Category** | **Normal** | **Positive** | **Indeterminate** | **Total** |
| **PISAPED 2** | Normal | 102 | 4 | 10 | 116 |
| | Positive | 1 | 24 | 0 | 25 |
| | Indeterminate | 1 | 2 | 11 | 14 |
| | **Total** | **104** | **30** | **21** | **155** |

| **Agreement** | **Expected Agreement** | **Kappa** | **StdErr** | **Z** | **p-value** |
|---|---|---|---|---|---|
| 88.39% | 54.56% | 0.7444 | 0.0604 | 12.33 | < 0.000 |

According to Table 4-4 above, 102 instances were classified as normal, 24 as positive, and 11 as indeterminate using the modified POIPED II and PISAPED 2. For both modified PIOPED II and PISAPED 2, 137 (or 57%) of the 155 cases were classified as normal, positive, or indeterminate. The observed agreement cannot be attributed to chance, given the Kappa value of 0.7444, the observed proportion of agreement between modified PIOPED II and PISAPED

2 (88.39%), and the proportion of agreement that would be projected merely by chance expected agreement (54.56%).

### 4.3 Assessing sensitivity and specificity of the diagnosis

Table 4-5: Sensitivity and specificity of modified PIOPED II versus PISAPED 1 and

| Method | diagnostic reading | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Modified PIOPED II vs PISAPED 1 | 97% (128/132) | 96% (24/25) | 97% (104/107) | 89% (24/27) | 99% (104/105) |
| Modified PIOPED II vs PISAPED 2 | 96% (126/131) | 96% (24/25) | 96% (102/106) | 86% (24/28) | 99% (102/103) |

PISAPED 1 findings against modified PIOPED II results are shown in Table 4-5. PISAPED 1 successfully identified 97% of the 132 outcomes utilized in this analysis. PISAPED 1 found 24 of the 25 positive results, giving it a sensitivity of 96%. Similarly, PISAPED 1 correctly recognized 104 of the 107 results categorized as negative by modified PIOPED II, yielding a 97% specificity. PISAPED 1 identified 24 of the 27 records as positive, with a PPV of 89%. The NPV was 100%.

The sensitivity and specificity results for PIOPED II and PISAPED 2 may be seen in table 4-5. PISAPED 2 correctly identified 126 out of 131 samples, resulting in a 96% accuracy rate. Furthermore, the sensitivity rate was 96% for 24 of the 25 positives. In comparison, modified PIOPED II recognized 102 of the 106 instances as negative, while PISAPED 2 identified 102 of the 106 cases as negative, yielding a 96% specificity rate. PIOPED II and PISAPED 2 also projected PPV and NPV of 86% and 99%, respectively. This is the percentage of PISAPED 2 positive records that were also true positive by modified PIOPED II (24/28).

## 4.4 Comparing diagnostic accuracy using chest x-ray reading by Radiologist versus PISAPED 1 (reviewer 1) and PISAPED 2 (reviewer 2)

Table 4-6: PISAPED 1 (x-ray 1) and PISAPED 2 (x-ray 2)

| Indicator | Normal | Abnormal | Total |
|---|---|---|---|
| Radiologist | 3 | 152 | 155 |
| PISAPED 1 | 80 | 75 | 155 |
| PISAPED 2 | 71 | 84 | 155 |

Table 4-6 shows a significant disparity between the radiologist's results and reviewer 1 (PISAPED 1 reader) and reviewer 2 (PISAPED 2 reader). The results show that the radiologist identified 152 abnormal chest x-rays out of a total of 98%. At the same time, reader 1 and reader 2 found 75 and 85 abnormal chest x-rays out of a total of 48% and 54%, respectively. Cardiomegaly was the most common abnormal finding on chest x-rays in this investigation. The radiologist recognized cardiomegaly in around 36% of all chest x-rays, while the PISAPED 1 and PISAPED 2 readers both found 21% cardiomegaly in their findings.

Table 4-7: Size of effusion

| Size of plural effusion | Frequency | Percentage |
|---|---|---|
| Small | 34 | 94 |
| Large | 2 | 6 |

Table 4-7 shows the frequency of pleural effusions on chest x-rays. Small pleural effusions accounted for 94% (34 out of 36) of the 36 pleural effusions identified on chest x-rays, while massive pleural effusions accounted for 6% (2 out of 36).

