



UNIVERSITI PUTRA MALAYSIA

***THE VALUE OF D-DIMER ASSAY IN DIAGNOSIS OF DEEP VEIN
THROMBOSIS:HOSPITAL SERDANG EXPERIENCE, 2012-2013.***

GROUP30

GROUP MEMBER:

SITI HAJAR BINTI DARUSSALAM

JACKY TEIN FUWEN

SUPERVISOR:

DR.SURAINI MOHAMAD SAINI

CO-SUPERVISOR:

DR.HASYMA BINTI ABU HASSAN

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THE VALUE OF D-DIMER ASSAY IN DIAGNOSIS OF DEEP VEIN THROMBOSIS: HOSPITAL SERDANG EXPERIENCE 2012-2013.

SitiHajarDarussalam¹, Jacky. T.F¹, SurainiMohamadSaini², HasymaAbuHassan²

¹Second Year Medical Student

²Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia

ABSTRACT

Background: Deep vein thrombosis (DVT) is a common complication of hospitalization. The risk factors of DVT are cancer, bedridden condition or inherited hypercoagulable condition. About 1 in 1000 adults is diagnosed with DVT.

Objective: To determine the correlation between D-dimer level and lower limb doppler ultrasound(DUS) in suspected DVT patients.

Material and methods: A cross-sectional study using retrospective data was conducted from January 2012 to July 2013 at Serdang Hospital. One hundred patients suspected of having DVT and underwent DUS were selected as samples. They were selected by convenience sampling method, and their data were recorded in the pro-forma. The data obtained was analyzed using statistical package for social sciences version 18.0 (SPSS 18.0) to determine any relationship.

Result: Sensitivity of D-dimer test in Hospital Serdang was 95.8% while the specificity was 17%. D-dimer value was increasing with the increase of age. However, there was no significant association between age and D-dimer level. There was also no association between D-dimer and (gender and race). There were no concordance between the D-dimer test and DUS among the low risk and moderate risk group patients. However, the sensitivity and negative predictive value (NPV) of D-dimer test in low risk group were found to be 100%. There was concordance between D-dimer test and DUS among the high risk group patients. The sensitivity and positive predictive value (PPV) of D-dimer test in high risk group patients were found to be 100%.

Conclusion: This study reveals that D-dimer test has a very low specificity but can be used as a rule out test of DVT in low risk patients thus obviates the need for further imaging test. Meanwhile the high risk group patients can directly proceed with DUS for confirmation without performing D-dimer test, thus saving time in patient's management as well as being cost effective.

Keywords: Deep vein thrombosis, D-dimer test, Doppler ultrasound, sensitivity, specificity, positive predictive value, and negative predictive value.

NILAI UJIAN D- DIMER DALAM MENDIAGNOSIS TROMBOSIS DALAM VENA :DAPATAN DI HOSPITAL SERDANG 2012-2013 .

SitiHajarDarussalam¹, Jacky. T.F¹, SurainiMohamadSaini², HasymaAbuHassan²

¹*Pelajar PerubatanTahunDua*

²*Jabatan Pengimejan, FakultiPerubatandanSainsKesihatan, Universiti Putra Malaysia*

ABSTRAK

Latar belakang: Trombosis vena bahagian dalam adalah satu komplikasi biasa di hospital. Faktor-faktor risiko trombosis vena ialah kanser, keadaan terlantar untuk tempoh lama dan kadar thrombosis tinggi yang diwarisi. Kira-kira 1 dalam 1000 orang dewasa menghidap trombosis vena.

Objektif: Untuk menentukan korelasi antara tahap D-dimer dan 'Lower limb Doppler ultrasound' (DUS) dalam pesakit yang disyaki menghidap trombosis vena.

Kaedah: Satu kajian keratan rentas yang menggunakan data retrospektif telah dijalankan dari Januari 2012 hingga Julai 2013 di Hospital Serdang. Seratus pesakit yang disyaki menghidap trombosis vena dan telah menjalani DUS telah dipilih sebagai sampel. Sampel dipilih dengan menggunakan kaedah persampelan mudah dan rekod mereka telah dicatatkan dalam pro-forma. Data yang diperolehi dianalisa menggunakan pakej statistik bagi sains sosial versi 18.0 (SPSS 18.0) untuk menentukan sebarang perkaitan.

