RETROSPECTIVE AUDIT OF THE APPROPRIATE USE CRITERIA FOR VENTILATION/PERFUSION IMAGING IN PULMONARY EMBOLISM IN A SOUTH AFRICAN POPULATION COHORT

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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

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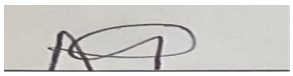
DECLARATION

I, Amanda P Sibindlana, declare that this Research Report is my own work. It is being submitted for the Degree of Master of Medicine (Nuclear Medicine) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

(Candidate's Signature)



11 September 2023

DEDICATION

I would like to thank my family for being with me throughout this journey.

ABSTRACT

Background: Venous thromboembolism (VTE) is blood clot formation comprising deep vein thrombosis (DVT) and pulmonary embolism (PE). Stasis, endothelial dysfunction and hypercoagulability place an individual at increased risk for developing DVT. VQ scans are crucial to determine the appropriate treatment in patients. The use of VQ scans is addressed in several clinical scenarios, including pregnancy, renal failure, contrast allergy, haemodynamic instability and abnormal chest X-ray findings.

Aim: This study assessed the appropriateness of VQ scan requests received by the nuclear medicine departments at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods: The appropriateness of referrals and VQ scintigraphy in patients with suspected PE at CMJAH and CHBAH nuclear medicine clinical departments was determined. A retrospective audit was done on the request forms of patients referred for VQ scintigraphy to diagnose pulmonary embolism over five years from 01 January 2015 to 31 December 2019. The clinical information in the request forms was compared to the appropriate use criteria (AUC) to determine the level of appropriateness and categorised as appropriate, maybe appropriate and rarely appropriate. Statistical software (STATA) was used for data analysis. T-tests were used for continuous variables, and Pearson's chi-squared tests were used for dichotomous data. A p-value of <0.05 was considered statistically significant.

Results: A total of 1167 records were reviewed, and fewer than 50% of the referrals were found to be appropriate overall. There were 440 records that fitted the relevant criteria, 580 were rarely appropriate, and 149 maybe appropriate. The median age of individuals referred was 45 years. Most records were for females, with 321 (73%) falling into the appropriate category. There were 72 (13%) confirmed pregnancies and 17 (24%) were appropriate for a VQ scan. The average D-dimer concentration for these patients was 2.15 mg/L. The average D-dimer concentration was the highest in patients where referrals for VQ scans were considered as maybe appropriate (2.6 mg/L; 1.18 – 6.7) compared to an average D-dimer concentration of 2.5 mg/L (1.35 – 6.78) in patients appropriately referred for VQ scans and 0.68 mg/L (0.41 – 1.51) for patients inappropriately referred for VQ scans. Some patients were still referred for VQ scans to exclude the possibility of PE.

Conclusion: The criteria used for referrals in our clinical setting were found insufficient due to the inefficient system and criteria used to refer patients in our clinical setting. This may result from a lack of required information and standardisation of the assessments with which clinicians judge the patient's risk for PE/VTE. This was the case even in a largely female cohort with many concurrent risk factors.

ACKNOWLEDGEMENTS

I want to express my heartfelt gratitude to my three supervisors, without whom I would not have managed to complete this research report.

Professor Vangu, many thanks for supervising me during this project. Your guidance, inspiration, support and encouragement throughout this research process greatly assisted me in completing this project.

Dr Malan and Dr Momodu, my other two supervisors, for always being there. Your sound advice, research knowledge and enthusiasm played an important role in my completion of this project.

CONTENTS

LIST OF ABBREVIATIONS AND SYMBOLS

ASH	American Society of Hematology
ACEP	American College of Emergency Medicine
AUC	Appropriate use criteria (AUC)
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CHBAH	Chris Hani Baragwanath Academic Hospital
CTPA	Computed tomography pulmonary angiography
CTR	Cardiothoracic ratio
CXR	Chest X-ray
DVT	Deep vein thrombosis
EANM	European Association of Nuclear Medicine
ECG	Electrocardiogram
ICAM-1	Intracellular Adhesion Molecule-1
VTE	Venous thromboembolism
MRI	Magnetic resonance imaging
NO	Nitric oxide
PE	Pulmonary embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PISAPED	Prospective Investigation Study of Acute Pulmonary Embolism
ROS	Reactive oxygen species
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single-photon emission computed tomography
STS	Society of Thoracic Surgeons
VCAM-1	Vascular Cell Adhesion Molecule-1

VQ Ventilation-perfusion

VTE Venous thromboembolism

VWF von Willebrand factor

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Venous thromboembolism (VTE), a term that describes the condition of blood clot formation, comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism is a significant contributor to the global disease burden.[1] Acute pulmonary embolism is defined as sudden occlusion of a pulmonary artery, mainly caused by a thrombus-derived embolus that usually develops in the presence of DVT.[2] VTE is currently the third most common cardiovascular disease after myocardial infarction and stroke.[1] Together, DVT and PE account for more than 250 000 hospitalisations annually in the United States.[3] In contrast, although more than 200 000 individuals suffer from DVT in South Africa, thromboembolic diseases account for 20 000 deaths per year.[4]

1.1.1 Pathophysiology

Three factors place an individual at increased risk for developing DVT. These factors, known as Virchow's triad, are stasis, endothelial dysfunction and hypercoagulability.[5]

1.1.1.1 Stasis

An alteration in blood flow from high shear to low shear increases the risk of forming a thrombus. Reduced shear (stasis) is observed in the venous circulation. It is worsened by damage to the valves, immobility, increased blood viscosity, vascular injury following trauma/surgery and certain inherited hypercoagulable states.[6] Reduced stasis leads to endothelial dysfunction by causing inflammation of the endothelium. Stasis and low levels of oxygen leads to the production of the reactive oxygen species (ROS) and has been shown to cause inflammation.[7,8]

1.1.1.2 Endothelial dysfunction

The blood clotting process is a series of chemical reactions controlled by the vascular endothelium. The vascular endothelium is a single layer of cells lining the lumen of blood vessels. These cells keep blood fluid by physically separating blood clotting factors from their activators found in the sub-endothelium. The endothelium further secretes prostacyclin, nitric oxide (NO) and CD39, which prevents the unnecessary activation of thrombocytes.[9] The endothelium also prevents the adhesion of leukocytes to its surface by not expressing the adhesion and signalling molecules required for leukocyte signalling.

A blood clot is composed of leukocytes, thrombocytes and other blood cells/molecules; the activation/adhesion of these cells need to be carefully balanced, so they remain free flowing in the absence of injury. However, in the presence of injury, the cells adhere and initiate repair of the damaged area. When cells adhere to the site of damage, it is also crucial that the process is controlled/limited to prevent occlusive thrombus formation. These processes are controlled by a healthy vascular endothelium.

