UNIVERSITI PUTRA MALAYSIA

EVALUATION OF D-DIMER ASSAY AS A'RULE OUT' TEST FOR PATIENTS SUSPECTED PULMONARY EMBOLISM WHO UNDERWENT CT PULMONARY ANGIOGRAM AT HOSPITAL SERDANG IN 2010 UNTIL 2013.

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ABSTRACT

Introduction: Pulmonary embolism(PE) is a common complication of hospitalization and contributes to 5 to 10 percent of deaths in hospitalized patients, making it one of the leading causes of preventable hospital deaths. Early diagnosis is essential as even patients with minor symptoms are at risk of recurrent pulmonary emboli. D-dimer serves as an indirect indicator of thrombotic activity, which used in conjunction with imaging studies and clinical signs and symptoms to exclude PE.

Objective: To evaluate the sensitivity and specificity of D-Dimer assay as a 'rule out' test in patients suspected Pulmonary Embolism at Hospital Serdang.

Method: We reviewed a total of one hundred and ten patients suspected Pulmonary Embolism from medical records at Department of Imaging, Hospital Serdang from December 2010 until June 2013 who fulfill our criteria. Data were analyzed by SPSS version 21.The negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity of the D-dimer assay results were calculated.

Result: Twenty-one patients (19.1%) had pulmonary embolism at Computed Tomography Pulmonary Angiogram(CTPA). D-Dimer results were positive in 96 patients (87.3%). The NPV and sensitivity of D-dimer were 85.71% and 90.48%, respectively. The specificity and PPV of D-Dimer were 13.5% and 19.8%, respectively. The sensitivity and NPV of D-Dimer combined with Well' s score in low risk patients was 100%.

Conclusion: This study showed D-Dimer results have high NPV and sensitivity for PE in low risk patients and, if negative, can be used to exclude PE in this population. Combining the assay with clinical symptoms and signs did substantially change NPV, PPV, sensitivity, or specificity.

Keyword: Pulmonary Embolism, Well's score, D-Dimer, CT Pulmonary Angiogram

PENILAIAN D-DIMER SEBAGAI UJIAN PENGECUALIAN BAGI PESAKIT YANG DISYAKI EMBOLISME PULMONARI YANG MENJALANI CT ANGIOGRAM DI HOSPITAL SERDANG PADA TAHUN 2010 SEHINGGA 2013.

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ABSTRAK

Pengenalan: Embolisme pulmonari adalah satu komplikasi yang biasa di hospital dan menyumbang kepada 5 hingga 10 peratus kematian di kalangan pesakit yang dimasukkan ke hospital, menjadikan ia salah satu punca utama kematian di hospital. Diagnosi awal penyakit adalah penting kerana pesakit dengan gejala kecil juga berisiko mendapat Embolisme Pulmonari yang berulang. D-dimer bertindak sebagai petunjuk aktiviti trombotik yang digunakan bersama dengan kajian pengimejan serta tanda-tanda klinikal dan gejalabagi mendiagnos PE.

Objektif: Untuk menilai sensitiviti dan spesifisiti D-dimer assay sebagai ujian pengecualian bagi pesakit yang disyaki Embolisme Pulmonari di Hospital Serdang.

Kaedah: Kami mengkaji sejumlah satu ratus sepuluh pesakit yang disyaki Embolisme Pulmonari daripada rekod perubatan di Jabatan Pengimejan, Hospital Serdang dari Disember 2010 hingga Jun 2013 yang memenuhi criteria. Data kami telah dianalisis menggunakan perisian SPSS versi 21. Nilai negatif ramalan (NPV), nilai positif ramalan (PPV), sensitiviti, spesifisiti keputusan assay D-dimer telah dikira.

Keputusan: Dua puluh satu pesakit (19.1%) mempunyai embolisme pulmonari di CTPA. Keputusan D-dimer positif dalam 96 pesakit (87.3%). NPV dan sensitiviti D-dimer adalah 85.71% dan 90.48% masing-masing. Spesifisiti dan PPV D-dimer adalah 13.5% dan 19.8%, masing-masing. Sensitiviti dan NPV D-Dimer apabila bergabung dengan Well's score dalam pesakit yang berisiko rendah menjadi 100%.

Kesimpulan: Ini menunjukkan kajian D-dimer mempunyai nilai NPV dan sensitiviti untuk PE pada pesakit berisiko rendah, dan jika negatif, boleh digunakan untuk mengecualikan PE dari pilihan diagnosis di kalangan pesakit ini. Menggabungkan assay dengan gejala klinikal dan tanda-tanda mengubah nilai NPV, PPV, sensitiviti, atau spesifisiti dengan ketara.

Kata Kunci: Embolisme pulmonari, *Well's score, D-Dimer*, CT Angiogram

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PE	Pulmonary Embolism
CTPA	Computed Tomography Pulmonary Angiogram
DVT	Deep Vein Thrombosis
PPV	Positive Predictive Value
NPV	Negative Predictive Value

1.1 INTRODUCTION

Pulmonary embolism is a common and potentially life-threatening sequela of deep venous thrombosis, with an estimated annual incidence as high as 69 per 100,000 (Silverstein,Heit, 1998). Mortality rates approach 30% in untreated individuals (Dalen,Alpert, 1975). A recent epidemiology study has found that PE is a major public health burden with an estimated 370,000 related death in 2004 in six European countries (Sanchez, Plaquette, & Meyer, 2009). Pulmonary embolism is a blockage of an artery in the lungs by fat, air, tumor tissue or blood clot. PE is a common disease which also has high morbidity and mortality, yet difficult to diagnose (Cobanoglu, 2012). In more than 95% of cases, PEs originate from lower limb deep vein thrombosis (DVTs), which occurs roughly two to three times more frequently than PEs (K.Abbas, A.K,& et.al.,2009).

The clinical presentation in patients with suspected PE ranges from shock or sustained hypotension to mild dyspnea (Agnelli & Becattini, 2010). Patients may also be asymptomatic and diagnosed during imaging procedures performed for other purposes (Agnelli & Becattini, 2010). Patients with suspected PE will present with new or worsening dyspnea, chest pain, or sustained hypotension without alternative causes (Agnelli & Becattini, 2010).

Besides DVTs, many risk factors contribute to occurrence of PE which are divided into two categories, genetic and acquired risk factors (Agnelli & Becattini, 2010). For genetic risk factors, antithrombin deficiency was first discovered as predisposition to thrombosis in 1965, followed by protein C and protein S deficiencies. These three deficiencies represent 15% of hereditary thrombophilia (Cobanoglu, 2012). Besides that, hyperhomocysteinemia and mutation in prothrombin were also shown to cause hereditary thrombophilia.

The acquired risk factors are pregnancy and post-partum period, cancer, oral contraceptive and hormone replacement therapy (Sanchez, Plaquette & Meyer, 2009). Immobilization after fracture or surgical procedures is also one of the acquired risk factors to cause PE (Cobanoglu, 2012).

The diagnosis of PE should follow a sequential diagnostic workup that consists of clinical probability assessment, D-dimer test and if needed to continue with Computed Tomography Pulmonary Angiography (CTPA) or ventilation-perfusion scanning (Agnelli & Becattini, 2010). The assessment of clinical probability is based on the clinical presentation and risk factors, made according to clinical judgement which can classify patients with suspected PE into several categories of pretest probability (Agnelli & Becattini, 2010). Wells scores are a clinical prediction rule for estimating the probability of DVT and PE. Different aspects including clinical signs and symptoms of DVT, unlikely alternative diagnosis other than PE, heart rate, past history, presence of hemoptysis or malignancies are assessed according to Wells score. Immediate CTPA is introduced to patients with a likely two-level PE Wells score (Agnelli & Becattini, 2010).

In many emergency departments, the D-dimer assay is used in conjunction with imaging studies and clinical sign and symptoms to exclude PE. Some studies have suggested that in patients with a low clinical probability, the D-Dimer assay may be used to reliably exclude PE or deep vein thrombosis (DVT) (Kearan et.al., 2006). The D-dimer assay is of limited value in patients with a high clinical probability of PE (Agnelli & Becattini, 2010).

This is due to reduced specificity of D-dimer level in patients with cancer, pregnant women, hospitalized and elderly patients (Agnelli & Becattini, 2010). D-dimer is a breakdown product produced by the normal clotting process.

It is normally present in small quantities in the blood. Increased level in blood is suggestive of increased clotting activity in the body (King, A.Vaze, & et.al., 2008). Immediate CTPA is introduced to patients when the result of D-dimer test is positive, even though the Wells score is low. CTPA has become a commonly used non-invasive modality to diagnose PE (King, A.Vaze, & et.al., 2008). In Hospital Serdang, CTPA is used, as it is readily available and is a quick study to perform, with relatively high sensitivity and specificity for PE.

However, CTPA also has its own risks, such as adverse reaction to intravenous contrast material, renal failure due to contrast nephrotoxicity and exposure to radiation (King, A.Vaze, & et.al., 2008). Thus, in our study, we need to identify the types of D-dimer assay being used and its own specificity and sensitivity before proceeding with CTPA. With highly specific D-dimer assay, PE may be excluded in patients with negative D-dimer assay thus avoid unnecessary CTPA examination.

1.2 PROBLEM STATEMENT

Research has shown that a prompt diagnosis of acute PE, within 48 hours of emergency department arrival, is associated with improved outcomes (Timothy, 2012) . Currently, the 'gold standard' test for PE is conventional pulmonary angiography globally, but it is invasive and usually unavailable urgently (Hartree, 2010). Hence there is no use of conventional pulmonary angiography at the radiology department in Hospital Serdang, Malaysia. All the suspected PE patients will undergo CTPA for the diagnosis. CTPA is the most sensitive test for the diagnosis of PE and its use has been associated with a rising incidence of the condition (Anderson, D.R, & et.al., 2009).

Diagnostic algorithms using either CTPA or V/Q scanning have proven to be comparably safe to exclude the diagnosis of PE (Anderson, D.R, & et.al., 2009). . However, there are several disadvantages including an increased non-diagnostic rate during pregnancy, nephrotoxic iodinated contrast injection, and significant breast radiation dose (Turner, 2012). Intravenous contrast injection can also cause local tissue damage and anaphylactoid reactions, which carries a 4% to 22% chance of contrast-induced nephropathy, thus limits the use of CTPA in patients with contrast allergies and renal problems such as renal insufficiency (Turner, 2012).

The interesting question here is "should all patients with suspected PE undergo CTPA?" Since the fact shows that there are a lot of health threatening disadvantages of CTPA, use of a simple risk stratification score such as Wells score coupled with a D-dimer level allow correct risk stratification in patients presenting with suspected PE and avoid unnecessary CTPA (Padley & S.P.G., 2012). In patients defined as unlikely PE, 98% of them have no PE on further investigation (Padley & S.P.G., 2012).