Keputusan: Kepekaan ujian D-dimer di Hospital Serdang adalah 95.8 % manakala spesifikasinya adalah 17%. Nilai D-dimer semakin meningkat dengan peningkatan umur. Walau bagaimanapun, tidak terdapat hubungan yang signifikan antara umur dengan nilai D-dimer. Tiada perkaitan juga ditemui antara D-dimer dengan (jantina dan bangsa). Selain itu, tidak terdapat sebarang keselarasan antara ujian D- dimer dan DUS dalam kalangan pesakit berisiko rendah dan sederhana. Walaubagaimanapun, sensitiviti dan nilai ramalan negatif (NPV) ujian D- dimer dalam kumpulan berisiko rendah didapati 100%. Terdapat keselarasan di antara ujian D- dimer dan DUS dalam kalangan pesakit berisiko tinggi. Kepekaan dan nilai ramalan positif (PPV) ujian D- dimer dalam kalangan pesakit berisiko tinggi pula didapati 100%.

Kesimpulan: Kajian ini menunjukkan bahawa ujian D- dimer mempunyai spesifikasi yang sangat rendah tetapi boleh digunakan sebagai ujian untuk menyingkirkan kemungkinan seseorang pesakit berisiko rendah untuk menghidap thrombosis vena. Oleh itu, golongan pesakit ini tidak perlu menjalankan ujian pengimejan. Sementara itu, pesakit berisiko tinggi disarankan untuk terus menjalankan DUS untuk mengesahkan trombosis vena, tanpa melakukan ujian D-dimer. Hal ini sekali gus menjimatkan masa dalam pengurusan pesakit serta merupakan langkah yang kos efektif.

Kata kunci: Trombosis vena bahagian dalam, ujian D- dimer, 'Doppler ultrasound', kepekaan, keperincian, nilai ramalan positif, dan nilai ramalan negatif.

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LIST OF ABBREVIATIONS

SPSS	–Statistical Package for Social Sciences Programme
FPSK	–Faculty of Medicine and Health Science
DVT	–Deep vein thrombosis
AT	–Antithrombin
APCR	–Activated protein C resistance
DIC	–Disseminated intravascular coagulation
PE	–Pulmonary embolism
PTS	–Post-thrombotic syndrome
FDP	– Fibrin degradation products
ELISA	–Enyme-linked immunosorbent assay
DUS	–Doppler ultrasound
LMWH	–Low molecular weight heparin

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Deep vein thrombosis (DVT) is a common and important complication of hospitalization, especially in individuals who undergo orthopedic or obstetric procedures. The likelihood of DVT is related to the number of clinical risk factors, such as cancer, paralysis, bedridden condition, or inherited hypercoagulable condition (Stein et al., 1999). Approximately 2% to 5 % of the people will suffer from DVT (Farzamnia, H., Rabiei, K., Sadeghi, M., &Roghani, F., 2011) and about 1 in 1000 adults is diagnosed with DVT (Severinsen et al., 2010). In general surgical patients, Asian studies revealed a lower incidence ranging from 2.2% to 5.3% (Tun, M., Shuaib, I. L., Muhammad, M., & MatSain. A. H., 2001). Most of the patients who come to the hospital with a complaint of DVT are because of inherited coagulation disorder or prolonged limb dependency (long air travel) (Haas, S. K., 2002). In most cases, DVT develops in the lower limb but can also occur in the upper limb. Meanwhile, the proximal DVT usually involves the femoral, popliteal and also the iliac veins (Zhu, T., & Matsushisa, 2011).

