Original Research Article

The Use of CTPA In Diagnosing Pulmonary Embolism During Pregnancy and Puerperium Period: A 5 year- Retrospective Study At A Regional Referral Hospital in Malaysia

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ABSTRACT

Introduction: The cumulative incidence of pulmonary embolism (PE) in South Asia is 1.03 per 10 000 pregnancies with maternal mortality rate of 11.1%. Given the morbidity and mortality of undiagnosed PE in pregnancy, the threshold to perform computed tomography pulmonary angiography (CTPA) is low due to the fear of missing the diagnosis of pulmonary embolism (PE). Often the pre-test clinical scores are bypassed especially the modified Well score, which is widely used in the general population yet not validated in pregnant women. The objectives of our studies are:
1. To assess CTPA ordering trend and its positive rate
2. To evaluate the diagnostic accuracy of modified Wells score (MWS) in predicting PE in pregnancy
3. To identify the rate of contrast-associated acute kidney injury (CA-AKI) ~~contrast-induced nephropathy (CIN)~~ post CTPA

Study design: This is a retrospective study which included all pregnant and postpartum patients who underwent CTPA for suspected PE in Hospital Raja Permaisuri Bainun, Malaysia from Jan 2018 to December 2022. A total of 185 CTPA results were retrieved and MWS were calculated retrospectively: ≤ 4 (unlikely PE) or >4 (likely PE).

Results: The positive rate of CTPA was 20/185 (10.5%). From 185 patients, the sensitivity, specificity, positive predicate value (PPV) and negative predictive value (NPV) of MWS were 90%, 14.5%, 11.3%, and 92.3% respectively, in predicting PE. The receiver operating characteristic (ROC) curve analysis showed a non-discriminating value (0.5). 7.1% of patients had CIN post-CTPA.

Conclusion: The trend of using CTPA in diagnosing PE in pregnant women had been steady despite our finding of its low diagnostic yield. Although Modified Wells score is widely used in the general population, its implications for pregnant patients are still a matter of debate.

***Keywords**: CTPA, modified Wells score, pulmonary embolism, venous thromboembolism*

1. INTRODUCTION

Venous thromboembolism is one of the leading causes of death in pregnant women. The incidence of VTE is about 1-2 per 1000, and the incidence of pulmonary embolism is almost 1 in 10,000 [1,2] A recent study[3] showed the cumulative incidence of pulmonary embolism (PE) in South Asia is 1.03 per 10,000 pregnancies with maternal mortality rate of 11.1%. With low prevalence but fatal consequences for mother and fetus, there is a low thresold to suspect pulmonary embolism due to the fear of missing a PE. In addition to the diagnostic challenges, the symptoms of pulmonary embolism often overlap with symptoms of physiological changes occurring during pregnancy, such as shortness of breath or tachycardia. Thus, CTPA has become the most widely used and reference standard of diagnostic imaging technique for patients suspected of PE. It is easily accessible in our setting, even bypassing the initial clinical probability assessment[36-38].

A study from a single tertiary center in Switzerland [4] showed an annual 4-fold increase in CTPA examinations in 17 years. A similar result from another center in Africa [5] showed an increase of 25% per year over the past 10 years. In a paper published in 2008, the PE positive rate for CTPA was only 10%, and they commented on the overuse of CTPA as a screening rather than a diagnostic examination[6]. Interestingly, the PE diagnostic yield from CTPA performed differs geographically[7]. The yield of positive CTPA in Europe is about 20–31%, while in the US it is only about 10%[8,9,10]. In Malaysia, we are using minimum of positive rate of 15.4% as recommended by the Royal College of Radiologists, while other studies in the general Malaysian population quoted about 25–33% of a positive rate[11].

In view of the concern about the low yield of PE-positive CTPA, C. Rotzinger [4] also suggested the need for new diagnostic strategies to safely exclude PE with fewer radiological examinations. With the introduction of pre-test clinical score in one of the large interventional studies[12], the yield of CTPA to diagnose PE has shown an increase from 9.2% to 12.6%. Recently, Medson et al. [13] showed the CTPA PE yield decreased by about 8–21% when the pre-test clinical score was bypassed. In a meta-analysis[14] showing similar accuracy using different pre-test clinical scores in diagnosing PE. More specifically, Wang et al[15] proved that with Wells criteria, there is a modest increase in CTPA yield in diagnosing PE.