1.3 OBJECTIVES

General objective: To evaluate the D-dimer assay as a' rule out' test in patients with suspected PE.

Specific objectives:

a)To study the relation between D-dimer level in patients of different age group.

b)To determine the D-dimer result in patient's serum with positive CT Pulmonary Angiogram in suspected PE.

c)To identify association between different D-dimer level with result of CT pulmonary angiogram.

d) To ascertain the sensitivity and specificity of D-dimer assay used in Hospital Serdang in excluding PE.

e) To identify the correlation between D-dimer level and CT Pulmonary Angiogram with different Well's score.

1.4 RESEARCH HYPOTHESIS

Null Hypothesis: There is no association between D-dimer level and occurrence of PE in suspected PE patients

Alternative Hypothesis: There is an association between D-dimer level and occurrence of PE in suspected PE patients

1.5 CONCEPTUAL FRAMEWORK

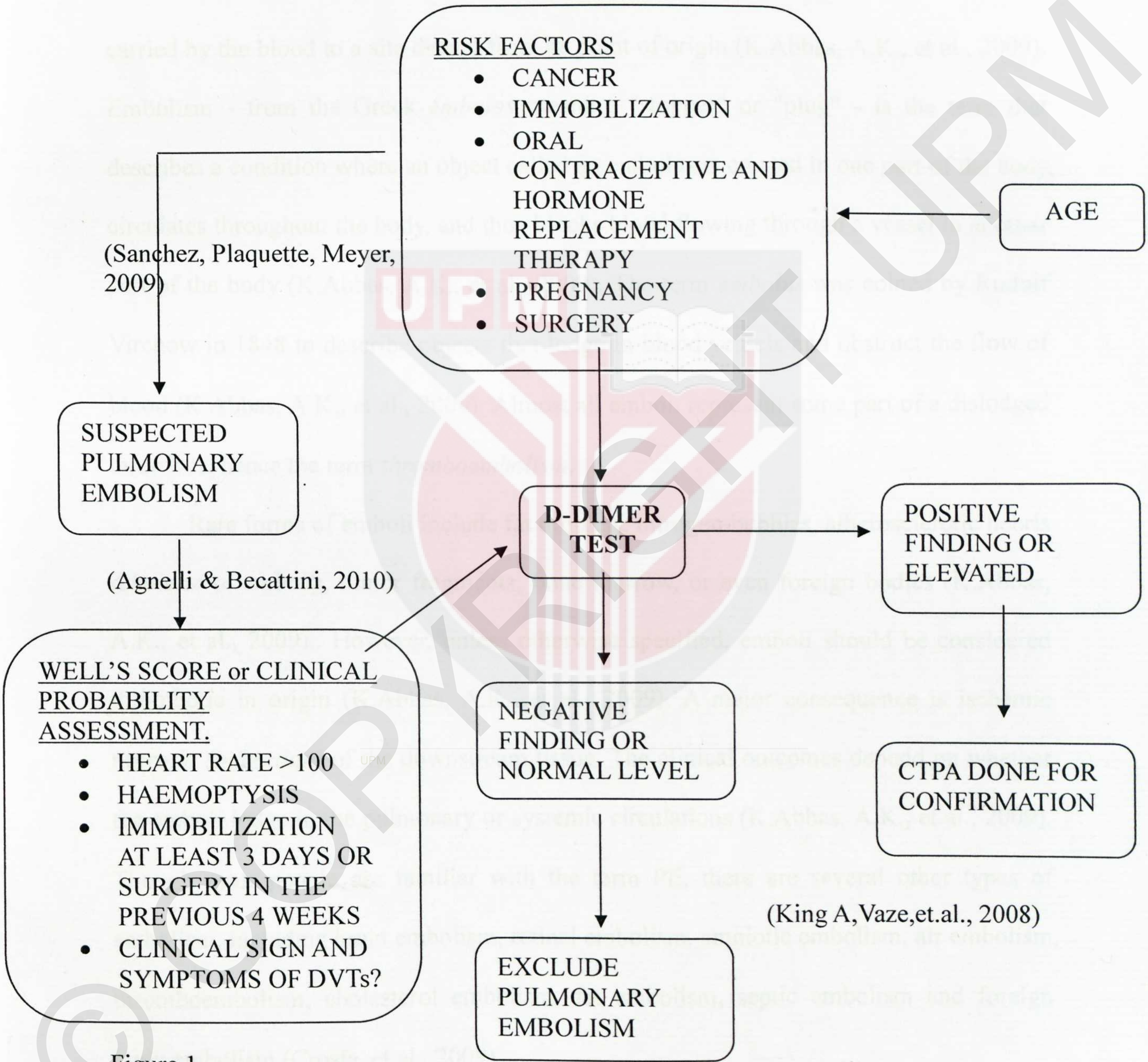


Figure 1

2.0 LITERATURE REVIEW

2.1 EMBOLISM

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin (K.Abbas, A.K., et al., 2009). Embolism - from the Greek *émbolos* meaning "stopper" or "plug" - is the term that describes a condition where an object called an embolus is created in one part of the body, circulates throughout the body, and then blocks blood flowing through a vessel in another part of the body (K.Abbas, A.K., et al., 2009). The term *embolus* was coined by Rudolf Virchow in 1848 to describe objects that lodge in blood vessels and obstruct the flow of blood (K.Abbas, A.K., et al., 2009). Almost all emboli represent some part of a dislodged thrombus, hence the term *thromboembolism*.

Rare forms of emboli include fat droplets, nitrogen bubbles, atherosclerotic debris *(cholesterol emboli)*, tumor fragments, bone marrow, or even foreign bodies (K.Abbas, A.K., et al., 2009).. However, unless otherwise specified, emboli should be considered thrombotic in origin (K.Abbas, A.K., et al., 2009). A major consequence is ischemic necrosis *(infarction)* of the downstream tissue. The clinical outcomes depend on whether the emboli lodge in the pulmonary or systemic circulations (K.Abbas, A.K., et al., 2009). Though most people are familiar with the term PE, there are several other types of embolism, including brain embolism, retinal embolism, amniotic embolism, air embolism, thromboembolism, cholesterol embolism, fat embolism, septic embolism and foreign body embolism (Crosta, et al., 2009).

2.2 PULMONARY EMBOLISM (PE)

PE has had a fairly stable incidence since the 1970s of roughly 2 to 4 per 1000 hospitalized patients in the United States, although the numbers vary depending on the mix of patient age and diagnosis (i.e., surgery, pregnancy, and malignancy all increase the risk) (K.Abbas, A.K., et al., 2009). While the rate of fatal PEs (as assessed at autopsy) has declined from 6% to 2% over the last quarter century, PE still causes about 200,000 deaths per year in the United States (K.Abbas, A.K., et al., 2009) compared with UK, where fatal PEs accounts for 2% of deaths in hospital inpatients during year 2007 and 2008 (Daneil, R.O., et al., 2011). In more than 95% of cases, PEs originate from DVTs, although it is important to realize that DVTs occur roughly two to three times more frequently than PEs (K.Abbas, A.K., et al., 2009).

2.2.1 Diagnosis of PE Globally

The current gold standard for diagnosing PE is by using conventional pulmonary angiography (Davis & C.P., 2012). In this case, a catheter is placed in a large vein in the groin and moved through the right side of the heart in to the main pulmonary artery. Dye is injected and X-rays of the pulmonary vessels is obtained (Davis & C.P., 2012). However, due to its invasive procedure, with inherent risks, requiring groin puncture, catheter manipulation into the pulmonary arteries, subsequent injection of contrast and a relatively significant dosage of radiation to the patient, the test is rarely performed in reality (Yue D., 2004).

VQ scan, or Ventilation – Perfusion scan, uses radiolabeled chemicals that identify the location of inhaled air and match it to the blood flow (Davis & C.P., 2012). If there is good airflow in the lungs but segments of the lung have poor or no blood flow, then this suggests that blood clot may be present (Davis & C.P., 2012). This test is often read as normal suggesting no pulmonary embolus is present. A low probability reading depending on the clinical situation can still have a 30% chance of PE while a high probability reading can have up to 90% chance of getting PE (Davis & C.P., 2012). The key issue related to this test is referred to as the pretest probability (Davis & C.P., 2012). This means that the clinical situation (history, physical, and other supporting tests such as D-dimer level and Well's score) may determine to some degree the likelihood of PE. If the possibility for PE is high then the VQ scan is more accurate and vice versa (Davis & C.P., 2012).

Computed Tomographic Pulmonary Angiogram (CTPA) is used increasingly in the diagnosis of PE (Davis & C.P., 2012). During the test, intravenous contrast is used to highlight the pulmonary vessels and to determine the presence of a clot in the lung. If the patient lies very still and the chest is stationary (breath hold) the quality of the scan is optimized (The Health Engine, 2013).CTPA is the most sensitive test for the diagnosis of PE and its use has been associated with a rising incidence of the condition (Anderson, D.R. et al., 2009). Diagnostic algorithms using either CTPA or V/Q scanning have proven to be comparably safe to exclude PE as a diagnosis (Davis & C.P., 2012). Negative multi-detector CTPA study results essentially ruled out the diagnosis of PE without the need to routinely exclude the presence of deep vein thrombosis (Anderson, D.R. et al., 2009).

However, the use of multi-detector CTPA is associated with significant radiation exposure that potentially increases risk of secondary malignancies (Anderson, D.R. et al., 2009). This is particularly a concern for young women given the risk of breast cancer (Anderson, D.R. et al., 2009). Excluding low risk patients for PE as defined by clinical scoring systems and D-dimer testing would enhance the yield of diagnostic testing (Anderson, D.R. et al., 2009).

2.2.2 Diagnostic of PE in UK

Patients present with signs or symptoms of PE will have an assessment of their general medical history, a physical examination and a chest X-ray to exclude other causes. When PE is suspected, physicians will proceed with two-level PE Wells score. Different aspects including clinical signs and symptoms of DVT, unlikely alternative diagnosis other than PE, heart rate, past history, presence of hemoptysis or malignancies are assessed according to Wells score. Immediate CTPA is then introduced to patients with a likely two-level PE Wells score (National Institute for Health and Care Excellent. 2012).

D-dimer test is used for patients with unlikely two-level Wells score. D-dimer is a breakdown product produced by normal clotting process (National Institute for Health and Care Excellent. 2012). It is normally present in small quantities in the blood; when increased it is suggestive of increased clotting activity in the body (The Health Engine, 2013). Immediate CTPA is introduced to patients when the result of D-dimer test is positive, even though the Wells score is low (National Institute for Health and Care Excellent. 2012).

