UTILIZATION OF WELLS SCORE IN CT PULMONARY ANGIOGRAPHY FOR THE DIAGNOSIS OF PULMONARY EMBOLISM IN SASMEC @IIUM

BY

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A dissertation submitted in fulfilment of the requirement for the degree of Master of Medicine (Radiology).

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ABSTRACT

Current evidence suggests computed tomography pulmonary angiography (CTPA) for diagnosis of pulmonary embolism (PE) is overutilized. This study was conducted to assess the utilisation of Wells score and diagnostic yield of CTPA in a single centre in Malaysia. In this cross-sectional study, we retrospectively analysed the CTPA dataset of patients from May 2017 to July 2021. A modified Wells score was used to determine if the imaging study was justified. Descriptive statistics, chi-square tests, and binary logistic regression were used for data analysis. A total of 361 patients underwent CTPA, among whom 107 (29.6%) patients were diagnosed with PE. There were 130 patients in the PE unlikely group who underwent imaging and 27.1% of them were positive for PE. A total of 52 patients in the low probability group underwent imaging and only 7.5% were diagnosed with PE. Among those who had positive D-dimer, PE was diagnosed in only 2.2% with a low Wells score. The Wells score was utilised in 78.5% of the cases. However, the local guideline was only followed in 32.1% of cases. The proportion of PE positive results was among the highest compared to the previous studies. Hence, CTPA was not overutilized, the resources were appropriately used, and the indication was justified for most patients. However, there was a significant deviation from the local guideline.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Master of Medicine

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DECLARATION

I hereby declare that this thesis is the result of my own investigation, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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This dissertation is dedicated to my loved ones and the people who supported me throughout my education. Thank you for making me see this adventure through to the end.

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LIST OF SYMBOLS

%	Percentage
~	Approximately
μg/l	Microgram/l
kVp	Kilovoltage peak
mAs	Milliampere-seconds

LIST OF ABBREVIATIONS

CI	Confidence interval
CIN	Contrast induced nephropathy
CT	Computed tomography
CTPA	Computed Tomography Pulmonary Angiography
DECT	Dual energy computed tomography
IV UFH	Intravenous unfractionated heparin.
LMWH	Low molecular weight heparin
MDCT	Multidetector computed tomography
OR	Odd ratio
PE	Pulmonary embolism
PERC	PE- rule-out criteria
PIOPEP	Prospective investigation of pulmonary embolism diagnosis
RIS	Radiology information system
SASMEC @ IIUM	Sultan Ahmad Shah Medical Centre @IIUM
US	United States
VTE	Venous thromboembolism
V/Q scan	Ventilation perfusion scan

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND AND JUSTIFICATION

The use of modern medical imaging has broadened the clinical indication of multidetector computed tomography, owing to its capacity to quickly yield vital diagnostic information that enables faster decision making in patients with potentially life-threatening conditions. Computed tomography pulmonary angiography (CTPA) is the gold standard in diagnosing pulmonary embolism (PE) due to its high accuracy, wide availability, and rapid turnaround time. Modern multidetector CT scanners that use high-pitch helical (Flash) mode in a second or third-generation dual-source scanner can conduct CTPA with less ionizing radiation and a lower dosage of iodinated contrast medium (Rajiah et al., 2019). According to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study, CT pulmonary angiography alone has a sensitivity of 83%, a specificity of 96%, a negative predictive value of 95% and a positive predictive value of 86% in the diagnosis of PE (Stein P.D., et al., 2006). Currently, the specificity of PE detection is further improved by merging functional and morphological data from the subtraction of CT iodine maps with CT pulmonary angiography (Grob, Smit, & Prince, 2019).

The use of CT for PE rule-out began in the early 1990s, and it had increased by 10 to 15 times in the last decade (Dhakal et al., 2019). Earlier studies had a larger positive yield for PE, ranging from 6-25%, contrasting sharply with the current rate of around 10% (Dhakal et al., 2019). Despite the lack of a clearly defined threshold, the rate of 10% is widely acknowledged as the point at which CTPA is overused (Dhakal et al., 2019). Aside from the issue of misuse, widespread use has resulted in overdiagnosis, in which CTPA is detecting PE of questionable significance (Hall et al., 2009). Another drawback is that it exposes the patient to hazardous ionizing radiation and the risk of using contrast material (Sauter et al., 2019). Excessive CT referral can also result in higher healthcare expenses and a significant increase in the radiologist's workload, with the possibility of increased weariness, a high error rate, and poor overall performance (Brady, 2017).