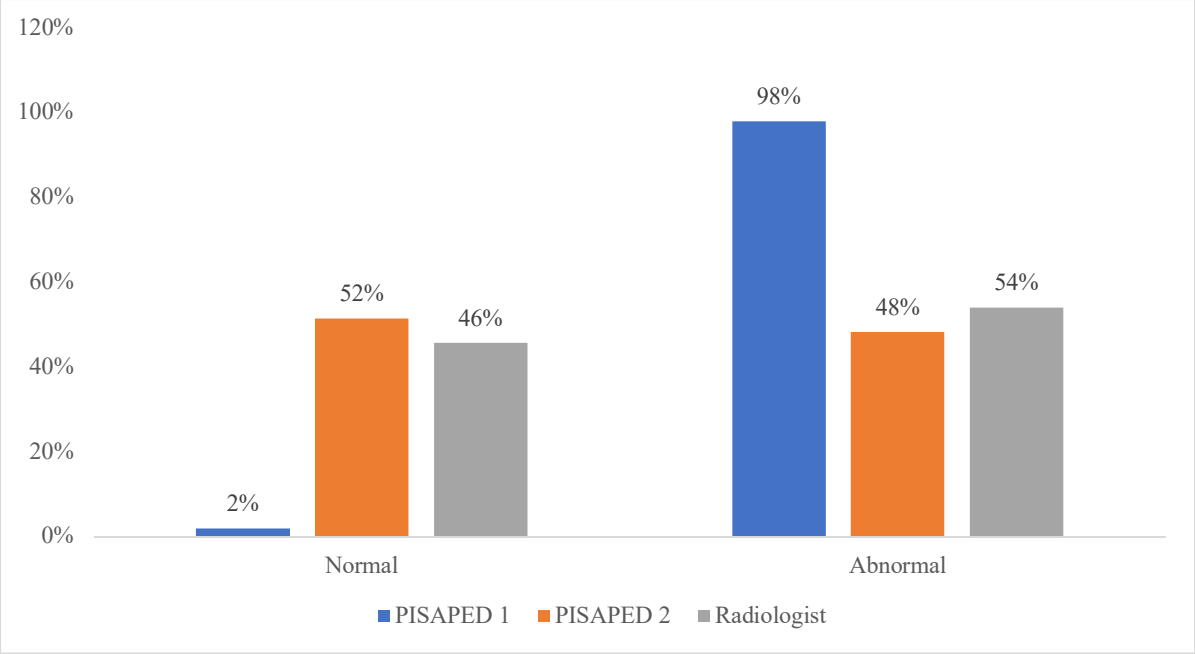


Figure 4-2: Percentage agreement of diagnosis using chest x-rays comparing the radiologist and the two PISAPED readers

Furthermore, the results from figure 4-2 above demonstrate no significant changes in the number of x-rays identified as normal or abnormal by reviewer 1 (PISAPED 1) and reviewer 2 (PISAPED 2), which contrasts with the radiologist's findings, which showed that around 98% of the chest x-rays were abnormal.

Table 4-8: Comparing radiologist (the gold standard) versus PISAPED 1 (reviewer 1)

| | **Radiologist (gold standard)** | | | |
|---|---|---|---|---|
| **PISAPED 1** | **Category** | **Normal** | **Abnormal** | **Total** |
| | Normal | 3 | 77 | 80 |
| | Abnormal | 0 | 75 | 75 |
| | Total | 3 | 152 | 155 |

| **Agreement** | **Expected Agreement** | **Kappa** | **StdErr** | **Z** | **p-value** |
|---|---|---|---|---|---|
| 50.32% | 48.45% | 0.0363 | 0.0215 | 1.69 | 0.0453 |

According to Table 4-8, PISAPED 1 reader misclassified 77 of the 152 instances designated as abnormal by the radiologist. Both the radiologist and reviewer 1 classified a total of 78 cases as either normal or abnormal. Given the extremely low Kappa value of 0.0363, the observed proportion of agreement between the radiologist and PISAPED 1 reader 1 (50.32%) and the proportion of agreement that would be expected simply by chance expected agreement (48.45%), there is poor or weak agreement between the radiologist and PISAPED 1 reader.