As CTPA uses contrast media during the test, those who have allergy to contrast media, or those who have renal impairment, as well as whose risk from irradiation is high need to avoid the usage of CTPA. V/Q SPECT scan or V/Q planar scan is the alternative to CTPA in these patients (National Institute for Health and Care Excellent. 2012).

2.2.3 Clinical Practice Guidelines of PE in Malaysia

Patients suspected of PE are stratified into high-, moderate- and low-probability groups (Tun M., Sathar J., & et al., 2003). However, clinical information by itself is inadequate to confirm or exclude the diagnosis of PE (Tun M., Sathar J., & et al., 2003). Patients who are hemodynamically unstable or severely hypoxic will start on treatment and further investigations may be needed to confirm the diagnosis. Spiral CT or CTPA in common, allows direct visualization of clot within the pulmonary arteries. Pooled analysis using pulmonary angiography has shown spiral CT to have an overall sensitivity & specificity of 72% and 95% respectively. The sensitivity is higher for central PE (94%). Spiral CT can also be used to make alternative diagnoses that would explain the symptoms and signs (Tun M., Sathar J., & et al., 2003).

In stable patients with suspected PE, a DVT demonstrated clinically and confirmed on ultrasound supports the diagnosis of PE. Ventilation-perfusion (V/Q) scan or a spiral CT can be used for further confirmation. A low level D-dimer concentration (<500 ng/ml), measured by ELISA, has been shown to effectively exclude PE (Tun M., Sathar J., & et al., 2003).

2.3 PRESENTATION OF PE

The clinical presentation of PE ranges from sustained hypotension to gradually progressive dyspnea (Agnelli & Becattini, 2010). In some conditions, the patients may even be asymptomatic and PE was diagnosed during imaging procedures performed for other purposes (Agnelli & Becattini, 2010). All patients who come with new or worsening dyspnea, chest pain or sustained hypotension without underlying causes, PE should be suspected (Agnelli & Becattini, 2010). In 11% confirmed cases, patients with suspected PE have clinically apparent deep vein thrombosis (DVT) without underlying cardiopulmonary disease (Demircan, Avgencel, & et al., 2009). However, the clinical presentation of patients with suspected PE can be variable and divided into three clinical syndromes which are pulmonary infarction, acute unexplained dyspnea, and acute corpulmonale (Demircan, Avgencel, & et al., 2009).

First, the pulmonary infarction syndrome usually occurs with submassive embolism in distal branch of the pulmonary circulation which is completely occluded (Demircan, Avgencel, & et al., 2009). Patient will present with pleuritic chest pain, hemoptysis, rales, and abnormal finding on chest X-ray (Demircan, Avgencel, & et al., 2009). Next, due to the submassive PE, the acute unexplained dyspnea pattern may also present without pulmonary infarction. Usually, the chest X-ray and electrodiagram are normal but the pulse oxygen saturation often depressed (Demircan, Avgencel, & et al., 2009).. The third pattern corpulmonale syndrome, is caused by complete obstruction of 60% to 75% of pulmonary circulation during which patients will experience shock, syncope or sudden death (Demircan, Avgencel, & et al., 2009).

2.4 RISK FACTORS OF PE

Risk factors of the PE are divided into two, which are patient-related and setting related risk factors (Sanchez, Plaquette, & Meyer, 2009). Usually the patient-related risk factors are permanent while setting-related are more often temporary (Sanchez, Plaquette, & Meyer, 2009). Somehow, PE can occur without any identifiable risk factors (Sanchez, Plaquette, & Meyer, 2009). The identification of risk factors not only help in clinical diagnosis of PE, but also guides decisions on prophylactic measures and repeat testing in borderline cases (Riedel, 2001).The risk factors for PE are:

2.4.1 Pregnancy and Post-partum period

PE leads to maternal morbidity and mortality. About two-third of PE occurs during pregnancy and one-third during post-partum period (Sanchez, Plaquette, & Meyer, 2009). A recent case-control study showed that the risk of PE was higher in pregnant females compared to non-pregnant female by five-fold with the highest during third trimester of pregnancy and the first 6 weeks after delivery (Sanchez, Plaquette, & Meyer, 2009). This is due to presence of pro-thrombotic abnormalities during pregnancy, thrombosis is, which involved 30 to 50 fold of common pro-thrombotic genetic variants (Sanchez, Plaquette, & Meyer, 2009).

2.4.2 Cancer

PE is the most common complication of cancer. Patients without malignancy have lower risk compared with patients with malignancy for developing symptomatic PE (Sanchez, Plaquette, & Meyer, 2009). A large population-based study was conducted among patients diagnosed with cancer to determine the incidence of PE. About 1.6% out of, 235,149 cancer patients was diagnosed with symptomatic PE within 2 years (Sanchez, Plaquette, & Meyer, 2009). All the hematological and solid tumor types can be associated with PE but to a variable degree depending on the types of cancer (Sanchez, Plaquette, & Meyer, 2009). Research by BLOM et.al defined that the highest risk of PE related to the age and sex were among patients with hematological malignancies, lung cancer and gastrointestinal cancer for which they become significant predictor of death during the first year for all cancer types (Sanchez, Plaquette, & Meyer, 2009).

2.4.3 Hormone replacement therapy and oral contraceptive therapy

The oral contraceptive therapy is usually a combination of estrogen and progesterone. The reduction in dose of estrogen in the oral contraceptive over the time shows the reduction in risk to get PE in female (Sanchez, Plaquette, & Meyer, 2009). The patients have the highest risk of PE during the first year of use (Sanchez, Plaquette, & Meyer, 2009). Different types of progesterone have different effects on venous thrombosis with a twofold higher risk with one containing the third generation as opposed to the second generation (Sanchez, Plaquette, & Meyer, 2009). The hormone replacement therapy used for control of menopause symptoms can increase the risk by two to four folds. Females who are using oral estrogen in the first year of treatment (OR 4.0, 95% CI 2.9–5.7) has higher risk of PE compared with treatment for one year (OR 2.1, 95% CI 1.3–3.8; p=0.05) (Sanchez, Plaquette, & Meyer, 2009).

2.4.4 Obesity

Another risk factor that contributes to PE is obesity, a modifiable risk factor which is an increasing pandemic in our society (Samuel, Goldhaber, & et al., 2003). Individuals with body mass index of 25-28.9 kg/m^2 have 1.7% relative risk of getting PE (Cobanoglu, 2012). For those with the body mass index of more than 29kg/m^2, the risk is increased by 3.2 fold (Cobanoglu, 2012).

2.4.5 Immobilization.

Immobilization is an important risk factor of PE, which is commonly seen in PE patients (Cobanoglu, 2012). The long-term immobilization will result in weakening of the muscles that help with the upward flow of the blood in the leg veins become weaken (Cobanoglu, 2012). This result in blood stasis which in turn causes local accumulation of the activated platelets and clotting factors that will lead to thrombus formation (Cobanoglu, 2012).

2.5 D-DIMER

The D-dimer is an antigen which is used as an unique marker of fibrin degradation formed by the sequential action of 3 enzymes, thrombin, factor XIIIa and plasmin (S. Adam, S. Key. & et al., 2009). It can be used as an excellent marker for fibrinolytic activity that occurs in our circulation (Timothy, et al., 2012).

The D-dimer production is as shown below (Timothy, et al., 2012):

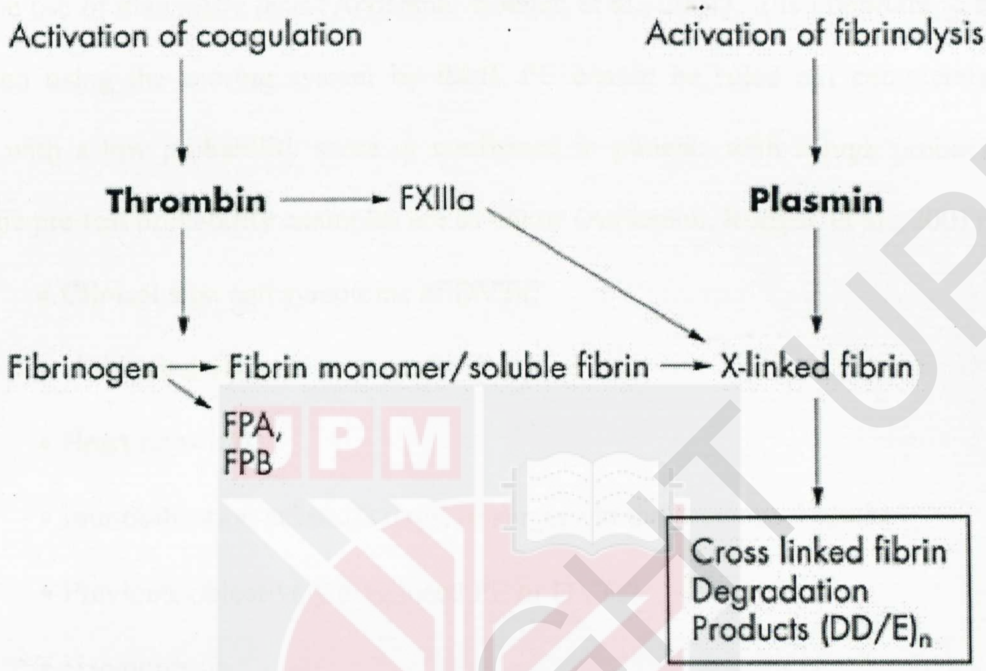


Figure 2

The D-dimer can be used as a diagnostic test in patients with suspected PE (Hatree, et al., 2010). The D-dimer assay is used in the emergency department as a 'rule out' test when pre-test probability is low for PE (Timothy, et al., 2012). The use of D-dimer level to rule out PE in patients with low or moderate clinical probability was suggested more than 10 years ago (Hatree, et al., 2010). The pre-test probability is best to assess using a clinical prediction guide (CPG) for example Well's criteria for deep vein thrombosis(DVT) or Geneva score which is for PE (Timothy, et al., 2012). The highly sensitive D-dimer assay can 'rule out' PE with proper utilization of Well's criteria (Timothy, et al., 2012).

Low/intermediate probability of PE (score 0 to 6)	-Well's criteria for PE
DVT unlikely (score 0 to 1)	-Wells' criteria for DVT

The diagnostic accuracy for PE improves when the clinical probability is estimated before the use of diagnostic tests (Anderson, Rodger, et al., 2001). It is important to note that, when using the scoring system by itself, PE cannot be ruled out completely in patients with a low probability score or confirmed in patients with a high probability score. The pre-test probability examples are as below (Anderson, Rodger, et al., 2001):

- Clinical sign and symptoms of DVTs?
- PE is first diagnosis or equally likely
- Heart rate>100
- Immobilization at least 3 days, or surgery in the previous 4 weeks
- Previous, objectively diagnosed PE or DVTs?
- Haemoptysis
- Cancer treatment currently or in the last 6 months (or receiving palliative care)
- Patients has none of these

The D-dimer test is useful in diagnosis of PE because it is non-invasive, quick and relatively inexpensive test which nowadays has become a higher priority (Hatree, et al., 2010). Moreover, the index of suspicion for PE has increased over the years which reduce its confirmed prevalence to < 20% in clinically suspected populations (Hatree, et al., 2010). D-dimer test is also more cost effective compared with angiography and spiral Computed Tomography which is useful when the patients have low D-dimer level (Hatree, et al., 2010).