Multiple algorithms have been investigated to identify high-risk patient groups; however, none of those are validated in obstetrics patients. More recently, pregnancy-adapted Geneva score [16] and YEARS [17] algorithm have been investigated in pregnant women. Without the need for imaging, those algorithms are shown to be able to safely exclude a small set of patients from pulmonary embolism in conjunction with D-dimer level. However, in present guidelines as well as in our setting, D-dimer is rarely ordered to exclude pulmonary embolism in view of the normally raised level in pregnancy, especially in maternal conditions such as preeclampsia, which causes more false ~~falser~~ positive results[18,19].

A commonly used pre-test clinical score is Modified Well's [20] score to risk stratify high-risk patients during pregnancy and the puerperium period. There are several studies looking into the diagnostic accuracy of MWS. Back in 2011, a study from Hospital Dublin single tertiary

referral hospital where a total of 125 women was investigated. The significant result for patients with MWS scores of 6 has 100% sensitivity and 90% specificity, with a 36% positive predictive value for PE on CTPA[21]. This study also showed that there was no patient with low MWS who had PE (NPV of 100%). It was the first application of MWS to pregnancy, and the article emphasized that low MWS scores could avoid unnecessary investigations by at least one third. Similar studies [22,23] also suggested a sensitivity of 100% and a specificity of 90% with a high MWS. However, there were a few subsequent studies that concluded CTPA was overused in patients with low and intermediate MWS. For example, Hanieh Raji *et al*. [24] found that from 120 patients, the positive CT angiography test in patients with low, intermediate, and high clinical probability was 18, 44, and 82%. Crichlow *et.al*. [25] studied 152 patients with suspected PE in the Hospital of the University of Pennsylvania and concluded that 13.8% of the CTPA procedures could have been avoided by proper use of Wells/D-dimer. In another study with 575 sample sizes, it was also shown that up to 25% of CTPA scans were unnecessary in those patients with a low or intermediate probability of PE[6].

Overuse of CTPA certainly imposes a financial burden on the hospital. Furthermore, there is a risk of administrating iodinated contrast material in pregnant women, causing contrast-induced nephropathy. A study by Clare O Connor *et al* [7] showed that 14% of the patients who underwent CTPA sustained AKI after CTPA. There is also small excess risk of breast malignancy in pregnant patient in relative to baseline cancer risk. Thus, there is a need for the proper use of pretest clinical score to reduce the use of CTPA in our pregnant population.

In this study, we are determining the imaging rate of CTPA over the past 5 years and its diagnostic yield. Subsequently, we retrospectively assessed the pre-test clinical score based on modified Wells score (MWS) and evaluated the diagnostic accuracy of MWS in predicting PE. The last part of the research ~~will be looking~~ investigated the rate of contrast-induced nephropathy in these patients after CTPA.

2. METHODOLOGY

This research has received ethical approval from the National Medical Research Registry of Malaysia (NMRR- ID-23-00208-Q6M). Informed consent was waived owing to the cross-sectional nature of this study.

2.1 STUDY SETTING

Hospital Raja Permaisuri Bainun is a tertiary hospital for the Perak state of Malaysia and provides care for about 670,000 people in Perak. The Obstetrics and Gynecology Department has over 3,000 deliveries per year. There are also a variety of services offered by the radiology department, including CT scans, and MRIs

2.2 STUDY POPULATION

This is a cross-sectional analytical study of all pregnant and postpartum patients who underwent diagnostic testing with CTPA for suspected PE from January 1st, 2018, to December 31st, 2022. This study was approved by the Medical Research and Ethics Committee (MREC) of Ministry of Health of Malaysia (MOH).

For a total of 199 studies, 14 CTPAs were excluded in view of a non-diagnostic result or a severely degraded image after being carefully reviewed by the radiologist. All other 185 patients who underwent CTPA in the study timeframe were included. Exclusion criteria of this study were all pregnant or postpartum patient with low suspicion of pulmonary embolism not requiring further definitive imaging. Also, patients with incomplete medical record were excluded from the studies.

2.3 STUDY DESIGN/DATA COLLECTION

All patient were identified via electronic medical record. The number of scans ordered each year were documented. In this retrospective study, all pregnant or postpartum patients with suspected PE who had a diagnostic imaging (CTPA) will be retrospectively assessed using MWS and corresponded to the CTPA result.

A data collection form used to collect data from patients' electronic record. The collected data included patient's age and trimester, clinical signs and symptoms of DVT (=3 points), an alternative diagnosis is less likely than PE (=3 points), heart rate more than 100(=1.5 points), immobilization for ≥3 days or surgery within 30 days (=1.5 points), previous diagnosed PE or DVT (=1.5 points), hemoptysis(=1 points), malignancy (on treatment/treatment in last 6 months or palliative) (=1 point), COVID status with CTPA result.

