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DETERMINANTS FOR POSITIVE COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY (CTPA) IN DIAGNOSING PULMONARY EMBOLISM IN NORTHEAST STATE OF PENINSULAR MALAYSIA.

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ABSTRACT

Background: This study was conducted to estimate the annual proportion of positive computed tomography pulmonary angiography (CTPA) in diagnosing pulmonary embolism and determine its socio-demographic and clinical determinants.

Materials and Methods: CTPA datasets of 431 patients from 2014 to 2017 were analysed retrospectively to estimate the annual proportion of cases with pulmonary embolism in Kelantan, a northeast state of peninsular Malaysia. Comparative cross-sectional study between positive and negative CTPA cases among 388 randomly selected patients that fulfilled the inclusion criteria was conducted to determine associated factors for positive CTPA finding. Descriptive statistics, simple and multiple logistic regressions were used for data analysis.

Result: The annual proportion of positive CTPA cases ranged from 25.2% to 33.3%. The mean age of patients with positive CTPA finding was 50.32 years old and majority of positive CTPA patients were male (67.0 %), cigarette smoker (67.0 %), non-hypertensive (58.9%) and had high Well's score (74.5%). Older age, male gender and high Wells score were the significant determinants for positive CTPA findings with an adjusted odds ratio (aOR) of 1.03 (95% confidence interval (CI): 1.01-1.05; $p = 0.004$), 5.42 (95% CI: 2.31-12.68; $p < 0.001$), and 13.45 (95% CI: 6.93-26.11; $p < 0.001$), respectively.

Conclusion: Patients with older age, male gender and high Wells score were more likely to get positive CTPA finding. These significant determinants might help clinicians in preventing unnecessary CTPA examination, thus unjustified radiation to the patient can be avoided.

Keywords: Computed Tomography Pulmonary Angiography, CTPA, pulmonary embolism, determinants, Malaysia.

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1.0 Introduction

Pulmonary embolism (PE) is a disease with presence of thrombosis in the pulmonary artery. It is a common disease which occurs as a complication of primary condition with non-specific symptom with potential high risk of mortality and morbidity (Gülşen *et al*., 2015). Due to non-specific features, it is a big challenge for the clinicians to diagnose acute pulmonary embolism. The diagnosis includes clinical and laboratory tests and available guideline or scoring system such as Wells' criteria and revised Geneva score. Computed tomography pulmonary angiography (CTPA) is the most sensitive and readily available method to diagnose pulmonary embolism in high probability cases (Hendriksen *et al*., 2015; Kennedy *et al*., 2015).

CTPA is usually the first line imaging to exclude pulmonary embolism if clinical suspicion is high due to its accuracy, fast result and can provide ancillary findings and alternative diagnoses (Costa *et al*., 2014). In Malaysia, the CTPA is the gold standard to diagnose pulmonary embolism and baseline CTPA is necessary before treatment is initiated (Ministry of Health, 2013). In most of the clinical situations, the CTPA outweighs the drawbacks of ionizing radiation, iodinated contrast usage and health care cost by using appropriate scoring system which have been identified to have association with pulmonary embolism. Multiple validation studies have been conducted previously showing that accuracy of the helical CT with average sensitivities vary between 64 to100% and specificities range from 89 to 100% (de Monyé and Pattynama, 2001; Rathbun *et al*., 2000). The general positive predictive value is 86%, however it is subdivided according to anatomical distribution. Positive predictive value is 96% for pulmonary embolism in main or lobar artery, 68% for segmental vessels and 25% for subsegmental and distal branches. CTPA with high clinical suspicion results in high predictive value but with clinical probability discordance, the predictive value is low. The sensitivity for pulmonary embolism increases to 90% by using CT venography together with CTPA (Stein and Hull, 2007).

In the absence of the proper treatment, the substantial morbidity and mortality is associated with pulmonary embolism and it accounts about 0.23-1.0% of hospital admission (Subramaniam *et al*., 2006). Prompt and accurate diagnosis is important in making sure patients have the correct and immediate treatment when pulmonary embolism is suspected and diagnosed. Early treatment with anticoagulant showed significantly good clinical outcome and decreased mortality up to 2-8% (Dismuke and Wagner, 1986; Horlander *et al*., 2003).