During VTE, however, the vascular endothelium is dysfunctional. Endothelial dysfunction refers to the development of changes to endothelial physiology that may be harmful.[10] A dysfunctional endothelium is characterised by the loss of its anti-thrombotic, anti-coagulant, and anti-inflammatory properties. Consequently, the endothelium expresses adhesion molecules such as Intracellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1) and E-selectin[11,12] translating to the adhesion of thrombocytes and leukocytes. The endothelium further releases P-selectin and von Willebrand factor (VWF)[13], molecules important in the recruitment and activation of thrombocytes and leukocytes. Other characteristics of endothelial dysfunction include reduced vasodilator bioavailability, particularly the availability of NO while increasing endothelial-derived contraction factors - an imbalance that diminishes endothelium-dependent vasodilation.[10,14] Thus, endothelial

dysfunction enhances plaque vulnerability and thrombus formation and possibly triggers atherosclerotic plaque rupture.[10]

1.1.2 Pulmonary embolism

Pulmonary embolism (PE) is a significant, treatable illness caused by a thrombus which commonly migrates from the veins of the lower extremities to the pulmonary circulation.[15] PE is the most serious complication of DVT, accounting for approximately 200 000 deaths per year and 10% of hospital deaths in the United States.[3] By travelling into narrower vessels, PE results in the occlusion of pulmonary vessels, which triggers complex pathophysiological changes responsible for a range of clinical presentations[15], including sudden onset dyspnoea, fainting, chest pain and haemoptysis.[16] Ventilation of under-perfused lung tissue increases pulmonary dead space, resulting in dyspnoea. Occlusion of pulmonary end arteries may lead to haemorrhage, pleural effusion and atelectasis.[15] Patients may present with pleuritic chest pain with the involvement of the parietal pleura.[17] Major PE results in haemodynamic changes manifesting as increased pulmonary vascular resistance (which requires greater efforts from the right ventricle to get the blood into the pulmonary circulation and causes stress that may lead to right ventricular failure), hypotension, syncope and sudden death.[15] In pregnancy, progesterone-induced venous dilatation and other systemic changes resulting in the classical trial of venous stasis, vascular damage and hypercoagulability increase the risk of developing PE.[18] According to World Health Organisation (WHO) data, VTE is responsible for 3% of all maternal deaths worldwide, with most cases occurring in the six-week postpartum period.[18] As a significant source of mortality, the early diagnosis and treatment of PE are vital for the appropriate and prompt initiation of therapy, which has been shown to promote clot lysis and reduce the risk of mortality and long-term complications such as chronic PE and pulmonary hypertension.[15] This is why using the right diagnostic tools is pertinent.

1.1.2.1 Pulmonary embolism diagnosis

In addition to clinical evaluation, diagnostic imaging is essential in diagnosing PE. The routine use of conventional imaging methods such as chest radiography, Doppler ultrasound, electrocardiogram (ECG) and magnetic resonance imaging (MRI) is limited by sensitivity, specificity and co-existing lung pathologies.[15] Computed tomography pulmonary angiography (CTPA) has shown value in diagnosing centrally located thrombi, especially in parenchymal lung disease.[19] However, its use is limited by high radiation exposure (especially to the female breast), contrast allergy and renal dysfunction.[15]

Nuclear medicine imaging for suspected pulmonary embolism using radioactive tracers has been available since the 1960's.[20] Ventilation imaging has evolved from using Krypton-81m and Xenon-133 up to the 1980s to the current use of Technetium-99m based radio-aerosols.[21] Perfusion imaging involves using Technetium-99m macro-aggregated albumin (MAA) to assess pulmonary perfusion defects.[20] Nuclear medicine routinely employs non-invasive planar ventilation-perfusion (VQ) imaging (VQ scan) to diagnose pulmonary embolism. The addition of single-photon emission computed tomography (SPECT) has been shown to increase diagnostic accuracy by identifying segmental and sub-segmental perfusion defects.[22,23]

The reporting of VQ scans, or scintigraphy, incorporates a patient's clinical information and pre-test probability with scan findings.[24] The Canadian model developed by Wells *et al*. is the most frequently used pre-test scoring system for suspected PE.[24] Findings on scintigraphy favouring the likelihood of PE are a wedge-shaped, pleural-based perfusion defect and perfusion defects that conform to the bronchopulmonary segments.[15] Ventilation is usually preserved when the bronchopulmonary segments are affected by PE.[15] A combined ventilation and perfusion study increases the specificity for PE diagnosis by mapping the lung outline and allows recognition of alternative pathologies that may be responsible for patients' symptoms.[15]

Interpretation of VQ scans involves probability criteria, the most common of which are the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) and the Prospective Investigation Study of Acute Pulmonary Embolism (PISAPED), which are named after their derivative multi-institutional studies.[25] The PISAPED interpretative criteria rely on chest radiograph and perfusion scan only. The initial PIOPED criteria were complex, demonstrating a high percentage of non-diagnostic scans and significant variability among physicians. Consequently, modified PIOPED II interpretative criteria (Table 1) were developed. These modified criteria rely on chest radiographs combined with ventilation and perfusion scans. A set of modified PIOPED II criteria (Table 1) which rely on a chest radiograph and perfusion-only scan, was also developed.[26] The Department of Nuclear Medicine (University of the Witwatersrand) typically uses modified PIOPED II interpretative criteria in reporting VQ scans and perfusion-only modified PIOPED II when ventilation scans cannot be acquired.

Table 1.1: Ventilation, perfusion, radiographic (CXR) interpretative criteria[26]

MODIFIED PIOPED II	**PERFUSION-ONLY MODIFIED PIOPED II**
High >2 large, mismatched VQ segmental defects	**PE Present** >2 large mismatched (Q/CXR) segmental defects
Non-diagnostic All other findings	**Non-diagnostic** All other findings
Very Low • Non-segmental • Solitary matched VQ/CXR defect (< segment) in the mid or upper lung • 1-3 small segmental defects • >2 matched (VQ) defects, regionally normal CXR. • Stripe sign • Solitary large pleural effusion	**PE Absent** • Non-segmental • Solitary matched VQ/CXR defect (< segment) in the mid or upper lung • 1-3 small segmental defects • Stripe sign • Solitary large pleural effusion
Normal No perfusion defects	