Three factors promoting venous thrombosis are venous stasis caused by immobility, age, vessel damage caused by trauma and hypercoagulability due to coagulable disorder (Hamid, 2011; White, 2003; Dickson, 2004). These three main factors favor the clot formation by disrupting the physiological balance between the coagulative and fibrinolytic systems. Other than that, increasing age is also a risk factor to develop DVT with only 5 out of 100,000 children will develop DVT as opposed to 400 out of 100,000 elderly over 80 years old (White, R. H., 2003). Other risk factors include smoking, aging, obesity, long air travel, recent surgery,

heart failure and bone failure (Hirsh, 2002; Kyrle, 2005). Persistence exposure to the risk factors such as smoking and cancer will cause an individual to have a significantly higher risk of recurrent thrombosis (Line, B. R., 2001). For the inherited hypercoagulability disorders, the common causes are due to Factor V Leiden mutation, thrombin mutation, deficiency of antithrombin III, protein S and protein C (Goldhaber, S. Z., & Elliot, C. G., 2003).

The most common complication of DVT is pulmonary embolism which is an occlusion of a portion of pulmonary vessel by an embolus. The embolus can be a blood clot, lipid, tissue fragment or air bubbles. Thrombus formed in the deep vein of thigh may travel as emboli and this is known as venous thromboembolism. In untreated DVT, about 30% of the patient will develop pulmonary embolism (Anderson, F. A. Jr., & Frederick, A. S., 2003) and the incidence is about 100,000 to 300,000 in United State every year (White, 2003; Anderson, 2003, Kearon, 2003, Stratmann, 2003). Another frequent complication is post thrombotic syndrome which is characterized by chronic, persistent pain, swelling and ulceration in the affected limb (Tovey, C., & Wyatt. S., 2003).

In the diagnosis of DVT, D-dimer test, Doppler ultrasound (DUS) and venography are used. D-dimer test measures the D-dimer level in the blood. D-dimer is a fibrin degradation product (FDP). It is a small protein fragment byproduct of fibrinolysis process. It is named so as it contains two crosslinked D fragments on the fibrin protein (Adam, S. S., Key, N. S., & Greenberg, C. S., 2009). In the normal physiological condition, the D-dimer is absent in the blood except when the coagulation system is activated (Adam et al., 2009). The principle of the D-dimer test is to detect the D-dimer concentration in the blood by using the monoclonal antibodies which will bind to the epitope of D-dimer (Adam et al., 2009). There are several D-dimer assays used clinically. However, the most popular method is the laboratory based VIDAS

enzyme linked immunosorbent assay (ELISA) and the SimpliRED whole blood agglutination test (Pittet et al., 1996).

Another test used in investigation of DVT is thrombus visualization. Examples of these investigations include contrast venography, DUS, computed tomography and magnetic resonance imaging (Ebell, M., 2001). However, DUS is the widely used modality. This test is performed with a high frequency linear-array transducer. The deep veins are evaluated for compressibility at 1-cm intervals from the common femoral vein to the point where the popliteal vein joins the calf veins. In patients with no history of DVT, DVT was diagnosed if the vein was noncompressible. In patients with a history of DVT, DVT is diagnosed if there is a new noncompressible site or if the diameter of a clot has increased by at least 4 mm from a previous measurement (Sidhu, S., & Alikhan, R., 2007).

1.2 PROBLEM STATEMENT

In order to provide excellent patient care at a minimal cost, Hospital Serdang requires diagnostic procedures that are safe, efficient and accurate. In addition, the procedures should be non-invasive and relatively pain free. In Hospital Serdang, methods to diagnose DVT include D-dimer test and DUS. In this research, we are going to find out the sensitivity and specificity of the D-dimer test as compared to DUS (the only diagnostic tool in Hospital Serdang). Although DUS is widely available, easy and non-invasive, it is largely operator dependent and time-consuming. The pitfalls and limitations of DUS are related to vein anatomy, flow changes and technical issues. Moreover, the procedure is difficult to be conducted in obese people. D-dimer test is a test that measures the concentration of D-dimer level in the blood by using monoclonal antibodies. In a normal person, the D-dimer test reads negative. Once the coagulation system is activated, D-dimer concentration will increase. In Malaysian Clinical Practice Guideline, the method used in diagnosing DVT is determined by clinical probability. Those people with clinical probability to have DVT, will be directly diagnosed by using DUS while those who are in low clinical probability, D-dimer test will be performed before going for further investigation.