Because of the overuse of CTPA for PE detection, clinical decision rules were developed to evaluate patients who might benefit from the procedure. The validated clinical decision rules preferred in the stepwise diagnosis of acute PE include the Wells score, modified Wells score, Geneva score, and PE-rule-out criteria (PERC). The current expert opinion is that CTPA is overused and has a low yield. However, no study has been conducted on the east coast of Malaysia to evaluate this assertion thoroughly. Given that such data for the Malaysian population is currently sparse, this study will be beneficial in expanding the body of knowledge.

1.2 RESEARCH OBJECTIVE

The objectives of our research are as follows:

1.2.1 General Objective

To assess utilization of Wells score and diagnostic yield of CT pulmonary angiography in Sultan Ahmad Shah Medical Centre @IIUM (SASMEC @IIUM)

1.2.2 Specific Objective

i. To describe patient demographic and Wells criteria in patients who underwent CTPA with and without PE.
ii. To measure the proportion of PE positive in patients who underwent CTPA in SASMEC @IIUM.
iii. To determine the relationship between Wells score and PE positive results among patients who underwent CTPA in SASMEC @IIUM.

CHAPTER TWO

LITERATURE REVIEW

2.1 PATHOPHYSIOLOGY OF PULMONARY EMBOLISM

Venous thromboembolism (VTE) is a general term that encompasses both PE and deep vein thrombosis (DVT). PE develops when a thrombus becomes lodged in a pulmonary artery and obstructs blood flow to the lung. PE is not a disease but a complication of underlying venous thrombosis. The thrombus originated from the deep venous system of the lower extremities, pelvic, renal, upper extremity veins, and the right heart chambers. Large thrombi can lodge at the bifurcation of the main pulmonary artery or the lobar branches after traveling to the lung which leads to hemodynamic compromise.

2.2 SIGN AND SYMPTOMS OF PULMONARY EMBOLISM

Sudden onset pleuritic chest discomfort, shortness of breath, and hypoxia are the hallmark symptoms of PE. Other symptoms include syncope, haemoptysis, signs of DVT, and palpitations. Dyspnoea is caused by a ventilation-perfusion mismatch. The dyspnoea symptom may not be evident in distal PE, instead the patient may complain of chest wall pain (Kaptein et al., 2021). Haemoptysis in PE is a result of alveolar haemorrhage. Thus, haemoptysis is expected to present in PE patients with lung infarction. However, it has only been reported in 13-19% of PE patients with lung infarction and much lesser (5%) in autopsy studies (Kaptein et al., 2021). Since the extravasation of blood into the alveoli may extend to the pleura, inflammation of the (insensitive) visceral pleura irritates the parietal pleura, which leads to pleuritic chest pain and a pleural friction rub.

Most patients with PE have no obvious symptoms at the time of presentation. Rather, symptoms range from a gradual progression of dyspnoea to catastrophic hemodynamic collapse. Therefore, the physician is more likely to miss a diagnosis due to the variability of presentation. As a result, patients who are suspected of having PE must undergo diagnostic tests until the diagnosis is confirmed or ruled out, or an alternative diagnosis is confirmed.

2.3 EPIDEMIOLOGY AND INCIDENCE

The global incidence of PE is unknown due to lack of precise epidemiology data. However, it is estimated to be 60-70 per 100,000 people (Bělohlávek, Dytrych, & Linhart, 2013). The rate of VTE in the Asian population and the incidence varies by region. Based on a few studies done in Korea, Taiwan, and Hong Kong, the population-wide incidence estimation of PE ranges from 3.7 to 7 per 100 000 (Liew et al., 2017). While there are no exact statistics on the incidence of PE in the general Malaysian population, PE is the third most common cause of maternal death in Malaysia, accounting for 12-30% of annual maternal deaths between 2008- 2015 (Mohmad Sallih et al., 2019).

2.4 AGE

Age is an independent and important risk factor for VTE. In two national population-based datasets in emergency rooms in the United States, the prevalence of PE was 10 times greater in elderly patients (>65 years old) compared to younger (18-35 years old) patients. However, younger patients underwent imaging almost as frequently as older patients (Mongan, Kline, & Smith-Bindman, 2015). The symptoms of dyspnoea, syncope, and jugular distension as well as the history of previous VTE were much more frequent in elderly patients (Castelli, Bergamaschini, Sailis, Pantaleo, & Porro, 2009). The in-hospital mortality rate was 10-fold in the elderly in comparison with younger patients (Castelli et al., 2009).