The D-dimer actually has different types and is divided into two categories, which are qualitative and quantitative (Anderson, Rodger, et al., 2001). Different types of D-dimer assay have varying sensitivity and specificity as they are not standardized, but they generally have high sensitivity and negative predictive value for the presence of the thrombus in patients with low pre-test probability (Anderson, Rodger, et al., 2001). The D-dimer test however has poor positive predictive value isolated elevation is not useful since it has low specificity (Padley & S.P.G., 2002). D-dimer may also be elevated in other conditions such as pregnancy, trauma, malignancy, surgery, liver disease, severe infection and disseminated intravascular coagulation (DIC) (Padley & S.P.G., 2002). Furthermore, not all the laboratories use the same 'cut off ' points for what constitutes as positive or negative result (Anderson, Rodger, et al., 2001).

The characteristic of the available D-dimer assay will affect their performance and its use in clinical management (Anderson, Rodger, et al., 2001). For example the HemoslL DD HS assay which is the 'second generation' latex agglutination D-dimer, is highly sensitivity which has similar presentation with the ELISA assay unlike the 'first generation' latex agglutination assay. The HemoslL DD HS using the 'cut offs' of 230 ng/mL and its data are (Anderson, Rodger, et al., 2001):

Sensitivity	: 100% (95%Cl 95.4-100%)
Negative predictive value	: 100% (95% Cl 96.5-100%)
Specificity	: 46.8% (95% Cl 40.1-53.6%)

On the other study stated, D-dimer (using a cutoff of 500 μ g/L) had a diagnostic sensitivity for PE of 99.5%. Overall diagnostic specificity of D-dimer was 41%, but it was lower among older patients (Arnaud, et.al., 1997). These assays have been reported to have a negative predictive value (NPV) of 94% and a sensitivity of 97% for PE (Quinn, et al., 1999).

2.6 TYPES OF D-DIMER ASSAY

Present commercially available assays are based on particle agglutination, immunoturbidimetry and ELISA (Stago BNL).

ELISA assays are the reference standard for D-dimer quantification. These assays utilize microtiter wells coated with an antibody with a high affinity for D-dimer. Incubation with plasma resulted in the binding of any D-dimer present (Stago BNL). A labeled antibody is then added and the amount of bound labeled substance is determined by a colormetric reaction.

In spite of their high sensitivity and specificity, conventional ELISA assays are expensive, labor intensive and time consuming to perform. Therefore, they have not been practical in most clinical situations, where rapidly available results are needed.

Latex agglutination (LA) assays use latex microparticles coated with monoclonal anti-bodies specific for D-dimer. Incubation with plasma results in the formation of macroscopic agglutinates. The sensitivity of the assay is usually adjusted to 1μg/ml during the manufacture of the latex particles. Although conventional latex agglutinationassays are inexpensive and rapid to perform, numerous studies have shown that they lack the sensitivity to detect D-dimers in critical clinical situations, particularly in the detection of pulmonary embolism and acute venous thrombosis (Stago BNL).

Immunoturbidometric assays are automated microparticle assays in which a beam of monochromatic light is passed through a suspension of latex microparticles coated by covalent bonding with monoclonal antibodies specific for D-dimer. The wavelength of the light (540 nm) is greater than the diameter of the latex microparticles and so the solution of latex microparticles only slightly absorbs the light. When the plasma is added to the suspension, any D-dimer present in the sample causes the latex micro- particles to agglutinate, becoming aggregates with diameters greater than the wave- length of the light. This increases the absorbance of the light, which is measured photometrically, and proportional to the amount of D-dimer present in the test sample. These assays are cost effective, relatively rapid to perform and have sensitivity comparable to conventional ELISA (Stago BNL).

A commercially available whole blood assay for D-dimer uses a bispecific antibody specific for D-dimer and a red blood cell antigen. A drop of whole blood is incubated with the monoclonal antibody solution, causing visible agglutination of the red cells if D-dimers are present. Many reports have indicated a high sensitivity for the assay, and it is widely used in clinical settings (Stago BNL).

2.7 THE RELATION BETWEEN AGE AND D-DIMER LEVEL

The D-dimer concentration increases with age and its specificity for embolism decreases, which makes the test less useful to exclude pulmonary embolism in older patients.

Raising the cut-off value to various points between 600 μg/l and 1000 μg/l increased specificity, but this came at the cost of safety, with more false negative test results (righini, reber, & et.al., 2001).

The clinical usefulness of the new cut-off value increased significantly with age: the proportion of patients in whom pulmonary embolism could be ruled out with the new cut-off value was a third higher in patients older than 50 and almost twice as high in patients older than 70 compared with the conventional cut-off. Increasing the cut-off point to improve clinical utility did not come at the expense of safety: in the derivation and validation sets there was no difference in the false negative rate, and for the total population and for patients aged >50 years the 95% upper confidence levels were well below 3% with the new cut-off value (DROUGMA, R.A, GAL,& et.al., 2010).

A cut-off value adjusted to age combined with clinical probability greatly increased the utility of the D-dimer test for the exclusion of pulmonary embolism among older patients without reducing safety (DROUGMA, R.A, GAL,& et.al., 2010).

2.8 COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAM (CTPA)

Computed Tomography Pulmonary Angiogram (CTPA) is becoming the imaging modality for investigation of PE (Turner, 2012). It is widely available on a 24 hour basis and can identify the alternative diagnoses when PE is excluded (Turner, 2012). The advantages of using CTPA for diagnosing PE is that it is non-invasive and widely available which is particularly valuable in ill patients (Padley & S.P.G., 2012). The role of imaging in the diagnosis of PE has been increasingly dominated by CTPA which can demonstrate filling defects in segmental and sub-segmental pulmonary arteries (Crosta, 2009). Multidetector-row CTPA has been shown to have a sensitivity of 100% and a specificity of 89% in the investigation of patients with suspected PE, equivalent to or possibly higher than that of conventional pulmonary angiography.

CTPA is now used as a guideline for the management of PE in both the United Kingdom and United States of America, and patients with a good quality negative CTPA do not require further investigation or treatment for PE (Crosta, 2009). One of the advantages of CT over other imaging modalities is its ability to concurrently present information on the lung parenchyma, mediastinum and pleural spaces, in addition to that provided on the pulmonary arteries (Crosta, 2009). It can also identify other pathologies which may be associated with PE or which may be incidental as part of its interpretation process which include assessment of these structures, as well as the visible bony skeleton and upper abdomen (Crosta, 2009). For these reasons, a sample of CTPAs was reviewed to identify what types of additional pathology were identified and how frequently, in the setting of CTPA examinations for suspected PE (Crosta, 2009).

2.9 CORRELATION BETWEEN D-DIMER AND CTPA

Recent British Thoracic Society (BTS) guidelines suggest three diagnostic step to diagnose PE , pre-test probability, D-dimer test and imaging which involves CTPA (Turner, 2012). Measurement of D-dimer level can become a risk stratification for patients with suspected PE as part of a clinical algorithm (Turner, 2012). As a part of clinical algorithm, multi-detector helical CTPA will be interpreted in conjunction with pre-test probability score and D-dimer which will diagnose clinically relevant PE in 98% of all cases (Turner, 2012). However, CTPA has shown only 70% sensitivity and 91% specificity with a true positive rate ranging from 65% to 100% depending on the location of embolus. When the D-dimer level is low, it can exclude PE in patients with low clinical pre-test probability thus no need to proceed with CTPA (Turner, 2012).

In haemodynamically stable patients with low or intermediate clinical probability of PE, normal results of d-dimer testing, as measured by a sensitive enzyme-linked immunosorbent assay, will avoid unnecessary further investigation (Agnelli & Becattini, 2010).

In such patients, if anticoagulant treatment is not given, the estimated 3-month risk of thromboembolism is 0.14% (95% confidence interval [CI], 0.05 to 0.41). If the patients are haemodinamically stable but with high clinical probability of PE or with high D-dimer level should undergo CTPA (Agnelli & Becattini, 2010).

In patients with negative findings on CTPA anticoagulation therapy should be commenced as the incidence of thromboembolic events will increase 1.5% in 3 months, PE incidence for high D-dimer level is 1.5% also while about 0.5% in patients with normal D-dimer level.

The negative predictive value of CTPA has been marginally improved from 95 to 97% (Agnelli & Becattini, 2010).

3.0 METHODOLOGY

3.1 STUDY LOCATION

This study was conducted in Department of Imaging, Hospital Serdang, located in Serdang, Selangor, Malaysia.

3.2 STUDY DESIGN

Cross sectional study was used in our research.

3.3 STUDY DURATION

This study was divided into two phases: which phase one was (from 25 March 2013 until 22 April 2013) which includes preparation of research proposal, presentation of proposal and acquiring ethics approval, while the second phase (from 15 July 2013 until 5 September 2013) which includes data collection and final preparation of the research.

3.4 SAMPLING

3.4.1 Study population

Patients with suspected PE who underwent CTPA will be selected as participants. The data are taken at the time of research without any intervention or follow-up.

3.4.2 Sampling population

Inclusion criteria : Patients with age ranging from 20 and above with suspected PE.

Exclusion criteria: Patients without D-dimer assay.

3.4.3 Sampling frame

All the patients with suspected PE who underwent CT pulmonary angiogram with the age of 21 and above from December 2010 until June 2013 at Hospital Serdang.

3.4.4 Sampling unit

A suspected PE patients based on medical record who fulfill our inclusion criteria, and underwent CTPA at Imaging Department in Hospital Serdang.

3.4.5 Sample size

$$\text{Sample size, } n = \frac{z^2 P (1-P)}{d^2}$$

$$n = \frac{(1.96)^2 (0.07) \times (1-0.07)}{(0.05)^2}$$

$$= 100$$

n = sample size

z = standard score (1.96)

P = prevalence of the occurrence of pulmonary embolism correlating with D-dimer level(7%)(N.Zairul.YA Gul.2003)

d = margin of error =0.05 (5%)

To account for missing information, we added 10% to the calculation above, so the total subjects in this research are 110.