Other than diagnosing PE, VQ scans are also indicated for the pre-operative quantification of lung function to predict post-surgical pulmonary reserve after resectioning a lung lobe or segment.[21]Several criteria have been developed to guide referral doctors on the appropriate use of VQ scans in patients with suspected PE.[23,27] These criteria incorporate various patient presentations and clinical scenarios, pre-test probabilities and findings on conventional imaging to guide requests for VQ scans in cases of suspected PE. This study was based on the appropriate use criteria (AUC) from the Society of Nuclear Medicine and Molecular Imaging (SNMMI) published in 2017.[23] The AUC had input from representatives of the SNMMI, the European Association of Nuclear Medicine (EANM), the American Society of Hematology (ASH), the Society of Thoracic Surgeons (STS), American College of Emergency Medicine (ACEP), chest radiologists, physicians, pulmonary critical care physicians and physician experts in thromboembolic disease, assembled as an autonomous working group.[23] The AUC used clinical scenarios for which VQ scans for diagnosing PE are described as either 'appropriate', 'maybe appropriate', or 'rarely appropriate' based on a scoring system.[23] The use of the VQ scans is addressed in several clinical scenarios, including pregnancy, renal failure, contrast allergy, haemodynamic instability and abnormal chest X-ray findings.

1.2 Research Aims and Objectives.

1.2.1 Aims

This study assessed the appropriateness of VQ scan requests received in the Nuclear Medicine Clinical Departments at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). The VQ scan requests were referenced against the SNMMI AUC[23] to determine their degree of appropriateness to ascertain the degree to which these major academic hospitals make appropriate use of VQ scintigraphy in patients suspected to have PE.

1.2.2 Objectives

1. The primary objective was to describe the appropriate use of VQ scintigraphy in patients with suspected PE at CMJAH and CHBAH.
2. The secondary objective was to determine the level of appropriateness of referrals for VQ scintigraphy in our clinical setting.

CHAPTER 2

METHODOLOGY

A retrospective audit of the request forms of patients referred for VQ scintigraphy to diagnose pulmonary embolism was done over five years from 01 January 2015 to 31 December 2019.

All requests sent to the Nuclear Medicine clinical departments at CMJAH and CHBAH for the stated period were reviewed. The clinical information in the request forms was compared to the AUC to determine the level of appropriateness and categorised into one of three groups, as indicated in the SNMMI AUC.

2.1 Sample Size and Sampling Method

In 2017 (the mid-point year for the study duration), the number of VQ scans for diagnosing pulmonary embolism in CMJAH and CHBAH was 587 and 580 (total = 1167). Considering this, the total number of studies available would be approximately 5800; However, only 20% of these studies will be used, meaning every 5th study will be selected, bringing the total sample size to approximately 1167.

2.1.1 Inclusion criteria

The study included all patients older than 18 years, referred for a VQ scan at CMJAH and CHBAH to diagnose pulmonary embolism between 01 January 2015 and 31 December 2019.

2.1.2 Exclusion criteria

Patients whose records were not available or lost were excluded.

2.2 Data Analysis and Statistics

The reference AUC for this study[23] divides the appropriateness of VQ scintigraphy for several clinical scenarios in suspected PE into three groups (Appendix 1):

- Appropriate
- Maybe appropriate
- Rarely appropriate

Each request form was assessed to determine patient symptoms, clinical history, D-dimers and results of anatomical imaging. This information was cross-checked with the reference AUC[23] to determine into which category of appropriateness the request falls. Demographic (gender, age, and race) and clinical data were also collected. Data was transferred into a data collection sheet designed for this study (Appendix 2). Variables were displayed using a Microsoft Excel spreadsheet. A coding system was used for each request form to remove patient identifiers on the data collection sheet or spreadsheet.

The prevalence of appropriateness was determined by the proportion of total VQ scan requests that fall into the 'appropriate' category. Descriptive statistics were reported using frequencies and percentages. T-tests and chi-square tests were used to compare variables such as symptoms and clinical history with the level of appropriateness.

The Student's T-test was used for continuous variables, and Pearson's chi-squared test for dichotomous data. A p-value of <0.05 was considered statistically significant. Statistical software (STATA) was used for data analysis.

2.3 Ethics

Ethics approval was sought from the University of the Witwatersrand Human Research Ethics Committee M210146. Permission was obtained from the relevant hospital authorities (CEOs of the CMJAH and CHBAH and the Head of the Department of Nuclear Medicine of CMJAH).

CHAPTER 3

RESULTS

3.1 Demographics

A total of 1167 records were reviewed. There were 440 records that fitted the appropriate criteria, 580 rarely appropriate and 149 with maybe appropriate. The median age of all referred patients was 45 years. Most of the records, 321 (73%), were for females fitting the appropriate category. There were 72(13%) confirmed pregnancies, and 17(24%) were appropriate for VQ scan. The main delivery method was a caesarean section, with 39(32%) having appropriate scores in 121 reviews.

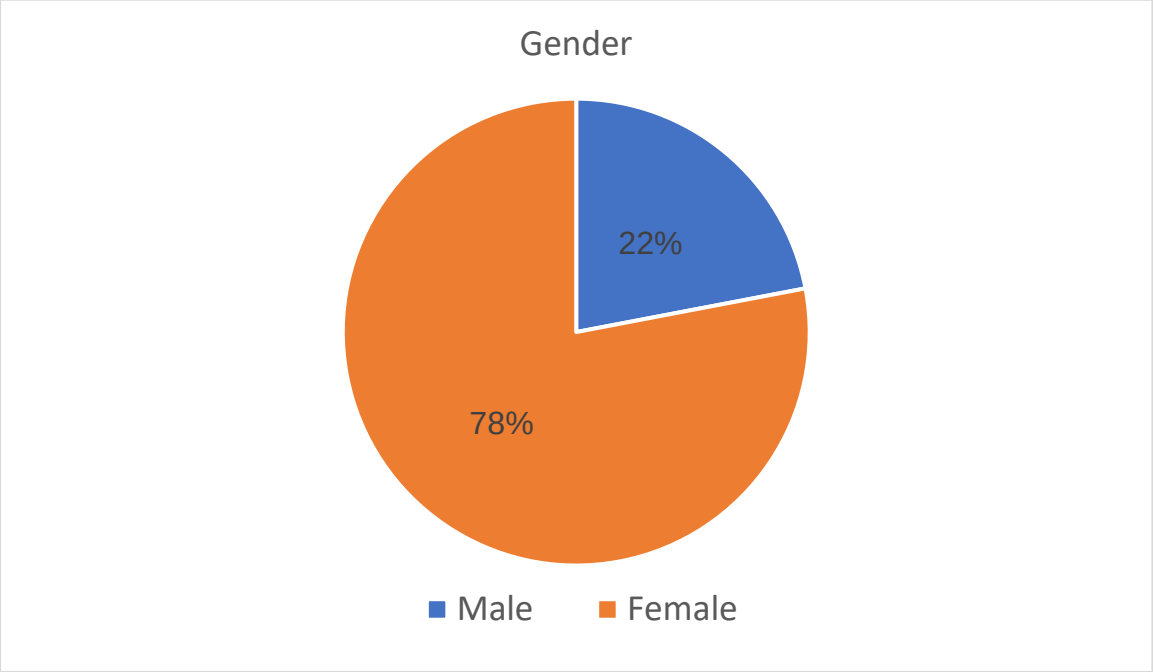

Figure 3.1 Gender distribution of referred cohort.