Several scoring systems have been developed to assist the clinician in diagnosing the acute pulmonary embolism. The most acceptable and widely used criteria include the Wells criteria, PERC (Pulmonary Embolism Rule-Out) score, Geneva score and PISA model (Hendriksen *et al*., 2015). The Malaysia's Clinical Practice Guideline (CPG) for Prevention and Treatment of Venous Thromboembolism which was issued in August 2013 adopted Wells criteria as the predictive scoring system to diagnose acute pulmonary embolism (Ministry of Health, 2013). The criteria which are included in Wells criteria are clinical signs and symptoms of deep vein thrombosis (DVT), tachycardia of more than 100 beats per minute, immobilization or surgery in previous 4 weeks, previous history of PE/DVT, hemoptysis and malignancy. The total Wells score is 12.5 points. The Wells criteria risk stratifies patients for pulmonary embolism and provides an estimated pre-test probability. The physician can then choose what further

testing is required for diagnosing pulmonary embolism such d-dimer or CTPA (Ministry of Health, 2013; Wolf *et al*., 2004).

Apart from scoring system, several socio-demographic and clinical determinants have been identified as predisposing factors for the development of acute pulmonary embolism. Age and gender have been identified as significant socio-demographic determinants in diagnosing pulmonary embolism. According to Silverstein *et al*. (1998), individuals aged more than 65 years old were more likely to develop venous thromboembolism and subsequently pulmonary embolism. The study also showed that incidence rate of PE was higher in men as compared to women with male-to-female ratio of 1.2:1. However, in female patient of childbearing age, the prevalence of PE was much higher due to different exposures such as hormonal changes during pregnancy, postpartum state or oral contraceptive use among younger women of childbearing age. It is difficult to subject the pregnant patient to ionizing radiation if low clinical suspicion is discovered. Due to the infeasibility of other non-radiation imaging modality such as V/Q scan, the CTPA is still the mainstay to diagnose pulmonary embolism in pregnant ladies (Silverstein *et al*., 1998).

Obesity is one of the predisposing factors to develop pulmonary embolism as reported by many studies due to their hypercoagulability and mechanical issue which lead to the venous stasis (Abdollahi *et al*., 2003; Goldhaber and Bounameaux, 2012; Silverstein *et al*., 1998). A person with a BMI of 30 or more is generally considered obese. Due to physical condition and vague clinical symptom such as dyspnea and poor oxygenation, it is difficult to diagnose PE in obese patients (Hawley and Hawley, 2011). Another possible predisposing factor for PE is cigarette smoking. Smoking usually considered as added factors of developing venous thromboembolism and pulmonary embolism (Cheng et al., 2013). The link between smoking and arteriosclerosis is undeniable and, although less evidence implicates smoking directly in the pathogenesis of thrombophilic state in the less platelet-dependent venous side of the circulation, there are strong suggestions of culpability (Tapson, 2005).

Currently, there is no well-published study in Malaysia to explore the factors related with positive CTPA finding in diagnosing pulmonary embolism. In this study, we sought to estimate the annual proportion of positive CTPA examination in diagnosing pulmonary embolism and determine its socio-demographic and clinical determinants. We expect that the findings of our study could provide important criteria to help clinicians in preventing unnecessary CTPA examination, thus unjustified radiation to the patient can be avoided.

2.0 Materials and Methods

We conducted a comparative cross-sectional study design based on a retrospective record review in the Department of Radiology, Hospital Raja Perempuan Zainab II (HRPZII), Kota Bharu, Kelantan. HRPZII is the main general hospital in northeast state of Peninsular Malaysia (Ab Aziz and Awang, 2019). The reference populations were all pulmonary embolism patients in Kelantan, and the study samples were patients with positive and negative CTPA findings in Kelantan registered in the institutional CTPA database from 2014 to 2017 who fulfilled study inclusion and exclusion criteria. The inclusion criteria were urgent adult CTPA cases (age 18 years old and above) and registered in the institutional CTPA

database from 1 January 2014 to 31 December 2017. Urgent CTPA refers to CTPA which was requested by primary team for patients who were suspected to have acute pulmonary embolism in that particular clinical setting based on clinicians' judgement. It includes patient with known risk factor such as cases of malignancy, established DVT and pregnant ladies. CTPA cases which was done for re-assessment to look for the efficacy of the thromboembolic treatment, and indeterminate findings due to artifacts and poor image quality were excluded from the study.