3.4.6 Sampling method

Convenient sampling method was used to choose samples from the list of medical records of suspected PE who underwent CTPA that matched our inclusion and exclusion criteria.

A standardized checklist or pro forma, which contains all the variables, was used prior to data collection.

Statistical Package for Social Science(SPSS) version 21 was used to analyze the selected data.Descriptive statistics were used to summarize the data regarding socio-demographic characters whereas statistical statistic were used to calculate the sensitivity and specificity of D-Dimer assay. Mcnemar test were used to determined the relation D-dimer level and CTPA result, Well's score and Pulmonary Embolism and correlation between D-Dimer results and CTPA results with different Well's score which stated in the specific objectives.

3.5 INSTRUMENTS AND DATA COLLECTION

3.5.1 Instrument/Questionnaire

Pro Forma which contain basic information of patients and risk factor based on Well's criteria.

3.5.2 Data collection technique

Review the medical records of suspected PE patients that fulfill our criteria from 'patients and laboratory system' and record the detail of patients through pro forma.

3.5.3 Quality control

A standardized pro forma was used to obtain data in each subject.

Our supervisor had revised the pro forma before it is used.

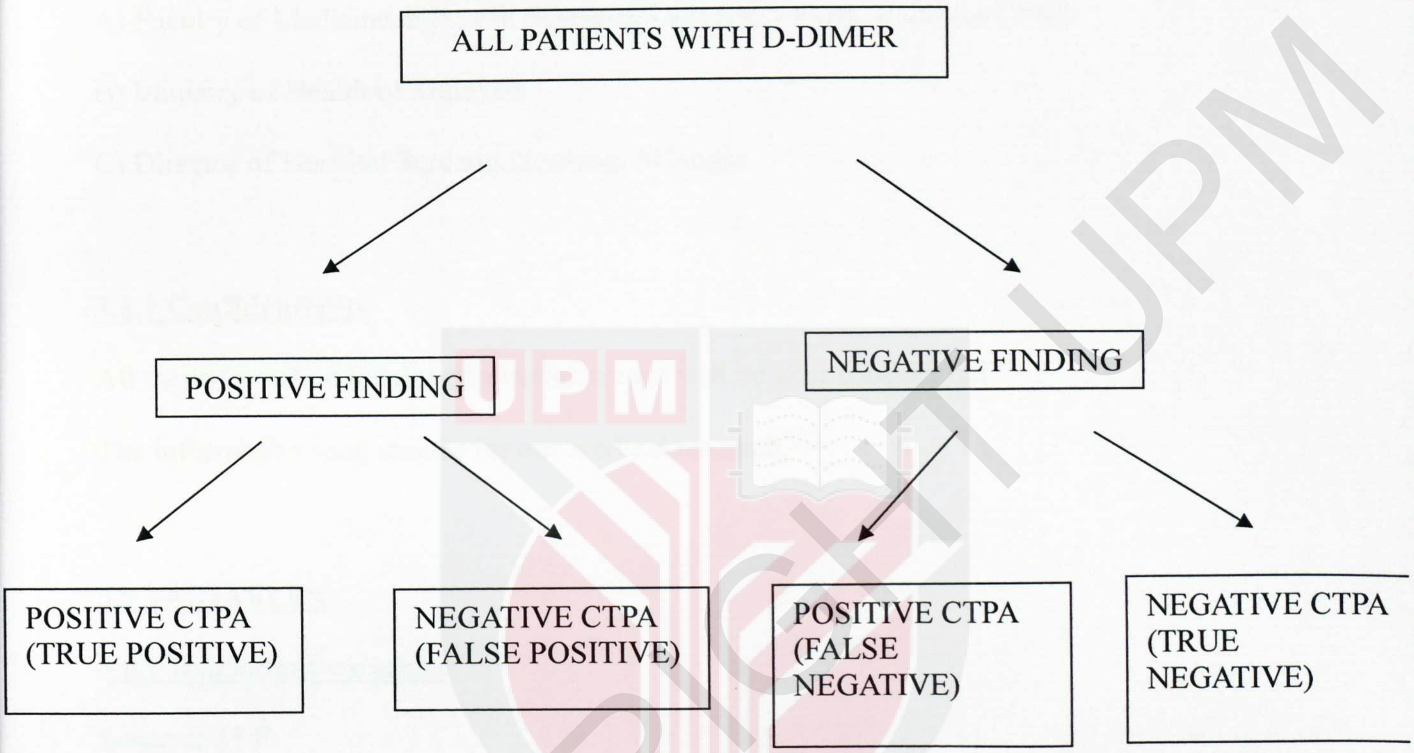
3.6 DATA ANALYSIS

3.6.1Statistical analysis

Sensitivity(true positive/[true positive+false negative]), specificity(true negative/[true negative+false positive]) and accuracy(true positive+true negative) were calculated using reference standard.

Sensitivity	: true positive/(true positive+false negative)
Predictive value of positive test	: true positive/(true positive+false positive)
%False negative	: [false negative/(false negative +true positive)]x100
Specificity	: true negative/(true negative+false positive)
Predictive value of negative test	: true negative /(true negative+false negative)
%False positive	: [false positive/(false positive+true negative)]x100

In our analysis, we can ensure that if D-dimer has high sensitivity and specificity with a positive result in suspected PE, we can proceed immediately to CTPA for confirmation. While, when we are sure that D-dimer assay has high negative predictive value (NPV), if patients has negative result of D-dimer , we can exclude PE from the differential diagnoses and no need to proceed with CTPA. The data analysis is drawn as below:



3.7 EXPECTED OUTCOME

1. To establish D-dimer test as the most appropriate test to exclude low risk or unlikely PE from CTPA.

2. Information regarding sensitivity and specificity of D-dimer test would significantly and appropriately change the management in the majority of suspected PE patients.

3.8 STUDY ETHIC

Ethical approval was obtained from

A) Faculty of Medicine & Health Sciences, University Putra Malaysia(UPM)

B) Ministry of Health of Malaysia

C) Director of Hospital Serdang, Serdang, Selangor

3.8.1 Confidentiality

All the information obtained from the subject will be kept confidential.

The information used strictly for our medical research.

3.9 VARIABLES

3.9.1 Dependant variables

Suspected PE

CT Pulmonary Angiogram

3.9.2 Independant variables

D-dimer level

Age

Risk factors

Well's score

3.10 DEFINITION OF TERMS

Pulmonary embolism (PE): is a blockage of one of the arteries (blood vessels) in the lungs that usually due to a blood clot. A PE can be in an artery in the center of the lung or one near the edge of the lung. The clot can be large or small and there can be more than one clot.It is also a potentially life-threatening complication from deep vein thrombosis due to the detachment (embolization) of a clot that travels to the lungs.

Deep Vein Thrombosis(DVT): is a blood clot that forms in a vein deep inside a part of the body. It mainly affects the large veins in the lower leg and thigh. Blood clots occur when blood thickens and clumps together. Most deep vein blood clots occur in the lower leg or thigh. They can also occur in other parts of the body. A blood clot in a deep vein can break off and travel through the bloodstream. The loose clot is called an embolus. It can travel to an artery in the lungs and blocks blood flow.

D-dimer level: A fragment produced during the degradation of a clot. The D here stands for domain. Dimer indicates two identical units, in this case two identical domains. D-dimer results from complete breakdown of the clot. Monoclonal antibody to the D-dimer fragment provides the basis for the main methods of detecting it. The presence of D-dimers in the blood is a reliable clue that clotting has begun. It used as a clinical marker for PE (blood clot in the lung) or deep venous thrombosis (DVT).

Computed Tomography Pulmonary Angiogram(CTPA): is a medical diagnostic test that employs computed tomography to obtain an image of the pulmonary arteries. Its main use is to diagnose PE. It is a preferred choice of imaging in the diagnosis of PE due to its minimally invasive nature for the patient, whose only requirement for the scan is an intravenous line.

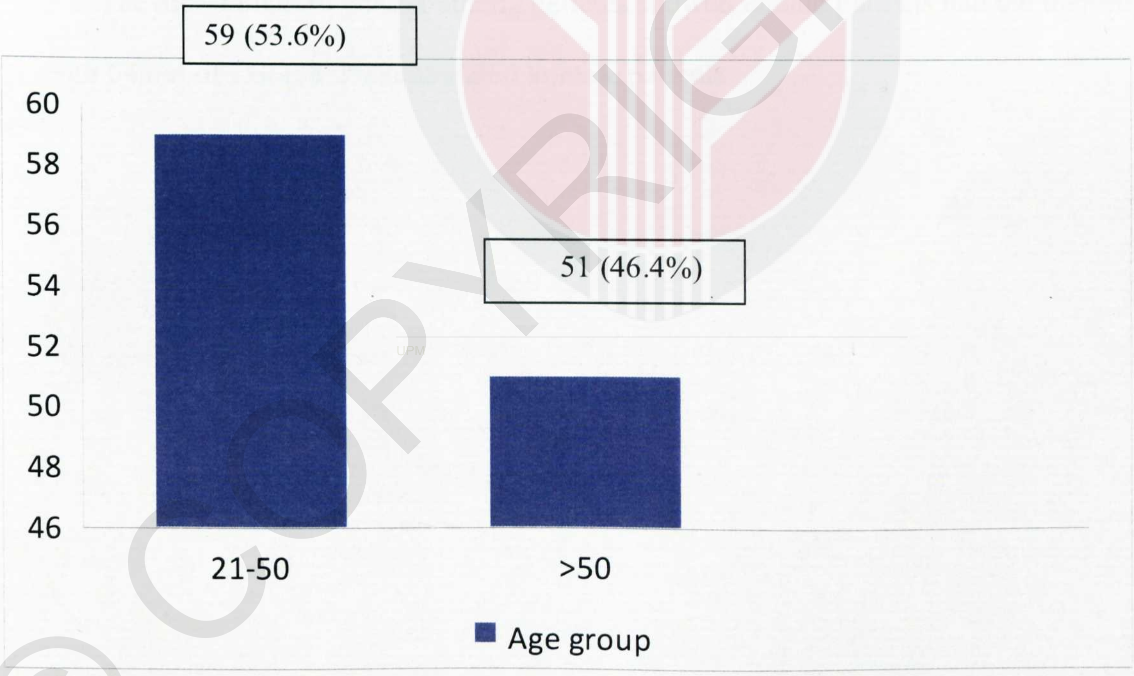
CHAPTER 4 : RESULT

4.1 RESPONSE RATE

There were altogether 110 patients with suspected with Pulmonary Embolism who underwent CT Pulmonary Angiography included in the study. As we use the secondary data by pro forma for data collection, hence all the 110 subjects were included in this study.

4.2 SOCIO DEOGRAPHIC

We analyzed data from a total of 110 patients with suspected Pulmonary Embolism (PE) who underwent CTPA from December 2010 to June 2013.