Table 1: Modified Wells Score

CRITERIA	**POINTS**
Clinical signs and symptoms of DVT	3 points
An alternative diagnosis is less likely than PE	3 points
Heart rate more than 100	1.5 points
Immobilization for ≥3 days or surgery within 30 days	1.5 points
Previous diagnosed PE or DVT	1.5 points
Hemoptysis	1 point
Malignancy	1 point
MWS ≤ 4 -> PE unlikely MWS >4 -> PE likely	

The modified well score (Table 1) was then calculated from a manual review of patients' electronic records for each component of the scoring system by a single observer blinded to the final diagnosis. The patients were stratified into 2 groups: PE unlikely with a score ≤ 4 and PE likely with scores > 4. The two categories of patients were compared with the CTPA outcome.

CTPA results were retrieved from Radiology Information System and classified into positive (presence of PE) or negative (absence of PE). Those indeterminate / non-diagnostic CTPA were further reviewed by experienced radiologist before excluded or included in the study.

Patients' creatinine values were identified (baseline and within 72 hours after CTPA). A 25% increase in serum creatinine from baseline within 48-72 hours of contrast administration is defined as contrast- induced nephropathy.

2.4 IMAGING TECHNIQUES

CTPA was acquired with 64- and 128- MDCT helical scanners (Canon and GE Healthcare). Two acquisition methods were used: bolus-tracking and timing bolus. With bolus tracking a region of interest (ROI) is placed over the main pulmonary trunk in the axial image and a few dynamic images are obtained in the same position after the injection of contrast material. When a pre-determined threshold is met (e.g., 100 HU), scanning is initiated. In the timing bolus method, a ROI is placed within the pulmonary trunk after a 20-mL timing test contrast bolus is given. 100 mL of nonionic low-osmolar contrast medium was administered via IV (iopromide, iohexol, or iopamidol). Caudocranial 1-mm helical images were acquired from the thoracic inept to the adrenal glands at 100–120 kV with automodulated mAs. Multiplaner reconstruction were performed. Malaysia Ministry of Health (MoH) recognized radiologists who interpreted the CTPA images. All studies were interpreted on a PACS workstation. The scans were classified as positive (presence of PE) or negative (absence of PE). Less than 15 of the scans were excluded due to indeterminate or non-diagnostic CTPA images within this cohort after being reviewed again by another experienced radiologist during our study.

2.5 DATA ANALYSIS

The number of CTPA orders for the past 5 years was recorded and compared as a number and frequency (in%). The CTPA diagnostic yield was the percentage of CTPA tests that were positive for PE.

Using CTPA as the reference diagnostic test, the diagnostic accuracy of MWS will be determined using sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivity was defined by the proportion of patients with CTPA-confirmed PE who had a PE-likely probability. Specificity was the proportion of patients with negative CTPA who had a PE-unlikely probability. The positive predictive value was the proportion of patients with a PE likely score who had CTPA-confirmed PE. The negative predictive value was the proportion of patients with PE-unlikely probability who had a negative CTPA.

The accuracy was determined using receiver operating characteristic (ROC) curve analysis (SPSS software, version 23.0).

3. RESULTS

A total of 199 CTPAs performed and 14 were excluded due to non-diagnostic images. The number of CTPA ordered increased about 39-46% form the year of 2018 and steadily ranging about 39-41 scans were ordered from 2020 to 2022. The positive rate of CTPA was 19/185 (10.3%). (Figure 1)