2.5 GENDER

There are few studies highlighting sex differences in PE. Women are twice as likely as males to undergo imaging (1.5-3.2% of men and 2.8-4.5% of women) across all age groups (Adam, Key, & Greenberg, 2009). However, the proportion of positive imaging is lower than men in the same age group, except for the elderly patients (>65 years old). But the overall mortality rate is higher in women (Tanabe et al., 2018).

Women are predisposed to VTE due to a sex-related risk factor. The thromboembolism risk is five times higher in pregnant women (James A. H., 2009). The higher incidence of VTE during pregnancy and puerperium may be due to venous stasis, endothelial injury, and a hypercoagulable state (Ministry of health (MOH) clinical practise guideline (CPG)., 2013). A meta-analysis and systematic review revealed the prevalence of PE among pregnant women ranged from 1-7%. There were no established clinical decision rules for PE in pregnant women, leaving physicians to make their own decisions (James, 2009).

VTE risk is doubled among hormonal contraceptive users (Plu-Bureau, Maitrot-Mantelet, Hugon-Rodin, & Canonico, 2013). The risk of VTE is greatest during the first few months after initiating hormonal contraceptives. The risk returns to the nonusers' levels within weeks of discontinuation (MOH CPG., 2013). Both the oestrogen and progestogen contents of combined oral contraceptives have been implicated in the observed differences in venous thrombotic risk between products. Even if these risks are real, the absolute risk difference between products is small, as the prevalence of venous thromboembolism in young women is essentially low (James, 2009).

2.6 CANCER

A hypercoagulable state is present in nearly all patients with active malignancy due to activation of the coagulation cascade (MOH CPG, 2013). One in every four symptomatic VTE cases is due to underlying malignancy. Furthermore, cancer-associated VTE has a high 28-day case fatality rate of 25% (Goldhaber, 2012). VTE is also an independent risk factor for poor prognosis in cancer patients. Patients diagnosed with cancer concurrently with acute VTE have a higher risk of distant metastases and a lower chance of survival. It is believed that the activated coagulation cascade associated with VTE promotes angiogenesis and metastases. There is now evidence that LMWH treatment may delay metastases and improve survival in various tumour types (Kakkar et al., 2004).

VTE has a different natural history in cancer patients than in non-cancer patients. It is typically associated with a larger and more significant thrombus, increased clinical deterioration despite anticoagulation therapy, and a higher rate of recurrence (MOH CPG., 2013). VTE in cancer patients should also be viewed as a recurring complication with prognostic implications; as the factors that predispose a cancer patient to VTE typically persist until the patient achieves remission (Heit et al., 2002).

2.7 VENOUS THROMBOEMBOLISM (VTE) RECURRENCE

Venous thromboembolism recurs frequently, particularly during the first six to twelve months, and persists for at least ten years after the initial VTE. Increasing age and body mass index, a neurologic disease with paresis, malignant neoplasm, and neurosurgery are all independent predictors of the first overall VTE recurrence (Heit et al., 2002).

2.8 PULMONARY EMBOLISM DIAGNOSIS

2.8.1 Chest Radiograph

Hampton was the first person to describe PE on a chest radiograph (Kaptein et al., 2021). Hampton's hump is a wedge-shaped, pleura-based triangular opacity with an apex pointing toward the hilum. After Hampton's hump, many other signs have been described such as the Westermark sign (lung oligemia), knuckle sign (abrupt tapering or cut-off of a pulmonary artery secondary to embolus), cardiomegaly, and pulmonary oedema. However, these findings are rarely seen.

The chest radiograph in a patient suspected of PE is rarely normal. In practice, the role of the chest radiograph is to exclude other differential diagnoses which can mimic PE symptoms and to aid in the interpretation of the ventilation-perfusion scan. The PIOPED study was conducted to investigate the sensitivity, specificity, as well as positive and negative predictive values of chest radiographic findings in patients suspected of having an acute PE. The study reported only 12% of the chest radiographs were normal among patients with PE (Worsley et al., 1993). The most common chest radiograph finding was atelectasis and parenchymal areas of increased opacity. The study also found that radiographic signs of PE were a poor predictor of PE. The sensitivity of the chest radiograph was only 24% and the specificity was 82% (with pulmonary angiography as diagnostic reference). Therefore, the chest radiograph cannot be used to exclude PE.