Table 3.1: Demographic data of VQ referral patients.

	Total	Appropriate	May be	Rarely	p - value
Department CHBAH CMJAH	 580(50) 587(50	 226(51) 214(49)	 105(71) 44(29)	 249(43) 329(57)	
Age	45(31-61)	45(31-62)	48(33-61	45(31-60)	
Gender Female Male	 909(78) 260(22	 321(73) 119(27)	 121(81) 28(19)	 467(81) 113(19)	0.009
Race African Mixed race Asian Undefined Caucasian	 970(83) 63(5) 34(3) 10(1) 91(8	 358(81) 29(7) 12(3) 3(1) 38(9)	 128(87) 9(6) 3(2) 0 8(5)	 484(83) 25(4) 19(3) 7(2) 45(8)	0.696
Pregnant No Yes	 491(87) 72(13)	 179(91) 17(9)	 63(88) 9(12)	 249(84) 46(16)	0.080
Post-partum No Yes	 48(23) 165(77)	 15(21) 57(79)	 7(23) 23(77	 26(23) 85(77)	0.914
Post-partum weeks	1	1	1	1	1
Delivery mode Caesarean MSB Natural	 121(86) 1(1) 19(13	 39(83) 1(2) 7(15)	 16(89) 0 2(11)	 66(87) 0 10(13	0.849

3.2 Clinical symptoms

Dyspnoea was observed in 475 records, and 209 (44%) were appropriate for a VQ scan. Tachycardia was noted in 401 records, and 165 (41%) were appropriate for VQ. Chest pain was stated in 230 records, and 111 (48%) were appropriate for VQ. DVT was noted in 59 records, and 52 (88%) were appropriate for VQ. Oxygen dependence was recorded in 17 records, and 6 (35%) were appropriate for VQ. Pulmonary embolism was recorded in 12 records, and 3 (25%) were appropriate for VQ.

Table 3.2 Clinical symptoms of VQ scan referral patients at CMJAH and CHBAH.

	Total	**Appropriate**	**May be**	**Rarely**	**p - value**
Dyspnoea No Yes	 7(2) 475(98)	 0 209(100)	 1(2) 58(98)	 6(3) 208(97)	0.038
Tachycardia No Yes	 12(3) 401(97)	 2(1) 165(99)	 0 51(100)	 10(5) 185(95)	0.045
Chest pain No Yes	 16(7) 230(93)	 2(2) 111(98)	 1(5) 20(95)	 13(12) 99(88)	0.006
DVT No Yes	 22(27) 59(73)	 5(9) 52(91)	 1(14) 6(86)	 16(94) 1(6)	<0.0001
Oxygen dependant No Yes	 19(53) 17(47)	 1(14) 6(86)	 2(20) 8(80)	 6(84) 3(17)	<0.001
Pulmonary embolism No Yes	 2(14) 12(86)	 0 3(100)	 0 4(100)	 2(29) 5(71)	0.692

3.3 Clinical History

Elevated D-dimers were noted in 309 records, and 225 (73%) were appropriate for VQ. Abnormal chest X-ray was recorded in 68 records, and 13 (19%) were appropriate for VQ. Previous PE was observed in 56 records, and 17 (30%) were appropriate for VQ. Recent surgery was recorded in 21 records, and 10 (48%) were appropriate for VQ. Immobility was recorded in 4 records, and 1 (25%) was appropriate for VQ. Previous DVT was recorded in 31 records, and 9 (29%) were appropriate for VQ. Cancer was recorded in 45 records, and 17 (38%) were appropriate for VQ. Haemodynamic instability was recorded in 3 records, and none were appropriate for VQ. Impaired renal function was recorded in 157 records, and 114 (73%) were appropriate for VQ. Abnormal CTPA was recorded in 13 records, and 4 (31%) were

appropriate for VQ. Of the 901 who had VQ scans, 343 (39%) were appropriate for VQ.

Table 3.3 Clinical history of VQ referral patients.

		Appropriate	**Maybe**	**Rarely**	**p- value**
Pulse rate	120(113-130)	115.5(113-120)	112(100-130)	121(120-130)	0.4032
D-dimers	2.15(117-6)	2.5(1.35-6.78)	2.6(1.18-6.7)	0.68(0.41-1.54)	<0.001
D-dimers level					<0.001
Elevated	309(96)	225(99)	56(98)	28(74)	
Normal	13(4)	2(1)	1(2)	10(26)	
Chest x-ray					<0.001
Normal	167(71)	146(92)	14(21)	7(70)	
Severely >50%)	68(29)	13(8)	52(79)	3(30)	
Previous PE					
No	19(25)	3(15)	1(11)	15(33)	0.242
Yes	56(75)	17(85)	8(89)	31(67)	
Recent surgery					0.008
No	18(46)	2(17)	0	16(64)	
Yes	21(54)	10(83)	2(100)	9(36)	
Immobility					0.01
No	18(82)	2(67)	0	16(94)	
Yes	4(18)	1(33)	2(100)	1(6)	
Previous DVT					0.003
No	20(39)	4(31)	0	16(57)	
Yes	31(61)	9(69)	10(100)	12(43)	
Cancer					1
No	1(2)	0	0	1(4)	
Yes	45(98)	17(100)	4(100)	24(96)	
Hemodynamically stable					0.600
Stable	3(50)	2(100)	0	1(50)	
Unstable	3(50)	0	2(100)	1(50)	
Renal function					0.478
Impaired	157(99)	114(99)	17(100)	26(96)	
Normal	2(1)	1(1)	0	1(4)	
CTPA					1.000
Abnormal	13(68)	4(67)	3(60)	6(75)	
Normal	6(32)	2(33)	2(40)	2(25)	
VQ scan					0.112
No	3(1)	3(1)	0	0	
Yes	901(99)	343(99)	130(100)	428(100)	

Of the 569 who had an appropriate record, 116 (20%) had renal failure, 224 (39%) had chest pain, and 229 (40%) had elevated D-dimers.