The data we obtained comprised of majority from age group 21-50 (53.6%) compared to age group >50.

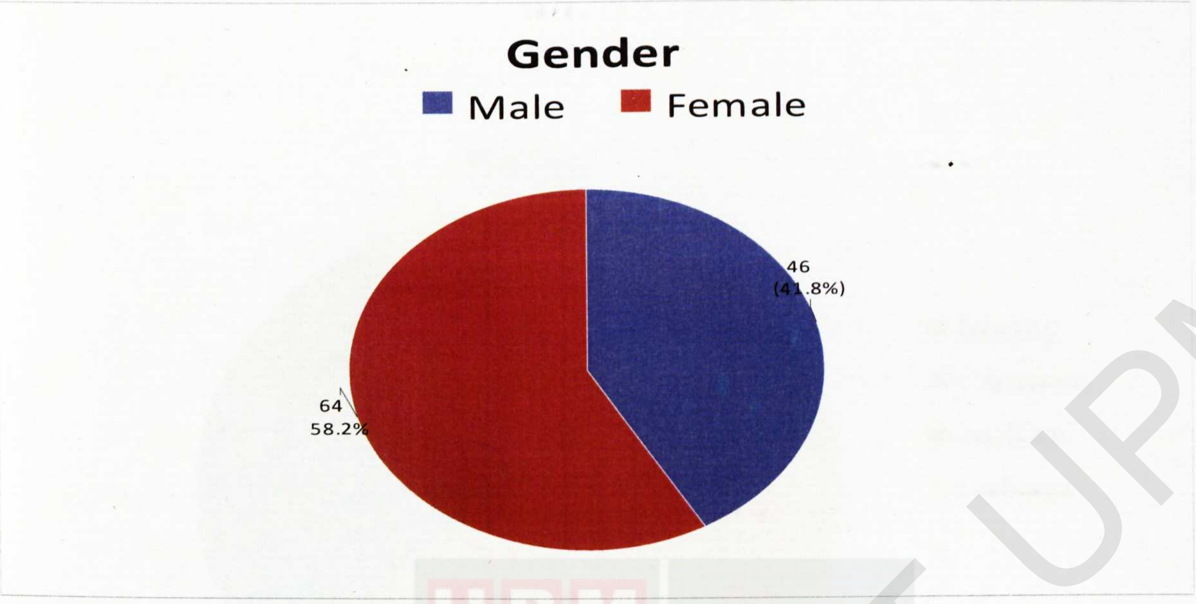


Figure 4.2.2 Distribution of gender among suspected PE patients.

The distribution of gender among patients showed female patients had the majority with 64 out of 110 (58.2%) compared to male patients.

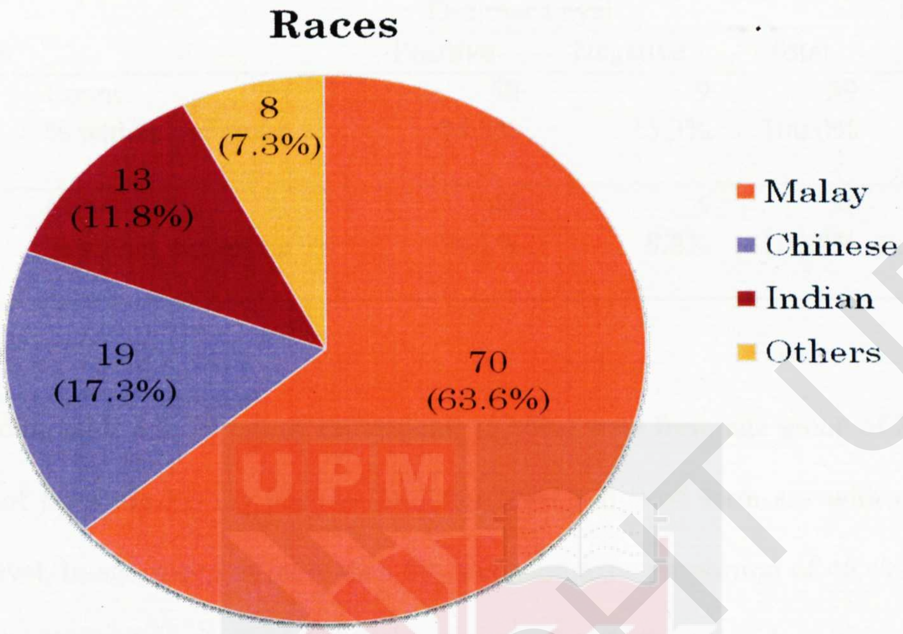


Figure 4.2.3 Distribution of races among suspected PE patients.

For the ethnicity, there were three different group of races included in this study; Malay, Chinese, Indian and others. Malay patients accounted for 63.6% in our studies compared to other races.

4.3 The relation between D-dimer level in patients of different age group

Age Group		D-dimer Level Positive	D-dimer Level Negative	Total	P-value
21-50	Count	50	9	59	0.392
	% within age group	84.7%	15.3%	100.0%	
>50	Count	46	5	51	
	% within age group	90.2%	9.8%	100.0%	

Table 4.3

According table 4.3, 59 out of 110 patients (53.6%) were from age group of 21 to 50 where 50 of them are having positive D-dimer level and 9 of them are with negative D-dimer level. In age group of more than 50, it constituted a proportion of 46.4% among 110 patients. While 46 out of 51 (90.2%) were positive D-dimer level while the rest of them were of negative D-dimer level. Since the p-value of the data is 0.392, which is >0.05, the result is not significant.

4.4The relation between gender and D-Dimer results in patients suspected PE.

			D-dimer Level			P-value
			Positive	Negative	Total	
Gender	Male	Count	44	2	46	0.001
		% within gender	95.7%	4.3%	100.0%	
	Female	Count	52	12	64	
		% within gender	81.3%	18.8%	100.0%	
Total		Count	96	14	110	
		% within gender	87.3%	12.7%	100.0%	

Table 4.4

From table 4.4, for the findings between gender and D-dimer level, 96 out of 110 patients (87.3%) from both genders have positive D-Dimer level. 95.7% of males having positive D-dimer level (>0.5μg/mL) whereas only 81.3% of females having positive D-dimer level. Since the p - value of the data is < 0.05 the result is significant. Thus, there is an association between gender and D-Dimer results.

4.5 The determination of D-Dimer level in patients blood of positive CTPA and sensitivity and specificity of D-Dimer assay in excluding PE.

			Pulmonary Embolism			P-value
			Present	Absent	Total	
D-dimer Level	Positive	Count	19	77	96	0.001
		% within D-dimer level	19.8%	80.2%	100.0%	
		% within Pulmonary Embolism	90.5%	86.5%	87.3%	
	Negative	Count	2	12	14	
		% within D-dimer level	14.3%	85.7%	100.0%	
		% within Pulmonary Embolism	9.5%	13.5%	12.7%	
Total		Count	21	89	110	
		% within D-dimer level	19.1%	80.9%	100.0%	
		% within Pulmonary Embolism	100.0%	100.0%	100.0%	

Table4.5

21 out of 110 patients (19.1%) were diagnosed with Pulmonary Embolism (PE) after being scanned using CTPA . Between D-dimer level and CTPA result, only 19 out of 96 patients who have positive D-dimer result diagnosed with Pulmonary Embolism (PE). While, 12 out of 14 patients have negative D-dimer result and negative PE that indicate true negative results. Meanwhile, patients who have false positive results account for 77 out of 96 and patients with false negative result only 2 out of 14. Sensitivity of D-dimer, calculated from the formula below is 90.48%. While D-dimer has a specificity of 13.5% from the data obtained. While the predictive value of positive test was 19.8% and predictive value of negative test was 85.7%. The calculation is shown as below:

Sensitivity : $\frac{\text{True positive}}{\text{True positive + false negative}}$

: $\frac{19}{19 + 2}$ X 100

: 90.48%

Specificity : $\frac{\text{True negative}}{\text{True negative + false positive}}$ X 100

: $\frac{12}{12 + 77}$ X 100

: 13.5%

Predictive value of positive test : $\frac{\text{true positive}}{\text{True positive + false positive}}$ x 100

: $\frac{19}{19+77}$ x 100

: 19.8%

Predictive value of negative test : $\frac{\text{true negative}}{\text{True negative + false negative}}$ x 100

: $\frac{12}{12 + 2}$ x 100

: 85.71%

Since the p - value of the data is 0.001 which is < 0.05, the result is significant. Thus, there is an association between D-dimer results and Pulmonary Embolism.

4.6 The relation between different D-Dimer level and result of CT Pulmonary Angiogram.

			Pulmonary Embolism			P-value
			Present	Absent	Total	
D-dimer Level	0.00	Count	2	12	14	0.041
		% within D-dimer level	14.3%	85.7%	100.0%	
	0.50	Count	4	4	8	
		% within D-dimer level	50.0%	50.0%	100.0%	
	1.00	Count	4	6	10	
		% within D-dimer level	40.0%	60.0%	100.0%	
	2.00	Count	3	21	24	
		% within D-dimer level	12.5%	87.5%	100.0%	
	4.00	Count	1	20	21	
		% within D-dimer level	4.8%	95.2%	100.0%	
	8.00	Count	7	26	33	
		% within D-dimer level	21.2%	78.8%	100.0%	
Total		Count	21	89	110	
		% within D-dimer level	19.1%	80.9%	100.0%	

Table 4.6

From table 4.6,for a detailed correlation between D-dimer levels and CTPA result, the total of patients distributed in every D-Dimer levels were about the same except for those with high D-dimer level of >8μg/mL was slightly higher than other levels (33.3%). However, there is no correlation of the D-dimer levels to that of positive pulmonary embolism since the p-value was 0.041.

4.7The relation between Well's score and occurrence of Pulmonary Embolism

			Pulmonary Embolism			P-value
			Present	Absent	Total	
Well's Score	Positive	Count	15	16	31	0.052
		% within Well's Score	48.4%	51.6%	100.0%	
	Negative	Count	6	73	79	
		% within Well's Score	7.6%	92.4%	100.0%	
Total		Count	21	89	110	
		% within Well's Score	19.1%	80.9%	100.0%	

Table 4.7

Between Well's score and CTPA result, 15 out of 31 patients who have positive Well's score (>4.5) were diagnosed with PE. In the meantime, for those who have negative Well's score, only 6 out of 79 patients have diagnosed with PE, which indicate a false negative result. While patients who have negative Well's score (< 4.5) and negative PE account 73 out of 79 (92.4%) which indicates true negative results. Since the p - value of the data is 0.052, which is > 0.05, the result is not significant. Thus, there is no association between Well's score and Pulmonary embolism.