2.8.2 Ventilation-Perfusion Scan (V/Q Scan)

Since the 1960s, the ventilation-perfusion (V/Q) lung scan has been utilized to diagnose PE. Following the release of the PIOPED study in 1990 and the introduction of CTPA in the mid-1990s, it lost its credibility (PIOPED investigators, 1990). Over the last few decades, considerable advancements in both methodology and image interpretation have contributed to re-establishment of the credibility of V/Q scan. V/Q scan diagnosed fewer subsegmental PEs compared with CTPA. These small PEs mostly do not require medical intervention. The false-negative rates for both procedures are approximately 1% and not substantially different from one another.

The PIOPED II trial replaced the traditional interpretations with a simpler and more precise trinary system (Gottschalk, Stein, Sostman, Matta, & Beemath, 2007). The V/Q result is categorized into high-, intermediate-, and low-probability criteria for V/Q based on specific criteria. This has rendered V/Q scintigraphy interpretations significantly easier to understand by the referring physician. The very low-probability criterion is the presence of three small (< 25% of a segment) segmental perfusion defects with normal chest radiographic findings. A very low-probability V/Q scan in patients, whose Wells score indicated a low pre-test probability of PE can reliably exclude PE (Gottschalk et al., 2007). In practice, the role of V/Q scan is to diagnose PE when CT scan is unavailable or if the patient has a contraindication to CT scan or iodinated contrast media. However, this investigation is only available in a few hospitals in Malaysia, thus is considered as not readily available.

2.8.3 Computed Tomography (CT)

Sinner et al., were the first to advocate using CT to detect pulmonary infarction. Since then, CT technology has advanced from a single-slice acquisition with no contrast enhancement to contrast-enhanced Multidetector Computed Tomography (MDCT) (Sinner, 1978). CTPA has become the gold standard for PE detection replacing the V/Q scan, and its clinical validity in diagnosing PE has been extensively established (Sinner, 1978; Yazdani et al., 2015). CT scans are readily available, and they can provide valuable information regarding alternate diagnoses (Ozakin, Kaya, Acar, & Cevik, 2014). A meta-analysis was done to assess the safety of withholding anticoagulation in patients with suspected PE. The negative results on CTPA found a 3-month VTE event rate after a negative CTPA of 1.4% (95% CI, 1.1%-1.8%) and a 3-month fatal PE rate of 0.51% (95% CI, 0.33%-0.76%) (Moores, Jackson, Shorr, & Jackson, 2004). The study concluded that it was safe to withhold anti-coagulation in patients with negative PE.

Factors that lead to misdiagnosis of PE are divided into patient related, technical, anatomy, or pathology. A false negative CTPA result occurs in 1% or less among patients with low to moderate pretest probability. However, a recent meta-analysis showed the proportion might be higher among patients with high pretest probability and in studies with a high prevalence of PE (Moores et al., 2004). The proportions of VTE in these patients are 2.8% and 8.1% respectively. The CTPA sensitivity depends on the location of the thrombus and the numbers of the CT detector rows. The dual energy CT (DECT) that exploits differences in attenuation spectra using two different energy levels for material detection has a sensitivity of > 90% for segmental and lobar acute PE (Monti et al., 2021).

DECT which is already available in some hospitals in Malaysia can be used to form a conventional CTPA plus a static iodine map. The latter represents a surrogate measure of microvascular circulation and perfusion, which leads to better detection of peripheral occlusions. The segmental distribution of the perfusion lesions may aid in the differentiation of infarction from other entities such as pneumonia or tumours (Bray, Mortensen, & Gopalan, 2014). Iodine maps can also be constructed without dedicated hardware, by subtraction of a low-dose pre-contrast scan from the contrast-enhanced scan (subtraction CT). Subtraction CT has a higher specificity (100%) in PE detection as compared to CTPA alone (94 %) and DECT (95 %) (Grob et al., 2019). Reading time is also not increased when iodine maps are added to CTPA.