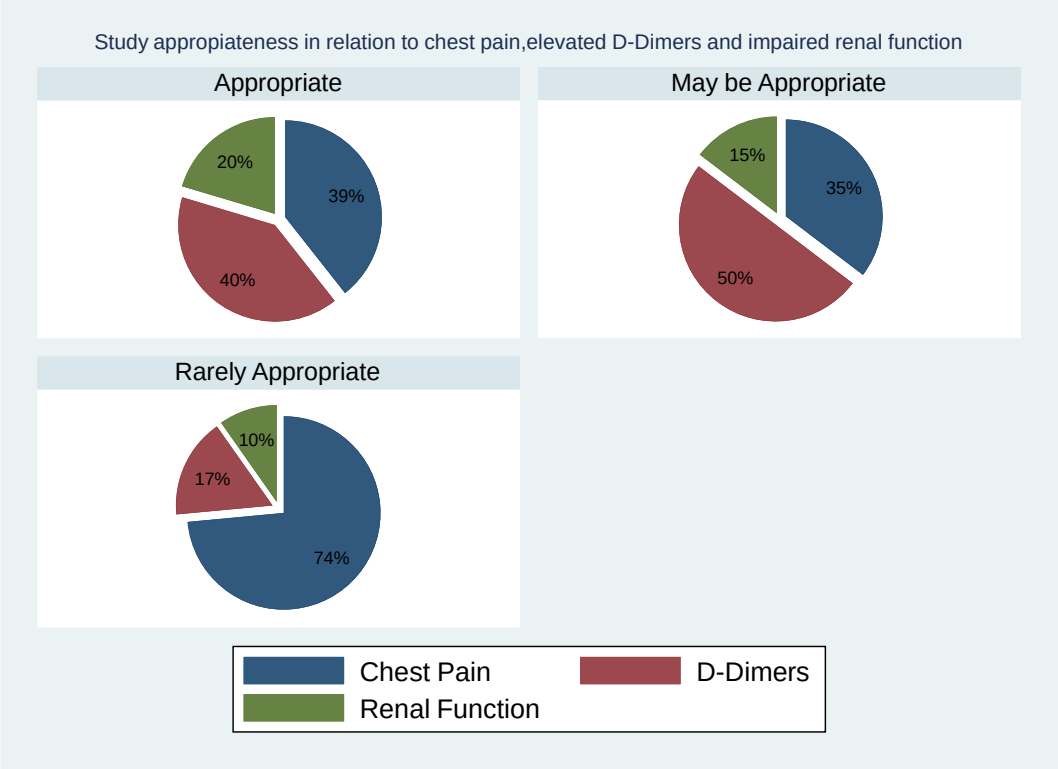

Figure 3.2: Pie chart showing the distribution of chest pain, D-dimer levels and impaired renal function amongst VQ referral patients.

The blood pressures were recorded for 10 patients. Three cases were inconclusive and were 104, >100 as we as 113>125.

Table 3.4*:* Blood pressure readings of VQ referral patients

Row Labels	Count of BP
103/64	1
107/63	1
123/66	1
128/81	1
134/98	1
140/84	1
149/95	1
99/55	1
Low BP	2
Incorrectly measured	3
Grand Total	**13**

The chest scan findings on CXR show three pleural effusions, two for bilateral pleural effusion, cardiomegaly, increased cardiothoracic ratio (CTR), upper lobe diversion, pulmonary oedema and hyperinflation.

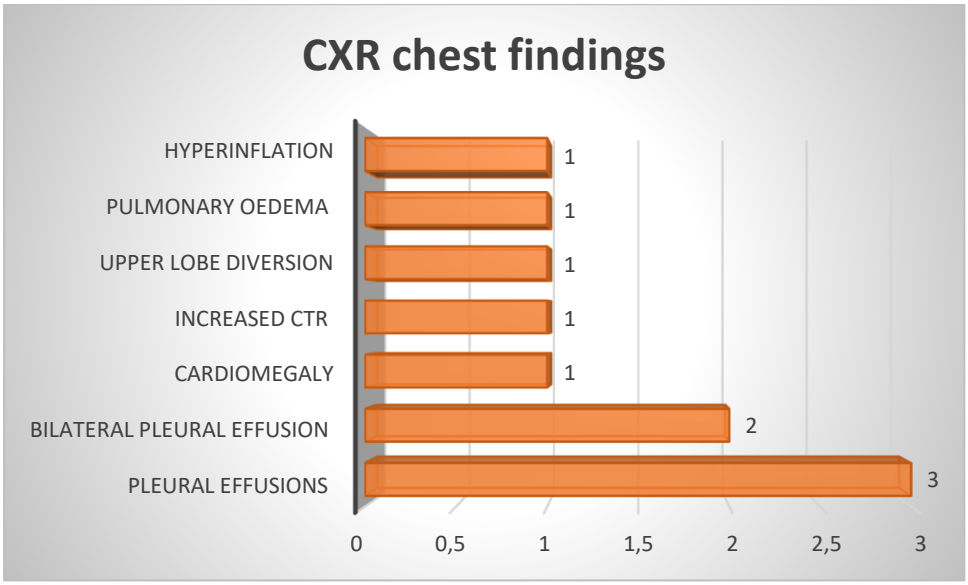

Figure 3.3: Bar graph showing chest scan findings of on CXR of VQ referral patients.

There were 30 reports stating inability to ventilate, 16 technical difficulties, and three pregnant women.

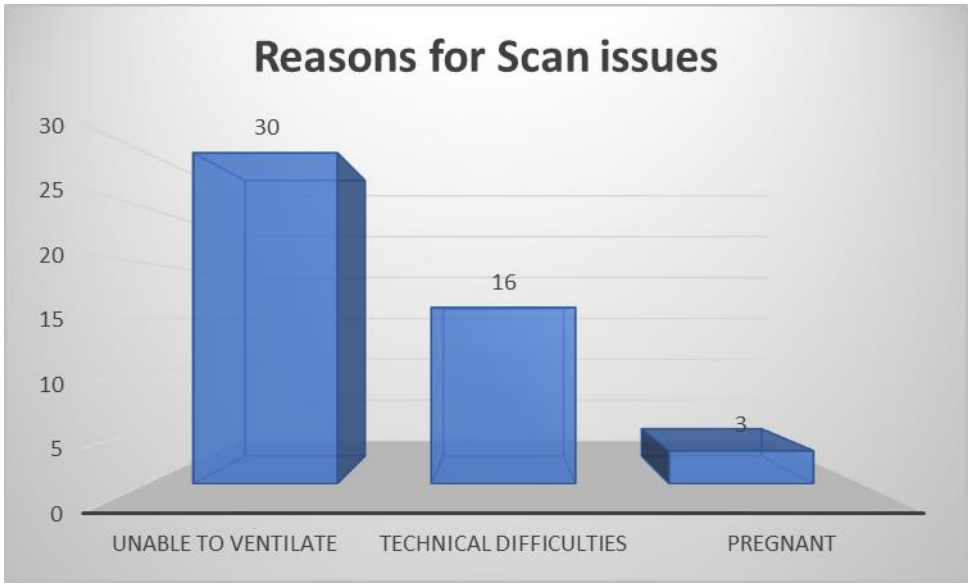

Figure 3.4: Bar graph showing reasons for scan issues encountered.