4.8The correlation between D-Dimer results and CTPA results with different Well's score.

			Pulmonary Embolism Present	Pulmonary Embolism Absent	Total	P-value
Well's Score + D-dimer Level	-ve Well's Score -ve D-dimer Level	Count	0	10	10	0.001
		% within Well's Score + D-dimer Level	0.0%	100.0%	100.0%	
		% within Pulmonary Embolism	0.0%	11.2%	9.1%	
	-ve Well's Score +ve D-dimer Level	Count	6	63	69	
		% within Well's Score + D-dimer Level	8.7%	91.3%	100.0%	
		% within Pulmonary Embolism	28.6%	70.8%	62.7%	
	+ve Well's Score -ve D-dimer Level	Count	2	2	4	
		% within Well's Score + D-dimer Level	50.0%	50.0%	100.0%	
		% within Pulmonary Embolism	9.5%	2.2%	3.6%	
	+ve Well's Score +ve D-dimer Level	Count	13	14	27	
		% within Well's Score + D-dimer Level	48.1%	51.9%	100.0%	
		% within Pulmonary Embolism	61.9%	15.7%	24.5%	
Total		Count	21	89	110	
		% within Well's Score + D-dimer Level	19.1%%	80.9%	100.0%	
		% within Pulmonary Embolism	100.0%	100.0%	100.0%	
		% of Total	19.1%%	80.9%	100.0%	

Table 4.8

In condition when both Well's score and D-dimer result are negative, there is no PE found on CTPA. Thus, for low risk patients (negative Well's score), predictive value of negative value for D-dimer is 100%. Also, for those positive D-dimer results in low risk patients, the sensitivity for D-dimer is 100%. 48.1% of the patients are diagnosed with PE when both Well's score and D-dimer result are positive. In high risk patients, the sensitivity of D-dimer is 86.67%, which is lower than sensitivity of D-dimer that without combination of Well's score. The p - value of the data is 0.001, which is < 0.05, the result is significant. Thus, there is an association between combination of Well's score and D-dimer results with Pulmonary embolism.

From the table above, concordance value was calculated as below:

Low risk group:

Sensitivity of d-dimer Combined Well's score : $\frac{\text{true positive}}{\text{True positive + false negative}} \times 100$

: $\frac{6}{6+0} \times 100$

: 100%

Specificity of d-dimer Combined Well's score : $\frac{\text{true negative}}{\text{True negative + false positive}} \times 100$

: $\frac{10}{10+63} \times 100$

: 13.7%

Predictive value of positive test : $\frac{\text{true positive}}{\text{True positive + false positive}} \times 100$

: $\frac{6}{6+63} \times 100$

: 8.7%

Predictive value of negative test : $\frac{\text{true negative}}{\text{True negative + false negative}} \times 100$

: $\frac{10}{10+0} \times 100$

: 100%

High risk group:

Sensitivity of d-dimer Combined Well's score :

$$\frac{\text{true positive}}{\text{True positive + false negative}} \times 100$$

$$: \frac{13}{13+2} \times 100$$

: 86.67%

Specificity of d-dimer Combined Well's score :

$$\frac{\text{true negative}}{\text{True negative + false positive}} \times 100$$

$$: \frac{2}{2+14} \times 100$$

: 12.5%

Predictive value of positive test :

$$\frac{\text{true positive}}{\text{True positive + false positive}} \times 100$$

$$: \frac{13}{13+14} \times 100$$

: 48.15%

Predictive value of negative test :

$$\frac{\text{true negative}}{\text{True negative + false negative}} \times 100$$

$$: \frac{2}{2+2} \times 100$$

: 50%

5.0 DISCUSSION AND CONCLUSION

The diagnosis or exclusion of pulmonary embolism depends on the combination of clinical suspicion and algorithms based on clinical pre-test probability for the event (Agnelli & Becattini, 2010). The D-dimer assay is used in the emergency department as a 'rule out' test when pre-test probability is low for PE (Timothy, 2012). D-dimer is a degradation product of fibrinogen by plasmin and is a great marker for fibrinolytic activity that occurs in our circulation (Timothy, 2012).

Today, highly sensitive D-dimer assays are used, however has poor positive predictive value since the test has low specificity (Padley & S.P.G., 2002). There are already reports about the different sensitivity of D-dimer in different age groups and of different risk factors, and it seems that d-dimer assay has better sensitivity and specificity when combined with clinical pre-test probability, well's score (K.Abbas, A.K., & et.al., 2009).

In this research, we tried to evaluate the D-dimer assay used in Hospital Serdang as a 'rule out' test in patients suspected with pulmonary embolism, in an attempt to reduce unnecessary imaging studies being done.

The sensitivity of D-Dimer assay in this study was 90.48% while the specificity of D-Dimer assay was 13.5%. From the result, it was also shown that the positive predictive value for D-Dimer assay was 19.8% while the negative predictive value was 85.7%. The p-value from the result shows 0.001, which is significant. From the study done by Quinn

DA,et.al., it showed that the sensitivity of D-dimer assay was 97-100% while the specificity of D-Dimer assay was 19-29%. Their study also stated the negative predictive value of D-Dimer assay was 94% (Quinn,Fogel,et.al.,1999). Their study showed the significant correlation between D-Dimer and occurrence of PE. The most sensitive D-dimer tests are the enzyme-linked immunosorbent (ELISA) assays. The initial ELISA membrane plate D-dimer assays had sensitivities of over 95% (Anderson,D.R,& et.al,2009).

Although the sensitivity of the d-dimer in our work is lower than the sensitivity of previous study (90.48% versus 97-100%), it still preserves quite high sensitivity. However, looking into the specificity of the d-dimer, it has a mere 13.5% which is much lower than 19-29% from previous work. This might be due to various risk factors that increased the d-dimer level of the patients such as pregnancy that can be seen in most female patients. The negative predictive value in our study was 85.71% while their study stated 94% but the NPV for our study still preserved high result. This is because D-dimer assays were most useful in patients without surgery within 3 month, without active malignancy, and with normal liver function which it give very poor specificity of the tests in these conditions (Quinn,Fogel,et.al.,1999).

Furthermore, when looking at the combination of Well's score and D-dimer level—those at low risk group—we can see that the sensitivity of the D-dimer assay is 100%, with a negative predictive value of 100% as well. Well's score is a pretest probability, by clinician, then when well's score is low, it suppose that the patient is probably free from PE, so this enhance the d-dimer test when combine together. This explains that, we can safely exclude low risk patients with suspected pulmonary embolism while having a negative D-dimer result. The p-value from the result shows 0.001, which is significant. We believe that until the high negative predictive value of a negative D-dimer assay shown in our study can be confirmed by prospective trials, imaging should be performed in patients with a high pretest probability for pulmonary embolism regardless of the D-dimer results.

Based on the study done by Geert-Jan,Petra M,et.al., the sensitivity and specificity of a score of ≤4 combined with a negative D-dimer test result were 94.5% (86.6% to 98.5%) and 51.0% (46.7% to 55.4%), respectively. In the patients with a Wells score of <2, the D-dimer test result was also negative. In their study, the patients at very low risk, two cases of pulmonary embolism were observed, yielding a failure rate of 1.2% (0.1% to 4.2%) and an efficiency of 28.1% (168/598). The sensitivity and specificity of this strategy were 97.3% (90.5% to 99.7%) and 31.

Almost half (45.5%) of 598 patients in their study with suspected pulmonary embolism in primary care were classified as low risk of the condition on the basis of a score of ≤4 on the Wells pulmonary embolism rule combined with a negative point of care D-dimer test result. Pulmonary embolism was observed in 1.5% of these patients (Geert-Jan,Petra M,et.al.,2012). These results are in accordance with studies done in secondary care, as documented in a recent meta-analysis on the performance of several clinical decision rules, including the Wells rule combined with both a qualitative and a quantitative D-dimer test (Geert-Jan,Petra M,et.al.,2012).

Still more: when looking in the subgroup of d-dimer levels—of those who were not diagnosed with pulmonary embolism— 75.3% of them are from high D-dimer levels of more than 2ng/ml. This high D-dimer level group with negative pulmonary embolism findings maybe results from the relation between age and D-dimer, especially those older than 50 years old. The study done by Drouma,Grégoire,et.al., clinical usefulness of the new cut-off value increased significantly with age: the proportion of patients in whom pulmonary embolism could be ruled out with the new cut-off value was a third higher in patients older than 50 and almost twice as high in patients older than 70 compared with the conventional cut-off.

Increasing the cut-off point to improve clinical utility did not come at the expense of safety: in the derivation and validation sets there was no difference in the false negative rate, and for the total population and for patients aged >50 years the 95% upper confidence levels were well below 3% with the new cut-off value. The age adjusted D-dimer cut-off point, combined with clinical probability, greatly increased the proportion of older patients in whom pulmonary embolism could be safely excluded (DROUMA, R.A, GAL, & et.al., 2010).

When compared with previous works, in our study, the relation of age group and d-dimer level is not significant. This might be because most of the patients of more than 50 years old had underwent CTPA under suspicion of pulmonary embolism due to high D-dimer level. However, the d-dimer level will usually increase in elderly (DROUMA, R.A, GAL, & et.al., 2010). Thus, without the use of adjusted cut off point for elderly, almost every elderly will proceed with CTPA, resulting in the average prevalence of pulmonary embolism among the age groups (DROUMA, R.A, GAL, & et.al., 2010).

CONCLUSION

The null hypothesis was rejected. There is an association between D-Dimer level and occurrence of PE in suspected PE patients. The data appears to support the use of a quantitative d-dimer assay as a 'rule out' test in evaluation for pulmonary embolism when the clinical probability of the presence of pulmonary embolism is low. The negative predictive value and sensitivity when combine the D-Dimer and Well's score were 100% for this low risk group. Because of the small sample size, the d-dimer assay is not recommended as a first-line test in the evaluation of patients at high risk.

We conclude that a negative D-dimer assay by the rapidly performed and inexpensive latex agglutination assays is a clinically useful tool in excluding the presence of pulmonary embolism in patients with low Well's score result within our population size. Although our study showed that a negative D-dimer should never have gone for further investigation of pulmonary embolism if the clinical suspicion for pulmonary embolism is low (Well's score <4.5) the latex agglutination D-D should undergo further prospective clinical trials to properly support our study.

LIMITATIONS

There were some problems identified when conducting our study which might influence our study outcomes.

We collected patients' data from the medical record, as we had not approached the patients ourselves. We only took the Well's score criteria based on the risk factors that had been recorded. The clinician also did not access patients who suspected with Pulmonary Embolism with the Well's score criteria.

Besides that, the level of D-Dimer level recorded were not the exact value which they only written it in range such as <0.5, >0.5, >1.0 and others. Thus, we cannot extract the value to find the cutoff point in where the occurrence of PE is higher.