Table 4-9:Comparing radiologist (the gold standard) versus PISAPED 2 (reviewer 2)

| | Radiologist (gold standard) | | | |
|---|---|---|---|---|
| | **Category** | **Normal** | **Normal** | **Total** |
| **X-Ray 2** | Normal | 3 | 68 | 71 |
| | Abnormal | 0 | 84 | 84 |
| | Total | 3 | 152 | 155 |

| **Agreement** | **Expected Agreement** | **Kappa** | **Std Err** | **Z** | **p-value** |
|---|---|---|---|---|---|
| 56.13% | 54.03% | 0.0456 | 0.024 | 1.9 | 0.0286 |

Only three cases were deemed to be normal by the radiologist, as shown in Table 4-9 above. The PISAPED 2 reader, on the other hand, identified 71 instances as normal. Both the radiologist and the PISAPED 2 reader correctly diagnosed 87 instances as either normal or abnormal. Given the extremely low Kappa value of 0.0363, the observed proportion of agreement between the radiologist and PISAPED 2 reader (56.13%), and the proportion of agreement that would be expected simply by chance expected agreement (54.03%), the radiologist and PISAPED 2 reader have a poor or weak agreement, and the observed agreement could be due to chance.

# 5 CHAPTER 5: DISCUSSION

## 5.1 Demographics of eligible patients

The majority (75%) of the patients who participated in this study were Black; this is similar to Dentan et al. (2014), Bulajic et al. (2019) and Danwang et al. (2017), who found a higher prevalence of PE in Black and associated this to the presence of communicable diseases such as tuberculosis (TB) which are themselves a hypercoagulable state. Even though we did not know the TB status of our subject, considering the high prevalence of communicable diseases, including TB in our environment, there could be an association between the Black race, TB status, and PE. Furthermore, the 50 – 59 years age bracket accounted for 45% of the total population investigated, with a median age of 50.09 years, similar to Dentan et al. (2014), who found the median age for PE to be 53 in their study. On the contrary, more females qualified to be included in this than men; however, the study conducted by Dentan et al. (2014) was the reverse, which suspected more males with PE.

Interestingly, there were 27 people in the 30-39-year-old age bracket (representing 17%) of the total eligible candidate compared to the 19 people in the 70+ age group representing only 13% of the total population investigated. Increased risk factors such as obesity and the use of hormonal contraceptives could account for the major cause of high PE suspicion among young people. Additionally, patient lifestyle and socioeconomic status could add value to the study if the association and findings in the research group could be linked.

Almost half of the patients in our study were hospitalized patients. This is particularly important in the chest x-ray findings because in-patients are most likely to have cardiopulmonary problems, abnormal x-ray findings and increased indeterminate interpretation. This was the main flaw of the PIOPED study, where 68% of in-patients were utilized, resulting in a 44% of indeterminate diagnosis of PE. In the modified PIOPED study, the number of in-patients was reduced to 11%, thus reducing the indeterminate results. Giving the high PPV of a normal chest x-ray by Stein et al. (2007) of 86%, the present study had indeterminate results of between 18-21%. This was slightly higher than their findings in the PIOPED II study, where the indeterminate findings were 14%. Our higher indeterminate rate could also be due to the significant number of suboptimal quality x-ray images as described by the radiologist.

## 5.2 Value of chest x-ray and diagnostic accuracy of chest x-ray/perfusion scan

Out of our estimated sample size of 386, only 40.1% of patients had a recent chest x-ray. Although there is limited data on the physician's chest x-ray referral pattern within 24 hours prior to V/Q studies, de Groot et al. (2000) reported that about 83% of patients had a chest x-ray done 48 hours before V/Q studies. However, a more recent chest x-ray is preferred for symptomatic patients. Further studies could be done to compare the value of chest x-ray done within 24 hours and 48 hours in PE assessment.