The sample size was calculated for each variable of associated factors for positive CTPA finding using power and sample size calculation software (Dupont and Plummer Jr, 1990) as well to compare two independent proportions. The largest estimated sample was 338 using the proportion of negative CTPA finding by the factor of male gender (0.56) (Silverstein et al., 1998), an estimated proportion of 0.73, 5% type 1 error, 80% power, and additional 20% missing data.

Data were collected from HRPZII CTPA database. The retrieved information includes sociodemographic data (age and gender) and clinical factors (cigarette smoking status, BMI level, hypertension status, pregnancy status and Wells score). Using the institutional CTPA database, we found a total of 431 patients underwent for CTPA examination from 2014 to 2017. These patients were randomly selected in accordance to the required sample size and subdivided into positive and negative CTPA sampling frames.

All CT examinations were performed using the same CT scanner , Toshiba Aquilion 64; a whole body 64-slice CT scanner (Toshiba Medical Systems Ltd, Japan). The X-ray tube potential used was 120-kVp and different CT radiation dose setting were applied according to patients' habitus. Green intravenous cannula (gauge size of 18G) in the antecubital fossa was used to administer the contrast media into the body. 50 ml of Iopamirol 320mgl/mL (Iopamiron ; Bayer Yakuhin, Ltd., Japan) was used as contrast media. The data were collected and were labelled with serial numbers to maintain the privacy and confidentiality of subject and images. Images were interpreted by two senior radiologists whose working experience are at least 10 years as radiologist, blinded to each other's findings. The impressions were either presence (positive) or absence (negative) of pulmonary embolism. The suboptimal (poor image quality) images were excluded from study as they had poor diagnostic value. It may be due to poor pulmonary arterial phase, severe motion artefact or lack of contrast in the pulmonary artery which could hide the filling defect in pulmonary arteries.

We used SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) for data entry and analysis. Descriptive statistics with mean and standard deviation (SD), frequency and percentages were calculated. Simple and multiple logistic regression analysis were used to determine factors associated with positive CTPA finding among patients underwent for CTPA examination. All significant variables with a p-value < 0.250 from univariable analysis and clinically important variables were chosen for multiple logistic regression analysis. A p-value < 0.050 was considered statistically significant.

This study was approved by National Medical Research Register (MREC NMRR-17-744-35227(IIR)) and Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/18020120), and was conducted in accordance with the ethical standards of the

institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments.

3.0 Result

There were 431 cases underwent for CTPA registered in institutional database during the four-year study period (2014–2017). The proportion of patients with positive CTPA finding in Kelantan was 29.0% or 125 cases out of total 431 cases for CTPA examination. Annually, the proportion of cases with positive CTPA finding ranged from 25.2% to 33.3% [Table 1].

Table 1. Proportion of positive CTPA findings from 2014 to 2017 at the Department of Radiology, HRPZII (n=431).

Year	Total CTPA cases	Positive CTPA cases	Percentage of positive CTPA cases (%)
2014	67	19	28.3
2015	72	23	31.9
2016	114	38	33.3
2017	178	45	25.2
Summative	431	125	29.0

A total of 338 samples were included in this study through simple random sampling [Table 2]. The mean age of patients with positive CTPA was higher compared to those with negative finding. The majority of cases with positive CTPA finding were male patients (n = 63, 67.0%). And among female patients, majority of cases with positive CTPA finding were not pregnant (n=25, 26.6%). Cigarette smokers were more prone to get positive finding in CTPA examination (n = 63, 67.0%). The majority of patients with positive finding in CTPA examination were non-hypertensive (n=55, 58.9%) and had high Well's score (n = 70, 74.5%). The mean BMI of patients with positive CTPA was slightly lower compared to those with negative finding.

Table 2. Sociodemographic and clinical characteristics among CTPA patients registered in HRPZII database, 2014–2017 (n = 338).

Factors	CTPA outcome, frequency (%)	
	Negative n= 244	**Positive n= 94**
Age *	44.11 (14.60)	50.32 (19.48)
Gender		
Male	87 (35.7)	63 (67.0)
Female	157 (64.3)	31 (33.0)
Smoking		
No	163 (66.8)	31 (33.0)
Yes	81 (33.2)	63 (67.0)
Hypertension		
No	134 (54.9)	55 (58.9)
Yes	110 (45.1)	39 (41.5)
BMI*	25.60 (4.36)	24.06 (4.56)
Pregnancy		
No	127 (52.0)	25 (26.6)
Yes	30 (12.3)	6 (6.4)
Not applicable	87 (35.7)	63 (67.0)
Well's score		
Low	188 (77.0)	24 (25.5)
High	56 (23.0)	70 (74.5)

*Mean (SD)

In univariable analysis, all variables besides hypertension and pregnancy status (p-value > 0.25) were chosen for multiple logistic regression analysis. Multiple logistic regression analysis revealed age, gender and Well's score were the significant determinants for positive finding among patients underwent CTPA examination [Table 3].