There was a low frequency of CTPA findings, as shown in Table 3.5 below.

Table 3.5: CTPA findings

Row Labels	Count of CTPA Findings
Bilateral irregular segmental arteries	1
Bilateral pulmonary embolus + pulmonary artery thrombus	1
Bilateral thrombus	1
CTEPH	1
CTPA insignificant	1
Features of peripheral chronic PTED	1
Highly suggestive of peripheral pulmonary embolic phenomena	1
Inconclusive	1
Mosaic perfusion	1
No thrombus	1
PE	2
Peripheral oligaemia and aortic aneurysm	1
Poor quality but - for PE	1
Possible filling defect, but suboptimal CT suggest VQ scan	1
Right atrial mass	1
Right pulmonary artery embolus	1
Segmental PE	1
Small PE	1
Suggested VQ scan	1
Suggestive of PE (not confirmed)	1
Suspicion of chronic pulmonary thromboembolism	1
Grand Total	**22**

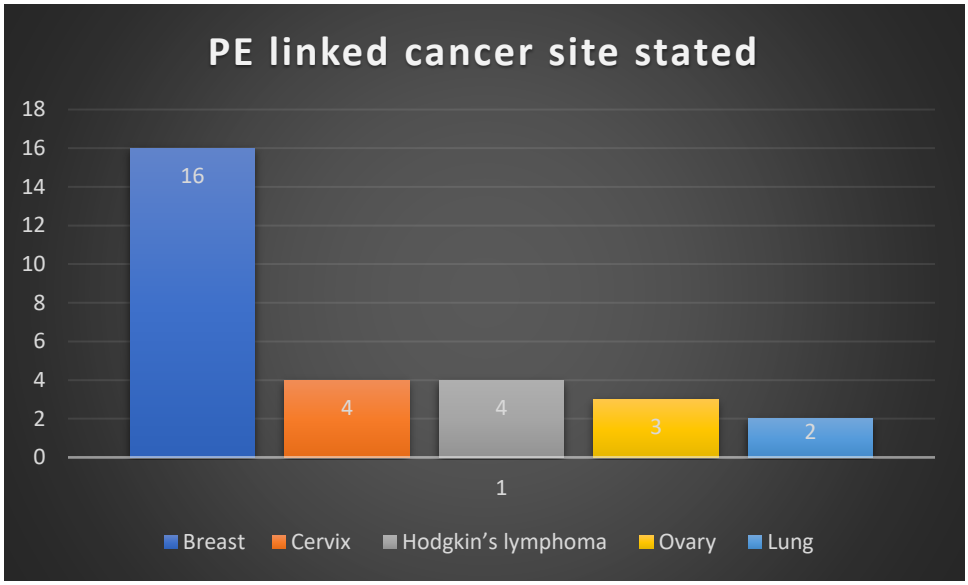

Figure 3.5: PE-linked cancer sites identified in the CMJAH and CHBAH cohorts.

The cancer site records linked to PE were sixteen breast, four cervix, four Hodgkin's lymphoma, three ovary and two lungs.

CHAPTER 4

DISCUSSION

The appropriate use of diagnostic tools is integral in hospital settings. A clinician's ability to determine the appropriate tests to run is a significant factor in the speed and efficacy of treating patients. The swift and appropriate identification and referral of patients with serious ailments such as PE (known to have high mortality and morbidity[28]) depend on the clinician's ability to refer the patient appropriately for further testing. This study assessed the AUC for VQ imaging in PE patients to ascertain whether hospital referrals were appropriate.

This study assessed a cohort of 1167 patient records across the CMJAH and CHBAH hospitals and found fewer than 50% of the referrals were appropriate. Furthermore, with a predominantly female sample population, the findings suggest a higher referral rate for female patients. This was in line with previous reports.[29] It has been reported that females over 40 years whose risk factors include age, surgery, hormone replacement and contraception treatments, having been pregnant or in a postpartum phase were at higher risk of developing PE.[29] This was the case in the current cohort, who had a mean age of 45.

Analysis showed that 59% of our female cohort was pregnant or in their first week post-partum, and only 36% were deemed appropriate. Further, it was noted that, although they had the highest appropriateness rate, those who had undergone caesarean births were still below 30%. This is lower than anticipated as pregnancy may promote a prothrombotic state which promotes PE.[30] This cohort subset has

multiple risk factors, including pregnancy, and the postpartum period is known to be higher risk than the antenatal.[29]

D-dimer is a molecule produced following the breakdown of fibrin strands by the enzymatic action of plasmin. As D-dimer can only be formed after the coagulation cascade has been activated, the presence of D-dimer molecules and the concentration thereof can be used as an indirect marker for the presence and extent of blood clot formation.[31] In the current study, D-dimer values were available for 322 (27.59%) patients referred for VQ scans. As D-dimer tests are: “not normally ordered for patients who have a high pre-test probability of PE”[32], this may explain why only 27.59% of the study cohort had recorded D-dimer concentrations. The average D-dimer concentration for these patients was 2.15 mg/L, a value considered four times higher than normal. The average D-dimer concentration was the highest in patients where VQ scan referrals were considered appropriate. These were 2.6 mg/L (1.18 – 6.7) compared to an average D-dimer concentration of 2.5 mg/L (1.35 – 6.78) in patients appropriately referred and 0.68 mg/L (0.41 – 1.51) for patients inappropriately referred for VQ scans.

A study measuring D-dimer values found that highly elevated D-dimer concentrations were associated with a higher risk for PE formation.[33] Despite the average D-dimer concentration being slightly higher than normal, the referral for VQ scans in 38 of the 322 patients where D-dimer was classified as rarely appropriate, the clinical symptoms documented for these patients indicated that a PE is unlikely. Sikora-Skrabaka *et al*. (2019)[33] showed that, in a cohort of 370 patients referred for CTPA, the gold standard for PE diagnosis, a low D-dimer concentration was associated with the absence of PE.