The study showed almost double the percentages of radiologists' abnormal chest x-rays compared to the PISAPED 1 and PISAPED 2 readers. According to our findings, reviewer 1 and reviewer 2 both recorded close identical proportions of chest x-rays classified as normal or abnormal. This contradicts the radiologist's results, which revealed that 98% of the chest x-rays were abnormal. As a result, the interobserver agreement between the radiologist's findings (designated as the goal standard) and PISAPED 1 and PISAPED 2 readers were exceptionally low (Kappa 0.0363). While the lung field could be interpreted, the true quality of the chest x-ray was determined to be unsatisfactory by the radiologist. The radiologist classified 70% of reader 1's "normal" chest x-ray as abnormal due to the presence of cardiomegaly and 30% as abnormal due to the presence of hyperinflation or other abnormalities – but noted that these changes did not affect the diagnostic performance of the interpretation as "positive" or "negative" or "indeterminate" for PE between modified PIOPED II and PISAPED 1 and PISAPED 2. All of the x-rays taken were of sick people and this could be related to the patient's health or situation. Additional research however is needed in our local area so that radiographers can improve. A future study comparing individuals suspected of PE to patients who had a chest x-ray for another cause and did not have similar symptoms will be encouraged to better understand the reasons behind the suboptimal chest x-rays. Various studies, including that of Al aseri et al. (2009), Gatt (2003) and Espinosa (2000), also confirm that chest x-ray evaluation interpretation is very varied among physicians and even more so among experienced radiologists. However, this was contrary to the studies by Tranovich et al. (2019), who found a good inter-reader agreement between emergency medicine physicians and radiologists. These discrepancies may require further investigations on the criteria of reporting between the two specialties. To increase the interobserver variabilities, a standard template for the diagnosis will be beneficial.

Out of possible abnormalities that could be visualized on chest x-ray in patients suspected of having PE, our study was similar to many others, including the ICOPER study by Goldhaber

et al (1999), which found cardiomegaly to be the most common abnormalities. Since the majority of our participants are of the child-bearing age, further studies should be conducted to understand the high frequency in this study population.

This study showed that the majority (95%) of patients referred for assessment for PE in the nuclear medicine department did not have a Wells score calculated. An indication that the majority of participants did not have an objective patient assessment to rule out PE before referral. This finding is higher than that of Smith et al. (2008), who found that there was no documentation of pre-test probability assessment in 64% of known VTE suspicious cases. Furthermore, in their study, 25% of the recorded decisions were at odds with current recommendations for a given set of test results, were misread or misapplied or both. The results of Runyon et al. (2007) may explain the low utilization of the wells ratings. In their study, 68% of respondents said they were familiar with at least one of two pre-test likelihood tools for PE. However, due to medico-legal considerations, difficulty memorizing and applying the guidelines, the assumption that clinical configuration is easier, and the belief that none of the rules has been tested to their satisfaction, the physicians did not use the pre-test likelihood methods. The low use of pre-test probability in our study is evident and close to that of Adams et al. (2013) in South Africa, who found that the recommendation to risk-stratify patients prior to CTPA using a pre-test algorithm (Well's score or updated Geneva score) was ignored, with less than half of CTPA referrals adopting these recommendations. The cause for the exclusion of the Well score may need to be investigated further.

Approximately half of the patients in our sample did not have their D-dimers tested prior to referral. In a country with limited resources, such as South Africa, a less expensive D-dimer test would be a cost-effective method of patient management. In our study, 12 patients had a normal D-dimer. These patients could have avoided additional diagnostic test for PE had their Wells score been calculated as recommended by Goodacre et al. (2005), Quiroz and Shoepf (2005), and Ravel et al. (2005) given the high NPV of D-dimer. This was also similar to Lee and Zierler's (2010) retrospective review of 1161 patients, which found that the diagnostic technique of pre-test probability and D-dimer as an initial screening for suspected VTE was underutilized. Also, Taira et al. (2010) found that the high probability, intermediate probability, and low probability of patients with suspected PE were 25%, 64%, and 11%, respectively, in their prospective study of 270 patients suspected with VTE. Even in this analysis, the D-dimer assay's sensitivity for ruling out VTE was 92% at a cut-off of 500 g FEU/l, which fell short of the other studies' sensitivities (>95%). They also concluded that normal D-dimer can rule out PE in at least low and intermediate risk patients.