Table 3. Determinants for positive CTPA patients attending HRPZ II from 2014 until 2017 by simple and multiple logistic regression (n=338).

Factors	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]	Wald statistics (df)[b]	p value[b]
Age	1.02(1.00,1.04)	1.03(1.01,1.05)	8.08(1)	0.004
Gender				
Female	1.00	1.00		
Male	3.67(2.22,6.07)	5.42(2.31,12.68)	15.17(1)	<0.001
Smoking				
No	1.00	1.00		
Yes	4.09(2.47,6.78)	0.65(0.27,1.56)	0.92(1)	0.34
BMI	0.92(0.87,0.98)	1.00(0.93,1.08)	0.01(1)	0.92
Well's Score				
Low	1.00	1.00		
High	9.8(5.6,16,16.99)	13.45(6.93,26.11)	58.9(1)	<0.001

Forward LR method applied.
[a]Simple logistic regression [b]Multiple logistic regression
No interaction and multicollinearity detected.
Classification table: 79.6
Area under Receiver Operating Characteristic (ROC) curve: 0.85

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4.0 Discussion

The proportion of positive CTPA findings in Kelantan was 29.0%. Comparison at local level is impossible since there is no well-published study on CTPA finding in Malaysia yet. As for cross-country comparison, our finding is relatively higher compared to the finding from a Canadian study where positive CTPA comprised about 15.0%% out of total CTPA cases (Champion *et al*., 2018). However, our finding is lower than the finding from Iranian study which was 37.8% (Molaee *et al*., 2015). The number of the CTPA examinations increased gradually from 2014 until 2016 which could be attributed to the increase request from all departments, awareness of the pulmonary embolism which lead to high mortality and morbidity if left untreated and development of new generation of anti-coagulants with lower side effect, risk of bleeding tendency and complications (More and Chauhan, 1996).

In our study, age was a significant determinant for positive CTPA finding (aOR = 1.03, 95%CI: 1.01-1.05; p = 0.004). Similar findings were reported from a cohort study in Minnesota, United States of America (Silverstein *et al*., 1998). With the age increment, the chance of likelihood to get venous thromboembolism is higher due to multiple factors. The most common reason is the unhealthy lifestyle which lead to metabolic and endocrine disease as well as obesity. All these factors will lead to hypercholesterolemia and higher blood viscosity which subsequently become the source of the thrombosis in blood vessel. Without proper diagnosis and treatment, the distal emboli could easily dislodge to the main and central vessel like common femoral vein, inferior vena cava and pulmonary artery (Upadhyay, 2015). Besides that, elderly group is more prone to get pulmonary embolism due to malignancy as shown in previous study conducted in Kuala Lumpur Hospital where significant association between age and PE secondary to malignancy were reported (p=0.02) (Lee *et al*., 2013).

We found significant association between gender and positive CTPA finding (p < 0.001). Male patients had 5.42 higher odds of getting positive CTPA finding as compared to female patients. Similar with our finding, Silverstein *et al*. (1998) reported that male patients had higher incidence of pulmonary embolism after age of 45 years old as compared to female patients. Male patients have higher tendency to get non-communicable diseases (NCDs) as compared to female and this rise of NCDs among male group has been driven by primarily four major risk factors; tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets (World Health Organization, 2018). The NCDs are the major risk factors for VTE and pulmonary embolism (Raskob *et al*., 2014). However, in contrast to our finding, Barrios et al. (2018) reported that female group were more likely to experience PE-specific mortality (aOR 1.85; 95% CI, 1.02 - 3.33; p = 0.04). The finding could be related to few factors such as hormonal changes during pregnancy, postpartum state or oral contraceptive use among younger women of childbearing age which predispose them to hypercoagulable state (Chan et al., 2008; Trenor III *et al*., 2011).