PE can be acute or chronic. It is seen as a filling defect in the pulmonary vessel. A completely occlusive acute PE may cause the affected artery to be enlarged. If the acute PE is nonocclusive, the thrombus is often centrally located, but it can form acute angles with the vessel wall when eccentrically located. In complete occlusive chronic PE, the vessels are smaller than the adjacent patent vessels. There is also evidence of recanalization, webs or flaps, and partial filling defects that form obtuse angles with the vessel wall (Wittram et al., 2004). The indirect signs of PE are parenchymal scars, a mosaic perfusion pattern, focal ground-glass opacities, and bronchial anomalies (Castañer et al., 2009). These signs are non-specific.

The CTPA examination has a relatively high radiation dose. CTPA image acquisition is equivalent to 800-1400 x-ray exposure (Lu et al., 2014). CTPA performed during the first trimester of pregnancy, increasing milliampere-seconds (mAs), kilovoltage peak (kVp), scan length, patient size, use of mAs modulation, and decreasing pitch are all factors that contribute to a higher effective radiation dose (Mayo & Thakur, 2013). Fortunately, advances in CT technology have allowed for significant reductions in radiation dose by tube current modulation, kVp modulation, scanning length modification, dynamic z-axis collimation, iterative reconstruction, and DECT (Mayo & Thakur, 2013).

Patients who underwent CTPA are at risk for contrast induced nephropathy (CIN). The proportion of CIN is much lower than previously believed (Stacul et al., 2011). However, patients with substantially impaired renal function are at a higher risk. The eGFR of 45 ml/min/1.73 m^2 is the CIN risk threshold for intravenous contrast media. The CIN risk can be further reduced by hydration with either saline or sodium bicarbonate (Stacul et al., 2011). Lowering the contrast media dose will reduce the risk of CIN, but the image quality needs to be maintained (Gurm et al., 2011). The dual-energy monoenergetic reconstruction technique and the high-pitch with low-kVp technique are the two main approaches used in recent studies to reduce the contrast media dose in CTPA ((Lu et al., 2014). Dual-energy techniques rely on sophisticated image reconstruction from dual-energy data to achieve their results. High-pitch techniques rely on the exact timing of a fast scan during contrast media transit, while DECT allows a sufficiently high time-current product (mAs) by using both X-ray tubes to produce low-kVp photon beams.

A problem that persists despite the advancement of multidetector scanner technology is poor image quality, which results in decreasing CTPA accuracy. Indeterminate study ranges from 0.5-10.8% (Yeo, Zhou, & Lim, 2017). Suboptimal timing of contrast bolus, hyperdynamic state due to pregnancy, transient interruption of contrast, excessive noise due to patient body habitus, and motion artifacts are among the causes of indeterminate studies (Yeo et al, 2017). Two major causes of indeterminate study are motion artifacts and poor contrast enhancement. If the quality of the study is poor and the study is rendered indeterminate, repeated imaging is necessary and potentially compromising the patients' clinical outcome.

2.8.4 Magnetic Resonance Pulmonary Angiography (MRPA)

MRPA is not readily available in Malaysia. Technically, it is difficult to obtain images for PE using MRI. Its role is reserved to the selected patient whom the standard test is contraindicated. Of note, it should only be performed in centres that routinely performed it well. According to PIOPED III study, the proportion of technically inadequate images ranged from 11-52% at various centre (Stein et al., 2009). Technically an adequate MRPA study has a sensitivity of 78% and specificity of 99%. A combination of MRPA and venography raised the sensitivity to 92% but lowered the specificity to 96 % (Stein et al., 2009).

2.9 CTPA TREND AND APPROPRIATE YIELD

Concern for over testing for PE has garnered considerable attention over the last few decades. Nonetheless, the public health problems persist. The basis for this argument centres on the analysis of a large dataset. Prior studies have a higher positive yield of CTPA ranging from 6-25%, but the current rate is lower (Dhakal et al., 2019). Nowadays, the yield of less than 10% is regarded as the point at which CTPA is overused (Chen et al., 2019). Across the United States (US), 2.5% of 120 million patients treated in the emergency department underwent CTPA for suspected PE from 2005 until 2010, yet the rate of PE diagnosis in the same sample is only 3% (Venkatesh et al., 2018). Ordering of CTPA increased by 450% from 2004 until 2016, with average annual growth of 16.3% per year (Wang et al., 2020). CTPA use was reported to experience rapid growth from 2004-2006 (annual growth of 19.8% for those age 18-64 years old and 18.3% for those that age >65 years old) and slowly yet persistent growth from 2006-2010 (annual growth of 4.3% for those age 18-64 years old and 3.0% for those that age >65 years old) (Wang et al., 2020). Although the exact