The documentation of the clinical history, signs and symptoms with which a patient presents are essential for determining the likelihood of PE using risk assessment models.[34] Some assessment models for assessing PE risk include the Wells and Geneva scores. The lack of documentation on the model used to score PE risk and associated scores is of great concern. Therefore, we calculated PE risk using the Wells score based on the patient history, signs and symptoms documented in the request forms.

Dyspnoea was the most common symptom patients manifested with (475 reported shortness of breath), followed by tachycardia (401) and chest pain (230). This finding agrees with a case study series conducted by Kistensamy *et al*. (2018)[35] at the Inkosi Albert Luthuli Central Hospital, where dyspnoea, tachycardia and chest pain were the most common presenting symptoms for patients admitted for PE.

Cancer increases the possible development of blood clots.[36] This results from the cancer cells' ability to activate the coagulation cascade and prothrombotic properties of proximal cells.[37] Furthermore, cancerous tissue causes venous compressions that result in abnormal or reduced blood flow or venous stasis, reduced shear stress, and hypoxia that promote thrombosis.[37] We assessed the cancer status of patients to assess the significant sites that affect PE development in patients. The associated cancer sites included breast, cervix, lymphoma, ovary, and lung, three of which are sex-related organ cancers. This is similar to Fujieda *et al*., (2021)[38], who found PE was linked to ovarian, endometrial, gallbladder and lung cancers. However, in contrast to our findings, they found a higher prevalence of ovarian than breast cancer.

Chest X-rays are performed not to diagnose PE specifically but to exclude other causes for the symptoms, which included dyspnoea, tachycardia, and chest pain in

this study.[39] Chest X-rays were available for 235 patients. Despite chest X-rays being normal for 71% of them, they were still referred for VQ scans as chest X-rays do not exclude the possibility of PE.[40] Further, chest X-rays are found to be normal in approximately 40% of patients, despite the presence of PE.[39] The fact that chest X-rays do not exclude PE, combined with the observation that: “a normal chest X-ray in patients with PE may determine clinical severity and may involve increased risk for massive PE”[40] makes referring patients for more sensitive testing important. According to the AUC, all patients with a strong likelihood of PE and displaying normal/abnormal chest X-ray findings should be referred for VQ scans.[32] Our findings showed that 10 (4.3%) patients were inappropriately referred for VQ scans. Although the chest X-ray was normal in seven patients and abnormal in three patients, the clinical symptoms/patient history available indicated that PE was unlikely, making referral rarely appropriate as per AUC criteria.

Major surgery has been linked to developing a hypercoagulable state[41]; consequently, prophylaxis in the form of low molecular weight heparin or aspirin is given to patients to prevent clots. Specifically, postoperative VTE leading to PE occurs due to inflammation at the surgery site, endothelial dysfunction and reduced mobility leading to blood stasis.[42] In the current study, 21 patients were reported as having undergone recent surgery.

DVT and PE can often be linked to trigger events such as extended immobility and major surgery and genetic or acquired risk factors.[36] For this reason, clinical presenting symptoms and medical history are integral in the referring doctor’s considerations. Due to the effects of VTE, physical presentations such as dyspnoea, tachycardia, chest pain and DVT are used as assessment criteria to inform the clinician’s decision to refer a patient for scanning. However, when conducting this audit, it has been noted that

records do not always contain responses or notations of all risk factors, as the information provided may differ from one doctor to the other. CTPA is an imaging diagnostic tool used to view pulmonary arteries to assess pulmonary emboli visually. CTPA findings were infrequent in our study. This may be due to a lack of standardised recording or missing patient information. Similarly, although important to suspicion and diagnosis of PE, blood pressure information was present in only 11 patient records (two of which were inconclusive). This is evidence of a flawed referral system at both CMJAH and CHBAH hospitals. This practice, or lack of standard recording requirements, may affect the ability to assess patients thoroughly before referral for a VQ scan and result in more patients being referred inappropriately.

CHAPTER 5

CONCLUSION

This study aimed to assess the appropriateness of VQ scan requests received in the clinical department of Nuclear Medicine at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). The VQ scan requests were referenced against the SNMMI AUC[23] to determine their level of appropriateness and assess the degree to which these major academic hospitals use appropriate VQ scintigraphy in patients suspected to have PE.

From the findings of the present study, we conclude that, although appropriate referrals are made for VQ scans for suspected PE, the rate was lower than the 'may be appropriate' and 'rarely appropriate' groups. This was the case even with a predominantly female cohort with many concurrent risk factors. This may result from a lack of required information and standardisation of the assessments with which clinicians judge the patient's risk for PE/VTE.

Limitations

This study was conducted based on patient records from the CMJAH and CHBAH hospitals serving primarily African communities. This, along with the lack of information in patient records, is a limitation of this study. In future, further analyses can include data from other hospitals to diversify the data, making it more representative of the South African population.

Recommendations

There should be in-service training on the AUC of VQ studies for physicians**.** Various departments should make it mandatory for patients to obtain a recent chest X-ray before receiving a recommendation for VQ investigations to ensure that patients are referred appropriately**.** It is essential to promote the use of pre-test probability, and these pre-test probability requirements should be posted on the walls of different departments. A checklist could be provided on request forms to help with accurate history taking and investigations before referral. Doctors should be urged to record the last menstrual cycle of their patients on request forms to identify possibly pregnant patients.

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APPENDICES

APPENDIX I: ETHICS CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs)

TO: Dr A Sibindlana
School of Clinical Medicine
Department of Radiation Sciences
Division of Nuclear Medicine
Medical School
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CC: Supervisor: Dr N Malan and Professor MDT Vangu
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and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2021/03/31

REF: R14/49

PROTOCOL NO: **M210146** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Retrospective audit of the appropriate use criteria for ventilation perfusion imaging in pulmonary embolism in a South African population cohort*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