Pregnancy and postpartum period are well known risk factor of developing thromboembolic event due to hypercoagulable state. However, our study only enrolled 36 pregnant women which substituted 10.7% of total sample with six pregnant ladies showed positive result for pulmonary embolism. Similarly, recent study conducted in Iran revealed pregnancy as one of significant contributing factors for pulmonary embolism and subsequently maternal mortalities (Borazjani *et al*., 1978). As there were few samples for pregnant women,

conclusion of positive CTPA was prevalent among pregnant woman cannot be made and thus, the variable cannot be used to test the causal hypothesis.

Other clinical determinants such as cigarette smoking and BMI were not significantly associated with positive CTPA finding. Although cigarette smoking is a well-established risk factor for atherosclerotic disease, but its role as an independent risk factor or effect modifier for venous thromboembolism remains controversial (Cheng *et a*l., 2013). Smoking is usually associated with other cardiovascular risk and malignancy risk. These risks would subsequently attribute to the increase in blood viscosity and blood vessel permeability due to anti-inflammatory mediators and cytokines release (Madani *et al*., 2018). Although the association between BMI level and CTPA positivity in our study is statistically insignificant, many studies have reported that obesity is a significant risk factor for deep vein thrombosis and pulmonary embolism (Abdollahi *et al*., 2003; Kabrhel *et al*., 2009; Stein *et al*., 2005; Stein et al., 2011). Obesity (BMI ≥30 kg/m2) increased the risk of thrombosis by two-fold (95% CI: 1.5 - 3.4), adjusted for age and sex. Obese individuals had higher levels of factor VIII and factor IX, but not of fibrinogen. The effect on risk of obesity was not changed after adjustment for coagulation factors levels (fibrinogen, F VIII, F IX, D-dimer). The relative risk estimates were similar in different age groups and in both sexes, indicating a larger absolute effect in older age groups. Evaluation of the combined effect of obesity and oral contraceptive pills among women aged 15 to 45 revealed that oral contraceptives further increased the effect of obesity on the risk of thrombosis, leading to 10-fold increased risk amongst women with a BMI greater than 25 kg/m2 who used oral contraceptives (Abdollahi *et al*., 2003).

The result of our study showed significant association between Wells criteria and CTPA positivity ($p<0.01$). Higher Wells score indicates higher risk for pulmonary embolism. According to Goldhaber and Bounameaux (2012), patients with a score less than 2 are low risk; 2 to 6 are intermediate risk; and 6 and above are high risk for pulmonary embolism. According to latest Malaysian Clinical Practice Guideline on venous thromboembolism, the CTPA is gold standard to diagnose pulmonary embolism and baseline CTPA is necessary before treatment is initiated. The Guideline also advocated Wells criteria as the predictive score of developing acute pulmonary embolism (Ministry of Health, 2013). Wells criteria are not meant to diagnose pulmonary embolism, but to guide work up by predicting pre-test probability of pulmonary embolism and appropriate testing needed to rule out the diagnosis. The Wells Criteria risk stratifies patients for pulmonary embolism and provide an estimated pre-test probability. The physician can then choose what further testing is required for diagnosing pulmonary embolism such as D-dimer or CTPA examination (Ministry of Health, 2013; Molaee *et al*., 2015). It was proven in previous study that Wells Criteria have a moderate to substantial inter-rater agreement and reliably risk stratify pre-test probability in patients with suspected pulmonary embolism (Wolf *et al*., 2004).

Among limitations of the study are its small sample size of pregnant patients. Moreover, the use of a cross-sectional study design may only reveal the association between sociodemographic and clinical factors with CTPA positivity rather than a proper sequence of cause and effect.

5.0 Conclusion and recommendation

The result of this study showed age, gender and Wells' criteria as significant determinants in predicting pulmonary embolism in Kelantan state. This study is beneficial in which it may assist physicians in deciding either patient is subjected to CTPA examination in clinically suspected pulmonary embolism or another pretest like laboratory investigation is needed before performing CT scan to prevent high negative result. This is important to prevent unnecessary examination, thus unjustified radiation to the patient can be avoided. Due to non-specific clinical symptom of pulmonary embolism, the biochemical test and echocardiogram might help in giving more predictive value in suspected pulmonary embolism patient.

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Declaration

The authors declare that we have no conflict of interest and this manuscript has never been published in any other journal.

Authors contribution

Author 1: information gathering, data entry, manuscript drafting.
Author 2: data entry, data analysis, manuscript drafting, editing and review.
Author 3: technical and logistic supports.

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