In the present study, 46% of the population investigated had some renal impairment, while 3% had not performed a kidney function before referral for V/Q studies. To prevent contrast-induced nephrotoxicity, which occurs in patients with chronic kidney disease associated with diabetes mellitus and other comorbidities, the guidelines recommend that these patients with renal dysfunction be referred for a V/Q study to test for PE rather than PE CTPA. The level of renal impairment in this study population is higher than those found in the PIOPED II report, which found that more than a third of eligible patients were turned down for CTPA due to elevated creatinine levels. Several international recommendations, including that of Waxman et al. (2017), advocated for the use of lung scintigraphy in renal impairment settings to avoid contrast nephropathy. Patients with a GFR of 30 mL/min/1.73 $m^2$ or more are deemed healthy for contrast without risking further kidney damage. Despite this, some authors have recently questioned whether contrast nephropathy is a serious issue.

### 5.3 Diagnostic accuracy and interrater agreement

When PIOPED II and the two PISAPED readers are compared, the readings are remarkably close. In PIOPED II, 75% of the patients had a normal study, 16% had scans positive for PE, and 9% had inconclusive studies. The PISAPED 1 group had 70% normal studies, 19% positive studies, and 12% indeterminate studies, whereas the PISAPED 2 reader saw 67% normal studies, 19% positive scans, and 14% indeterminate studies. Even though several studies such as that of Sostman et al. (2008) and J vans Es et al. (2015) reported lower indeterminate results, our study showed a higher frequency for both our PISAPED 1 and PISAPED 2 readers. Further studies will be needed to understand these differences.

The PISAPED 1 reader had a sensitivity and specificity of 96% and 97%, respectively, and an NPV and PPV of 99% and 89%. The PISAPED 2 reader had a sensitivity and specificity of 96% and an NPV and PPV of 86% and 99%, respectively. The agreement between the PIOPED II and the PISAPED 1 and PISAPED 2 was 88.39% (Kappa value of 0.7348) and 88.39% (Kappa value of 0.7348), respectively. Given their Kappa values, this remarkable agreement in interpretation is unlikely to be attributable to coincidence. These findings were similar to those of da Silva et al. (2014) and Miniati et al. (1996), who found that the modified PIOPED II and PISAPED parameters had comparable sensitivities and specificities (84.9% and 92.7% for modified PIOPED II and 80.5% and 96.6% for PISAPED) as well as similar NPV and PPV (96% and 90% for the PIOPED II criteria and 95% and 96% for the PISAPED criteria respectively). Our results, however, had higher sensitivity, specificity, NPV and PPV than the

by J vans et al. (2015), which found a sensitivity of 60%, specificity of 86%, NPV of 83 and PPV of 71.4% in their research. However, with a Kappa value of 89%, both investigations demonstrated very strong interobserver agreement. This demonstrates that the diagnostic accuracy of the PISAPED criteria is highly dependent on the reader's level of experience and ability to include other parameters, such as pre-test probability tools, to improve diagnostic accuracy. However, in this analysis, the number of indeterminate studies was substantially larger than in other studies, such as that of Sostman et al. (2008), who had no patients in their indeterminate category. This is most likely due to the high number of suboptimal x-ray quality found in this investigation

# 6 CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

## 6.1 Conclusions

This study demonstrates that using a chest x-ray in conjunction with perfusion scintigraphy (PISAPED) is accurate and can reliably replace ventilation/perfusion scintigraphy (Modified PIOPED II) in the diagnosis of PE. Even though in our environment, majority of the chest x-ray taken are of subquality, the PISAPED criteria had a comparably good accuracy and with very good interobserver agreement. Although the PISAPED readings yielded more uncertain results than the PIOPED II criteria, they seem to be more beneficial in the hands of an experienced reader who uses pre-test probability tools to improve diagnostic accuracy. The PISAPED criteria are also more helpful in younger patients, pregnant and breastfeeding mothers, and others in other patients in whom reduction of ionizing radiation is desired. Also, in a resource-constrains country like South Africa, the ventilation portion of lung scintigraphy could be omitted to reduce cost and save time, thus assisting in service delivery.

## 6.2 Recommendations

The referring physician should be encouraged to use the pre-test probability tools such as the Wells and the Geneva scores and document their findings on the request forms before referring the patients for a diagnostic scan. This will help them decide whether the scans are necessary or not. It will also help to increase the diagnostic accuracy of the studies.

The percentage of patients with a recent chest x-ray (taken within 24 hours) is very low. The referring physician should use this single important cost-effective tool in their work-up. This will either help in the diagnostic work-up or make the perfusion only study useful in the nuclear medicine department to reduce patients' exposure to radiation.