Another limitation that we faced in this study was financial limitation. Because of this limitation, the researchers could not travel and look at the data in other nearby hospitals. Thus, our study population was based only in one hospital that is Hospital Serdang. The data from Hospital Serdang might not be similar to data in those nearby hospitals. So the data that we had from this study could not be extrapolated to the general population.

RECOMMENDATION

The sample size of the study should be more than ours in the next study and increase the time duration of the studies in collecting data for example from 2008.until 2013.This will not only give better but more accurate result as bigger samples can represent whole population.

From our findings, the high risk group for PE (Well's score >4.5) has no need to have D-Dimer test but immediately proceed to CT Pulmonary Angiogram as it will prolong time for actual diagnosis and incur more expenses. While for the low risk group for PE (Well's score <4.5), a negative D-Dimer result will exclude PE thus there is no need to proceed with CT Pulmonary Angiogram. This in turn will save the patients from unnecessary radiation and contrast adverse reaction, reduce the expenses in performing CTPA (which is much higher than acquiring D-Dimer level) and save time in patients management.

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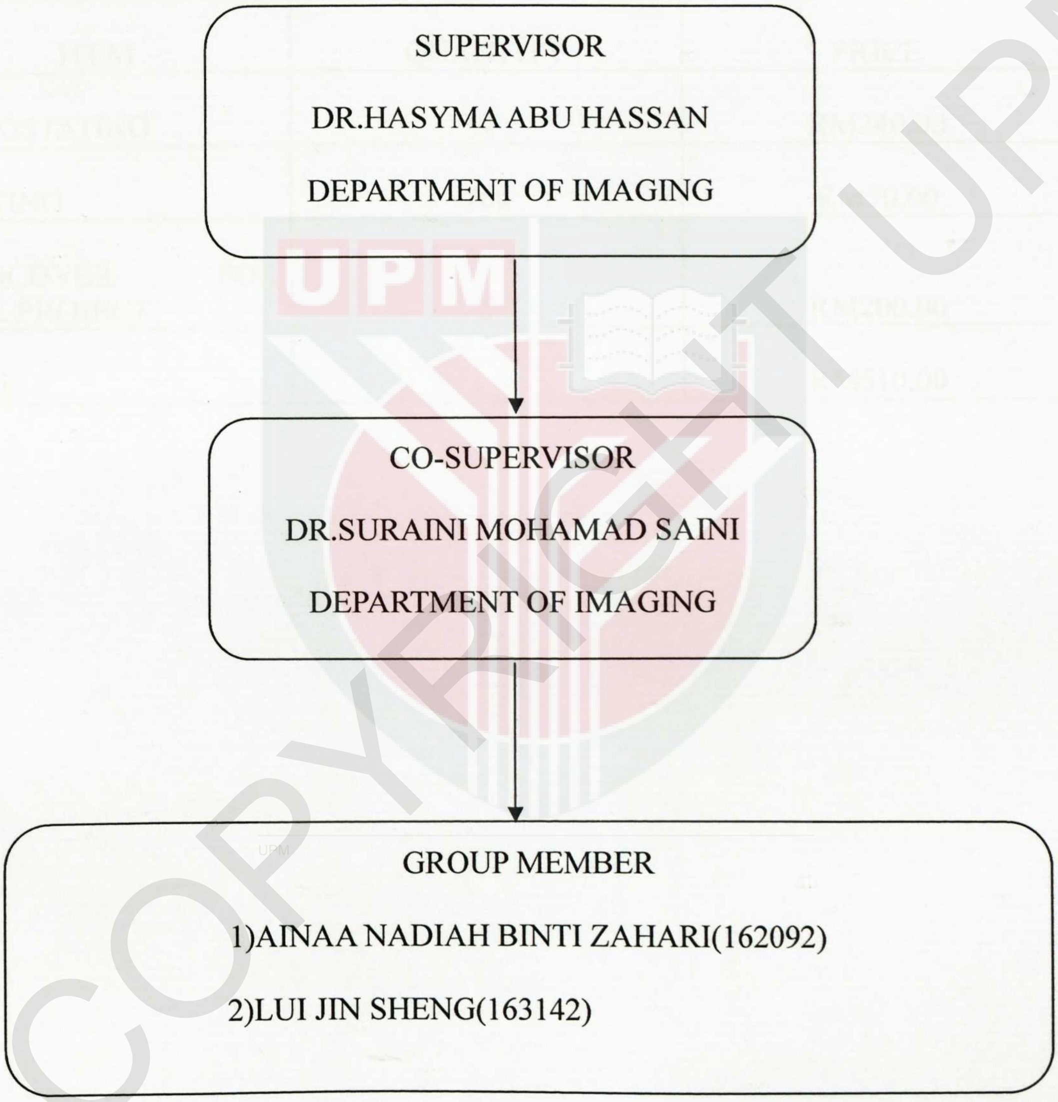
APPENDIX 1

GANNT CHART

Months / Events	**March**	**April**	**May**	**June**	**July**	**August**	**September**
Writing proposal	✓	✓					
Presentation		✓					
Preparing ethical approval to organisation		✓	✓				
Data collection				✓	✓	✓	
Data analysis						✓	
Data Analysis Presentation						✓	
Report writing							
Final Presentation and submission final report						✓	✓

APPENDIX 2

MEMBER GROUP ORGANISATION



APPENDIX 3

BUDGET PLANNING

ITEM	QUANTITY	PRICE
PHOTOSTATING	-	RM240.00
PRINTING	700	RM70.00
HARDCOVER FOR FINAL PROJECT	5	RM200.00
TOTAL		RM510.00

PRO FORMA

STUDY: Evaluation of D-Dimer assay as a 'rule out' test for patients suspected with Pulmonary Embolism who underwent CT Pulmonary Angiogram at Hospital Serdang in 2010 until 013.

PROFILE:

SD NUMBER:

DATE OF ASSESSMENT:

AGE:

RACES:

SEX: FEMALE ☐ MALE ☐

D-DIMER LEVEL: POSITIVE ☐ NEGATIVE ☐

LEVEL:.......................

CTPA DONE: YES ☐ NO ☐

PULMONARY EMBOLISM :

RISK FACTOR BASED ON WELL'S CRITERIA:

CLINICAL FEATURE	POINTS	PATIENTS SCORE
1.Clinical Signs and Symptoms of DVT? (minimum leg swelling and pain with palpation of deep vein)	3	
2.Pulmonary Embolism is the first diagnosis or equally likely	3	
3.Heart rate >199 beats per minute	1.5	
4.Immobilization for more than 3 days or surgery in the previous 4 weeks	1.5	
5.Previous,objectively diagnosed Pulmonary Embolism or DVTs?	1.5	
6.Hemoptysis	1	
7.Malignancy (on treatment ,treated in the last 6 months,or palliative)	1	
8.Pregnancy	1	
9.Patients has none of these	None present	

CLINICAL PROBABILITY SIMPLIFIED SCORE:

PULMONARY EMBOLISM LIKELY	MORE THAN 4.5	
PULMONARY EMBOLISM UNLIKELY	4.5 POINTS OR LESS	

Attachment 1

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN YANG MELIBATKAN MANUSIA (JKEUPM)
UNIVERSITI PUTRA MALAYSIA

Research title	:	**The Evalution Of D-Dimer Assay As A Rule Out Test For Patients Suspected With Pulmonary Embolism Who Underwent CTPA At Hospital Serdang In 2011-2013**
Study Site	:	**Hospital Serdang**
JKEUPM Ref No.	:	**FPSK_Mei (13)50**
Principal Investigator	:	**Ainaa Nadiah Zahari & Lui Jin Sheng**
Supervisor	:	**Dr. Hasyma Abu Hassan**

Documents received and reviewed with reference to the above study:

1. Ethics Application Form, received on 20/5/2013.
2. Proposal, Version English.

The University Research Ethics Committee, Universiti Putra Malaysia (JKEUPM) operates in accordance to the ICH-GCP Guidelines.

Decision by JKEUPM:

[X] Approved

[ ] Conditionally Approved

[ ] Disapproved

Please be informed that you are required to submit annual reports, completion reports and "all adverse events, both serious and unexpected" to the committee.

Date of Decision:2/8/2013

PROFESSOR DR. NORLIJAH OTHMAN
Chairman
University Research Ethics Committee
(JKEUPM)
Universiti Putra Malaysia

Attachment 2

JKEUPM Ref No. : FPSK_Julai(13)01

Members of the JKEUPM who reviewed the documents:

Prof. Dato' Dr. Lye Munn Sann

Date of approval: 16/7/2013

Endorsed at JKEUPM Meeting on **2/8/2013**, attended by:

NAME	DESIGNATION	GENDER	TICK IF PRESENT
Prof. Dr. Norlijah Othman	Paediatrics& Dean, Faculty of Medicine and Health Sciences	Female	√
Prof. Dr Zamberi Sekawi	Medical Microbiologist & Deputy Dean of Research and Internationalization, Faculty of Medicine and Health Sciences	Male	√
Prof. Dato' Dr. Lye Munn Sann	Medical Statistician, Dept of Community Health, Faculty of Medicine and Health Sciences	Male	
Prof. Dr. Tengku AizanAbd Hamid	Gerontologist & Director, Institute of Gerontology	Female	√
Prof. Dr. Lekhraj Rampal	Medical Statistician, Dept of Community Health, Faculty of Medicine and Health Sciences	Male	
Prof. Dr. Elizabeth George	Pathologist, Dept of Pathology, Faculty of Medicine and Health Sciences	Female	√
Prof. Dr. Lim ThiamAun	Anesthesiologist, Dept of Surgery, Faculty of Medicine and Health Sciences	Male	
Prof. Dr. Wan Omar Abdullah	Medical Parasitologist, Dept of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences	Male	
Prof. Dr. Patimah Ismail	Professor of Biomedicine, Dept of Biomedical Sciences, Faculty of Medicine and Health Sciences	Female	√
Assoc. Prof. Dr. Johnson Stanslas	Pharmacologist, Dept of Medicine, Faculty of Medicine and Health Sciences	Male	√
Assoc. Prof Dr. Mansor Abu Talib	Assoc. Professor of Guidance and Counselling, Dept of Human Development and Family Studies, Faculty of Human Ecology	Male	
Assoc. Prof. Dr. Noritah Omar (Lay Person)	Assoc. Professor of English Language, Dept of English Language, Faculty of Communication and Modern Languages	Female	√
Dr. RojanahKahar (Lay Person)	Lecturer of Dept of Human Development and Family Studies, Faculty of Human Ecology	Female	√
Tan Sri Dato' Napsiah Omar (Lay Person)	Chairman, National Population and Family Development Board	Female	