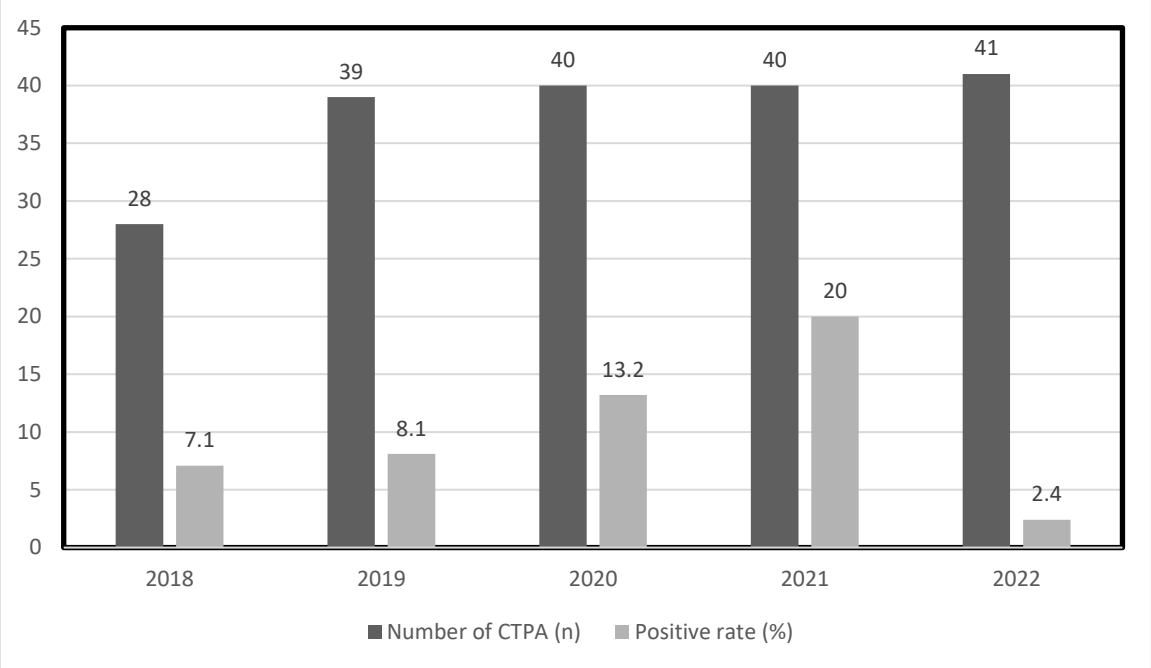

Figure 1: Number of CTPA over the year of 2018-2022 and their positive rate

Among 185 patients, 159 (82%) were dichotomized into high probability group and 26 patients (17%) were in low probability category. The percentage of patients diagnosed with PE in these 2 groups were 7.6% and 11.3% respectively (Table 2). The positive rate of CTPA is linearly proportional to Well score.

Table 2: Classification of patients and the prevalence of PE in the two probability groups according to the Modified Wells Scores.

	Modified wells score		**Total**
	Low	High	
All patients, n (%)	26 (17)	159 (82)	185 (100)
Patients with PE, n (%)	2 (7.6)	18 (11.3)	20 (100)

Table 3 Diagnostic accuracy of MWS

Diagnostic accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Modified Wells score	90%	14.5%	11.3%	92.3%

The sensitivity, specificity, positive predicate value (PPV) and negative predictive value (NPV) of MWS were 90%,14.5%, 11.3% and 92.3% respectively in predicting PE. The receiver operating characteristic (ROC) curve analysis showed non-discriminating value (0.5) (figure 2)

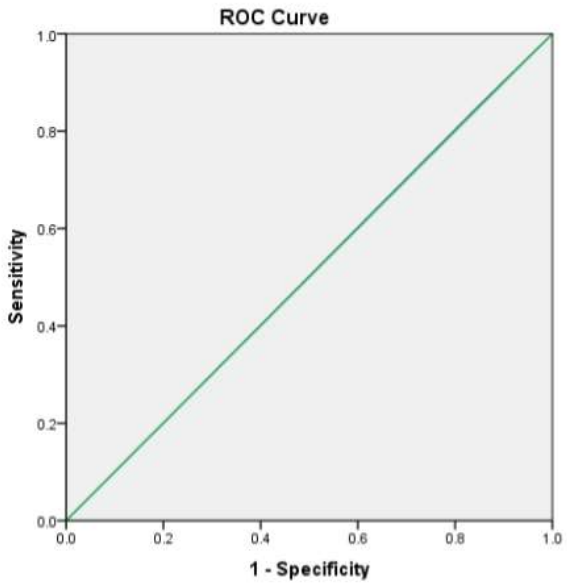

Figure 2: ROC curve analysis of MWS

74% (136 out of 185) had pre-CTPA renal function, and out of 136 of patient only 84 had post-CTPA renal function test done (62%). About 7.1% of patients had contrast-associated AKI post CTPA (*n*=84).

4. DISCUSSION

Despite the low incidence of PE in pregnancy, it remains the second most common cause of maternal death in Malaysia[26,27]. With the widely available CTPA in tertiary hospitals throughout the Malaysia and the significance of timely diagnosis of PE in pregnancy, there is always a low test threshold for diagnostic imaging in this group of patients[28]. To our knowledge, this is the first study in Malaysia looking into the number of CTPA orders and the diagnostic yield of CTPA in pregnant and puerperium women over 5 years.

We observed a substantial increase in the number of scans ordered from 2019 to 2022. However, the positive rate was in a wide range of about 2.4–20%. In the cohort of 2020–2021, the CTPA positive rate was as high as 13.2-20%, with 1/5 of the scans ordered for

pregnant patients with COVID-19. This might be a reflection of the association between thrombotic events and PE in pregnancy during the COVID-19 pandemic[29].