It was apparent in the study that most of the chest x-rays available for reporting were suboptimal. Radiographers in all units should be encouraged to use the appropriate protocols for chest x-rays imaging and have regular in-service training in quality assurance.

Physicians interpret chest x-rays differently. Even though this is a common occurrence, it can be minimized by using a uniform template for reporting chest x-rays. To increase the agreement between chest x-ray findings, nuclear medicine physicians should get frequent education and in-service training in chest x-ray interpretation. This improves the diagnostic accuracy of studies that use this criterion.

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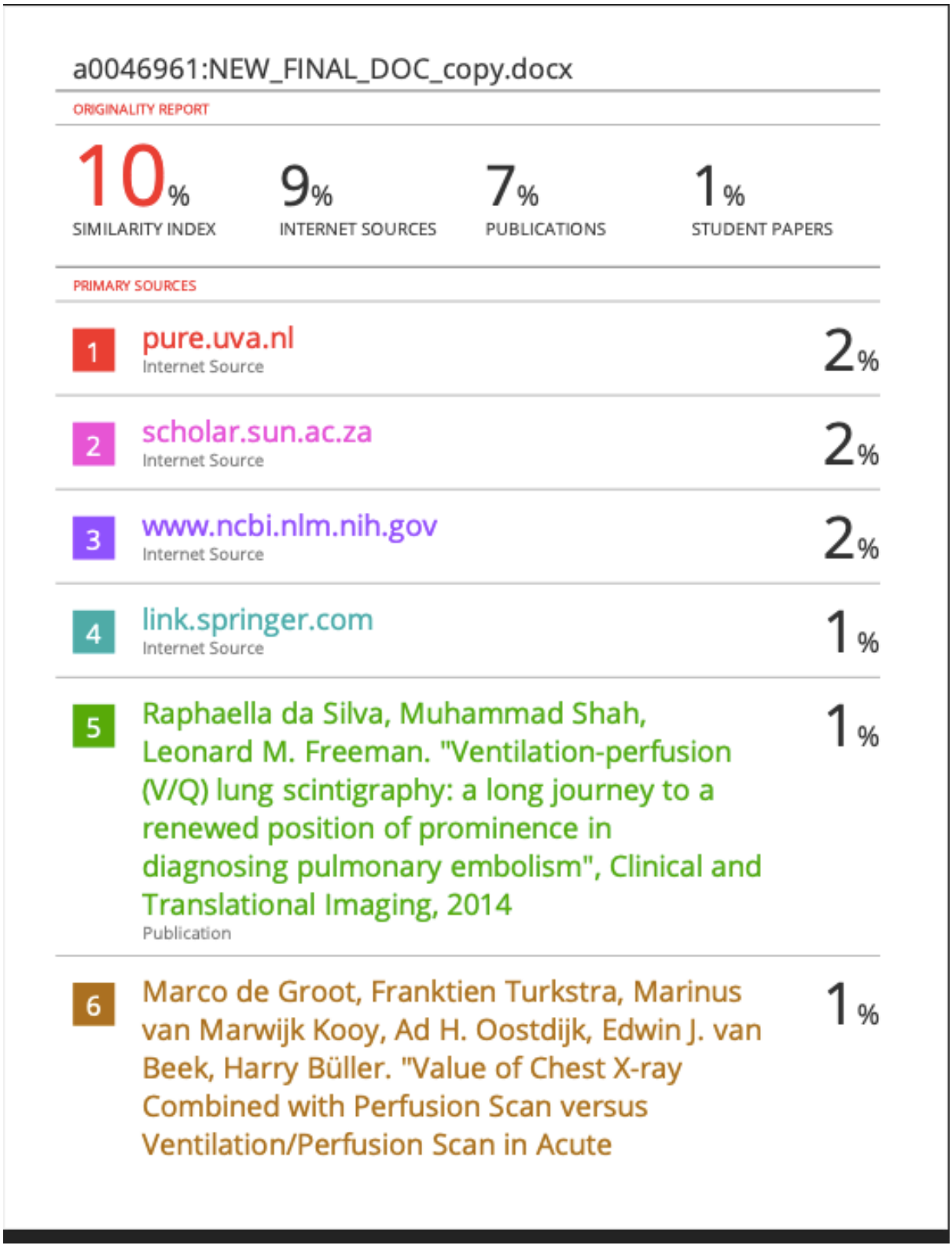
**APPENDIXES**