APPENDIX II: TABLE OF PE SCENARIOS

Clinical Scenarios for PE in Adults

Scenario no.	Description	Appropriateness	Score
1	PE unlikely, D-dimer negative	Rarely appropriate	1
2	PE likely, D-dimer negative	Appropriate	8
3	PE unlikely, D-dimer positive	Appropriate	8
4	PE likely, male or nonpregnant female with normal chest radiograph	Appropriate	9
5	PE likely, male or nonpregnant female with mild abnormal chest radiograph	Appropriate	9
6	Suspected PE, male or nonpregnant female with significant abnormal chest radiograph	May be appropriate	5
7	PE likely, patient with abnormal renal function	Appropriate	9
8	PE likely, patient at risk for contrast complication	Appropriate	9
9	PE likely, patient who cannot cooperate for ventilation imaging, perfusion only	May be appropriate	5
10	PE likely, CTPA inconclusive or discordant with clinical probability	Appropriate	9
11	PE likely, hemodynamically unstable patient, portable V/Q equipment available	Appropriate	7
12	PE likely, hemodynamically unstable patient, portable V/Q equipment unavailable	Rarely appropriate	1
13	PE likely, ultrasound of lower extremity with clot	Appropriate	9
14	PE (clinically) unlikely, ultrasound of lower extremity with clot	May be appropriate	5
15	PE likely, pregnant patient with normal/mild abnormal chest radiograph, low-dose perfusion only	Appropriate	9
16	PE likely, pregnant patient with severe abnormal chest radiograph, perfusion only	Rarely appropriate	3
17	PE likely, patient ventilator-dependent	May be appropriate	5
18	Recent/prior documentation of PE with CTPA, suspected new PE	Rarely appropriate	2
19	Recent/prior documentation of PE with V/Q scan, suspected new PE	Appropriate	9
20	Recent documentation of PE by CTPA, patient now on anticoagulation; imaging to document disease status when clinically indicated	Rarely appropriate	2
21	Recent documentation of PE by V/Q scan, patient now on anticoagulation; imaging to document disease status when clinically indicated	Appropriate	9

PE likely or unlikely is determined by the referring clinician.

APPENDIX III: DATA COLLECTION SHEET

RETROSPECTIVE AUDIT OF THE APPROPRIATE USE CRITERIA FOR VENTILATION-PERFUSION IMAGING IN PULMONARY EMBOLISM IN A SOUTH AFRICAN POPULATION COHORT

Data Collection Sheet **Code:**

Department of origin:

(Circle or tick as appropriate)

Age (years):

Gender: M F

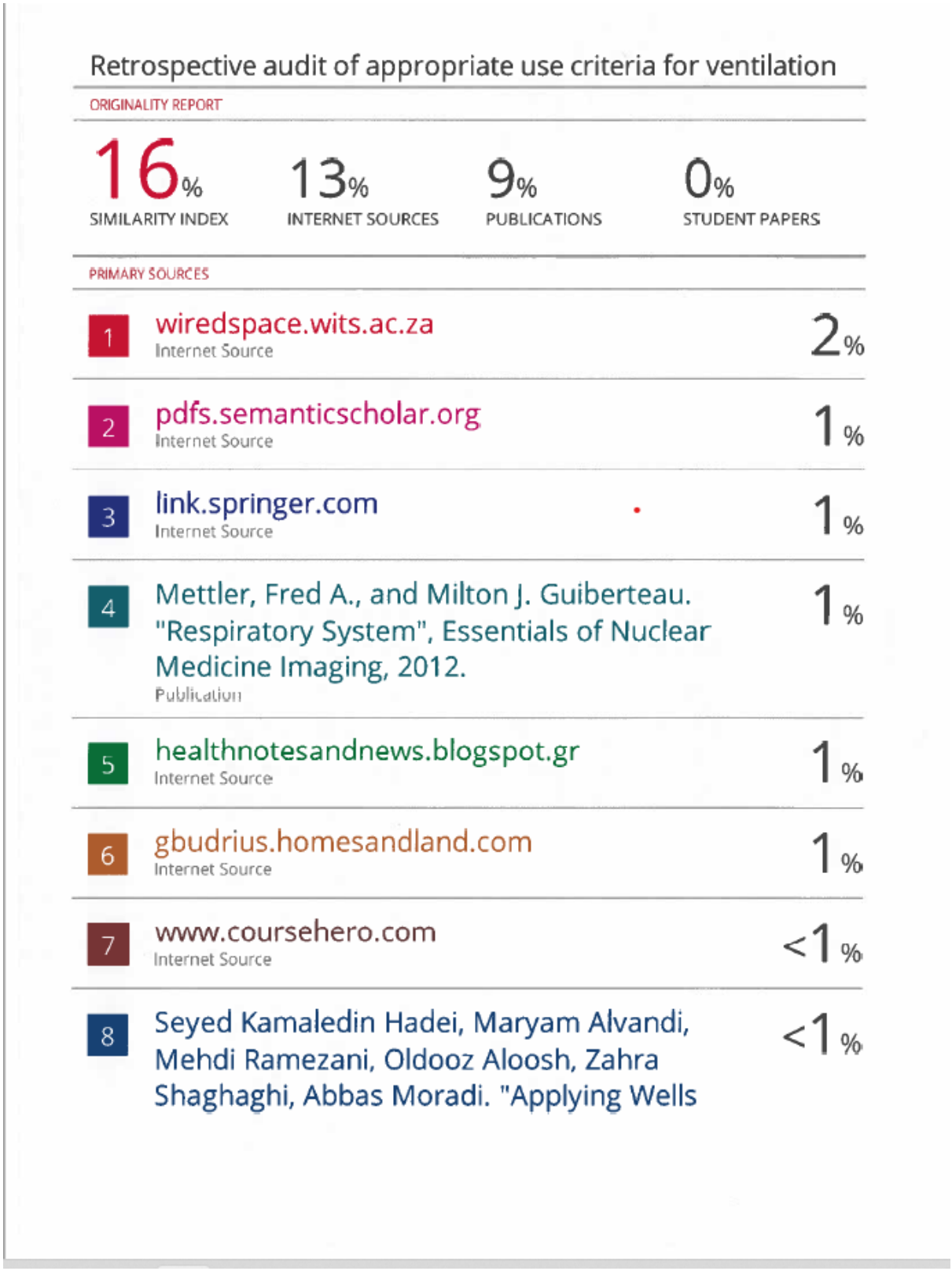
Race: B W C I Other

Pregnant: Y N (If yes, state trimester……)

Post-partum: Y N (If yes, state how many weeks……)

Delivery mode:

Clinical Symptoms Dyspnoea: Y N Tachycardia: Y N Chest pain: Y N DVT: Y N (above/below knee) Oxygen-dependent: Y N PE likely: Y N	Clinical History Previous PE: Y N Recent surgery: Y N Immobility: Y N Previous DVT: Y N (above/below knee) Cancer: If Yes, site
Blood pressure: Pulse rate:	Hemodynamically Stable Unstable
D-Dimers: Normal Elevated Level:	Renal Function: Normal Impaired Known contrast allergy: Y N
Chest x-ray: Normal Severely (>50%) abnormal Relevant findings:	CTPA: Normal Abnormal Relevant findings:
VQ scan: Y N Perfusion only scan: Y N If yes, state reason	
Study: is Appropriate May be appropriate Rarely appropriate	Other comments:



Retrospective audit of appropriate use criteria for ventilation

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