Overall, our diagnostic yield was only 10.3%. This diagnostic yield was below the recommendation by Royal College of Radiologists and other studies conducted in the general population. Nonetheless, the finding was in line with a 17-year Swiss study in pregnant population (7%)[4]. This has further validated the challenges of diagnosing PE in pregnancy.

Prior research has indicated that MWS is applicable to pregnancy with notable results demonstrating great sensitivity and specificity with the conclusion of low MWS score could avoid unnecessary imaging by at least one third [21,22]. However, the unblinded study with retrospective nature and small sample size rendered the identification of low-risk group less reliable in those studies.

On the other hand, our result revealed a lower sensitivity rate of 90% and specificity of 14.5% which was partially supported by another study[30]. Low specificity might be contributed by a significant percentage of pregnant women who presented with nonspecific clinical symptoms and signs; in our study, about 82% of patients were classified as high-probability PE group. Pregnancy-related physiological alterations like tachycardia are frequently the most prevalent presenting signs that lead to the suspicion of PE. The utilization of MWS is even more limited during the COVID-19 pandemic, where tachycardia is not uncommon in COVID-19 pregnant women[31]. In addition, one of the score components, "alternative diagnosis less likely than PE, was also debated for its subjectivity causing interobserver variability [32,33]. Furthermore, there is also a lack of inclusion of pregnancy-specific variables that may be associated with PE, such as caesarean, delivery, preeclampsia, and infection, in the scoring system. All these highlight the drawbacks of Well's score and the majority of the clinical prediction model scores in this group of patients.

Previous studies also showed that none of the patients with low MWS had PE (NPV 100%)[21,22]. This is inconsistent with our finding, where the prevalence of PE was 7.6% with an NPV of 92.3% in the low probability group. This outcome can be due to the distinct patient profile, symptoms, and multi-ethnicity population in our study. Out of the 26 patients with low MWS, there are 2 patients diagnosed with PE: one patient has COVID-19, and the other patient's primary symptom was chest pain. From scan, both patients had filling defect over left branch of pulmonary arteries and diagnosed with mild pulmonary embolism. The positive rate of CTPA is linearly proportional to the Well score (7.6% for a low score and 11.3% for high risk); however, the receiver operating characteristic (ROC) curve analysis demonstrated poor discriminatory accuracy of MWS in predicting PE in pregnancy. Essentially, it is important to have personalized risk assessment despite low clinical probability.

According to the Malaysia Clinical Practice Guideline of venous embolism, the first step in the algorithm to diagnose PE in pregnancy is by imaging modality[34]. There is always a risk of contrast-associated AKI with CTPA. The reported incidence ranged between 6.5 and 19%[35]. In our studies we discovered that up to 7.1% patient had CIN post- CTPA. All the 6 pregnant patients with CIN had either a pre-existing medical condition such as systemic lupus erythematosus, multiple myeloma, or were critically ill. However, in view of the fact that about half of the patients did not have a post-CTPA renal profile as it was not routinely performed, the actual rate might be underestimated. Nevertheless, there is little prospective research on the reversibility of renal function post-contrast in obstetrics patients and those studies often include multiple confounding variables.

The strength of the study was the consistent application of MWS by a single reviewer who was blinded by the CTPA result. There were a few limitations in our study: the retrospective assignment of MWS instead of the physician evaluating the patient. This study had a relatively small sample size from a single tertiary center and may not be representative of the population. In addition, our study did not involve patients with suspected PE who had not undergone CTPA. In some cases, compression ultrasonography of the lower limbs is performed instead of CTPA when a patient suspected of PE has lower limb symptoms. Patients suspected of PE with a diagnosis of DVT will be treated without proceeding to advanced imaging. In our study, we did not identify this small group of patients, but we believe that we included those patients in our study as clinical sign and symptoms of DVT is one of the components of MWS, so the diagnosis of PE without CTPA has little effect on our study.

5. CONCLUSION

CTPA has been the first diagnostic modality in diagnosing PE and the diagnostic yield of CTPA performed at our facility has been comparable with larger world studies.
Modified Well's score is widely used in the general population but its implications for pregnant patients are still a matter of debate. With the lack of validated pretest clinical scores in this specific patient category, it is improbable that we are overusing CTPA when a prompt diagnosis is necessary for this fatal disorder. To avoid the unnecessary risk of CTPA to pregnant mothers, future studies on large prospective cohorts are needed to investigate the safety and efficacy of other pretest clinical scores to rule out PE in pregnant women.

ETHICAL APPROVAL

This research has received ethical approval from the National Medical Research Registry of Malaysia (NMRR- ID-23-00208-Q6M). Informed consent was waived owing to the cross-sectional nature of this study.

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