**Appendix 1: plagiarism form**



a0046961:NEW_FINAL_DOC_copy.docx

ORIGINALITY REPORT

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| 5 | Raphaella da Silva, Muhammad Shah, Leonard M. Freeman. "Ventilation-perfusion (V/Q) lung scintigraphy: a long journey to a renewed position of prominence in diagnosing pulmonary embolism", Clinical and Translational Imaging, 2014<br>Publication | 1% |
| 6 | Marco de Groot, Franktien Turkstra, Marinus van Marwijk Kooy, Ad H. Oostdijk, Edwin J. van Beek, Harry Büller. "Value of Chest X-ray Combined with Perfusion Scan versus Ventilation/Perfusion Scan in Acute | 1% |

## Appendix 2a: Ethics clearance form

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Samuel Teye et al

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**

**CLEARANCE CERTIFICATE NO. M191138**

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Samuel Teye et al |
| **DEPARTMENT:** | Radiation Sciences/ Nuclear Medicine and Molecular Imaging Charlotte Maxeke Johannesburg Academic Hospital |
| **PROJECT TITLE:** | Imaging of patients suspected of having pulmonary thromboembolism; the value of chest x-ray combined with perfusion scan in South Africa |
| **DATE CONSIDERED:** | 29/11/2019 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Prof Mboyo-Di-Tamba Vangu |
| **APPROVED BY:** | Dr CB Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 29/11/2019 |

**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 **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 10/12/2019

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

## Appendix 2b: CEO approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

**Enquiries:**
**Ms. N. Mzila**
**Office of the Clinical Director**
**Email: Nolwazi.Mzila@gauteng.gov.za**
**Tell: (011): 488-4812**
20th September 2019

Dear Dr. S. Teye

**STUDY TITLE: Imaging of the Patients Suspected of Having Pulmonary Thromboembolism; the Value of Chest X-Ray Combined with Perfusion Scan in South Africa.**

Permission to review patient file for conduction of the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / ~~not supported~~

**Dr. M.I. Mofokeng**
**Clinical Director**
**DATE:** 20/09/2019

Approved / not approved

**Ms. G. Bogoshi**
**Chief Executive Officer**
**DATE:** 23.09.2019

**Appendix 3: STATA syntax for Cohen kappa statistical test**

PIOPED & PISAPED1
cross-tabulation
*tab PISAPED1 PIOPED, m r col*

*Percentage of agreement*
*label def interrate 1 "agree" 0 "disagree"*
*ge poiped_pisaped1 = cond( (PIOPED == PISAPED1), 1, 0)*
*labe values poiped_pisaped1 interrate*
*tab poiped_pisaped1*

***Kappa statistics***
*kap PIOPED PISAPED1, tab*
PIOPED & PISAPED2
cross-tabulation
*tab PISAPED2 PIOPED, m r col*

*Percentage of agreement*
*ge poiped_pisaped2 = cond( (PIOPED == PISAPED2), 1, 0)*
*labe values poiped_pisaped2 interrate*
*tab poiped_pisaped2*

***Kappa statistics***
*kap PIOPED PISAPED2, tab*

***Radiologist & X-Ray 1***
cross-tabulation
*tab CXR1 Radiologist, m r col*

*Percentage of agreement*
*ge rad_xray1 = cond( (CXR1 == Radiologist), 1, 0)*
*labe values rad_xray1 interrate*
*tab rad_xray1*

***Kappa statistics***
*kap CXR1 Radiologist, tab*

***Radiologist & X-Ray 2***
cross-tabulation
*tab CXR2 Radiologist, m r col*

*Percentage of agreement*
*ge rad_xray2 = cond( (CXR2 == Radiologist), 1, 0)*
*labe values rad_xray2 interrate*
*tab rad_xray2*

*Kappa statistics*
*kap CXR2 Radiologist, tab*

**Appendix 4: Data collection tool**

**THE UNIVERSITY OF THE WITWATERSRAND**

**FACULTY OF HEALTH SCIENCES, SCHOOL OF NUCLEAR MEDICINE**

**IMAGING OF PATIENTS SUSPECTED OF HAVING PULMONARY THROMBO-EMBOLIC DISEASE; DOES A CHEST X-RAY ASSIST IN OUR ENVIRONMENT?**

A GUIDE FOR DATA COLLECTION **(VENTILATION/PERFUSION ONLY**)

PATICIPANT CODE: A…

| NO | VARIABLE | RESPONSE |
|---|---|---|
| | **SECTION A: PATIENTS DEMOGRAPHICS (*TICK √ WHERE APPLICABLE*)** | |
| 1 | Patient age | ……. |
| 2 | Patient sex | Male ◯ |
| | | Female ◯ |
| 3 | Patient race | White ◯ |
| | | African ◯ |
| | | Others ◯ |
| 4 | Patient status | Inpatient ◯ |
| | | Outpatient ◯ |
| | **SECTION B: BIOCHEMISTRY / TREATMENT / PATIENT PARAMETERS (*TICK √ WHERE APPLICABLE*)** | |
| 5 | D-dimer | Normal ◯ |
| | | High ◯ |
| 6 | Blood urea / creatinine | Normal ◯ |
| | | High ◯ |
| 7 | Anticoagulation therapy | Commenced ◯ |
| | | Not commenced ◯ |
| 8 | Wells' score | Low probability ◯ |
| | | Moderate probability ◯ |
| | | High probability ◯ |
| | **SECTION C: CHEST X-RAY DETAILS (*TICK √ WHERE APPLICABLE*)** | |
| 9 | Has the patient had an X-ray done? | Yes ◯ |
| | | No ◯ |
| 10 | If Yes to Q10, when was it done? | < 24 hours ◯ |
| | | > 24 hours ◯ |
| 11 | Findings on X-ray | Normal ◯ |
| | | Abnormal ◯ |
| | Consolidation, atelectasis, pleural effusion (small, large), diaphragmatic elevation, hilar enlargement and cardiomegaly *(Please underline)* | |
| | **SECTION D: FINDINGS OF PERFUSION (*TICK √ WHERE APPLICABLE*)** | |

| | | |
|---|---|---|
| 12 | PE present | ≥1 wedge shape defect |
| 13 | PE absent | Near normal |
| | | Conture defect |
| | | Perfusion defect not wedge shape |
| 14 | Non-diagnostic | Cannot classify |

**THE UNIVERSITY OF THE WITWATERSRAND**

**FACULTY OF HEALTH SCIENCES, SCHOOL OF NUCLEAR MEDICINE**

**IMAGING OF PATIENTS SUSPECTED OF HAVING PULMONARY THROMBO-EMBOLIC DISEASE; DOES A CHEST X-RAY ASSIST IN OUR ENVIRONMENT?**

A GUIDE FOR DATA COLLECTION **(PERFUSION/ CHEST X-RAY ONLY)**

PATICIPANT CODE: B……..

| NO | VARIABLE | RESPONSE |
|---|---|---|
| | **SECTION A: PATIENTS DEMOGRAPHICS (*TICK √ WHERE APPLICABLE*)** | |
| 1 | Patient age | ……. |
| 2 | Patient sex | Male ◯ |
| | | Female ◯ |
| 3 | Patient race | White ◯ |
| | | African ◯ |
| | | Others ◯ |
| 4 | Patient status | Inpatient ◯ |
| | | Outpatient ◯ |
| | **SECTION B: BIOCHEMISTRY / TREATMENT / PATIENT PARAMETERS (*TICK √ WHERE APPLICABLE*)** | |
| 5 | D-dimer | Normal ◯ |
| | | High ◯ |
| 6 | Blood urea / creatinine | Normal ◯ |
| | | High ◯ |
| 7 | Anticoagulation therapy | Commenced ◯ |
| | | Not commenced ◯ |
| 8 | Wells' score | Low probability ◯ |
| | | Moderate probability ◯ |
| | | High probability ◯ |
| | **SECTION C: MODIFIED PIOPED II (*TICK √ WHERE APPLICABLE*)** | |
| 9 | PE present | 2 or more segments of perfusion defect ◯ |
| 10 | PE absent | Normal perfusion ◯ |
| | | Perfusion defect smaller than radiographic lesion ◯ |
| | | 1-3 small defects ◯ |
| | | Solitary chest radiograph ◯ |
| 11 | Non-diagnostic | All other findings ◯ |