DUS method offers an accurate, versatile, simple, and rapid method of detecting DVT. Several reports have suggested that the sensitivity of the DUS may exceed 95% in detecting the DVT at or above the knee level. However, this method brings some problems to certain group of people. False negative examination can occur in obese patients and patients with edematous extremities, which are therefore difficult to examine. Besides that, small non-occlusive thrombi in profunda femoral vein and the distal popliteal vein in particular are prone to being missed (Lewis et al., 1994). Hence, we need to find another easier, faster and minimal costly method to

represent others methods. D-dimer test is a test that tests the concentration of D-dimer by using monoclonal antibodies. This method has sensitivity of 97 % but it is non-specific. D-dimer level is expected to be negative in normal people. Meanwhile the D-dimer level is elevated but is elevated in a normal people, it is negative when tested but it is elevated in patients who have recent surgery, trauma, sepsis, and malignancy. However, it is very useful in excluding DVT having a negative predictive value of 97 % (Fraser, J. D., 2004). In certain group of patients, D-dimer combined with clinical assessment has been shown to safely reduce or eliminate the need for non-invasive testing (Fraser, J. D., 2004)

There are however, limited studies on the above in Malaysia. Therefore, this study aims to determine the sensitivity and the specificity of the D-dimer test and its correlation with the doppler ultrasound test.

1.3 OBJECTIVE

1.3.1 GENERAL OBJECTIVE

The general objective of this study is to determine the sensitivity and the specificity of the D-dimer test used in Hospital Serdang in predicting DVT.

1.3.2 SPECIFIC OBJECTIVE

1. To identify the relationship between demographic factors (gender, age and race) as well as Well's score with D-dimer level.
2. To determine the D-dimer result in positive lower limb doppler ultrasound examination of suspected DVT patients.
3. To determine the concordance between D-dimer level and lower limb doppler ultrasound in low, moderate and high risk group patients.

1.4 HYPOTHESIS

H_1 : Sensitivity and specificity of the D-dimer assay is not comparable with the DUS in the diagnosis of DVT.

CHAPTER 2

LITERATURE REVIEW

2.1 THROMBOSIS

Thrombosis is the formation of a blood clot in the vasculature. Thrombosis can either be physiological or pathological. Physiological thrombosis results from body's natural response to vascular injury. This type of thrombosis is localized and is formed to prevent excess blood loss. Whereas pathological thrombosis can be caused by inherited or acquired conditions. It is divided into two: arterial and venous thrombosis (Dickson, B., 2004).

Arterial thrombosis is mainly composed of platelets with small amount of red cells and white cells which is referred as "white clot". Complications associated with arterial thrombosis are occlusions of the vascular system leading to infarction of tissues (Deitcher, S. R, 2000). Factors causing arterial thrombosis are hypertension, hyperviscosity, qualitative platelet abnormalities and atherosclerosis. Meanwhile, venous thrombosis is composed of fibrin clot and red cells (Dickson, B., 2004). It is associated with venous stasis, coagulation activation, impairment of fibrinolytic system and deficiency of physiological inhibitors. The most serious complication of venous thrombosis is pulmonary embolism.

Thrombosis may result from vascular injury, platelet activation, defects in the fibrinolytic system and defects in physiological inhibitors. It is an activation of the haemostatic system at an inappropriate time in the vessel. Thrombi formed in this fashion are pathologic and beyond the normal haemostatic mechanism. If physiological anticoagulants are decreased in the circulation, there will be a clot (Furie, B., 2008).

Arterial and venous thrombosis along with complicating thromboembolism is the most important cause of death in the developed countries. More than 800,000 people die annually from myocardial infarction (MI) and thrombotic stroke in the United States (Deitcher, S. R., 2000). It has also been reported that venous thromboembolic disease is the most common vascular disease after atherosclerotic heart disease and stroke (Deitcher, S. R., 2000).

2.2 DEEP VEIN THROMBOSIS

Deep vein thrombosis, (DVT) is the formation of a blood clot (thrombus) in a deep vein (Dickson, B., 2004). In a year, about 1 in 1000 adults is diagnosed to have DVT (Severinsen et al., 2010) and approximately 2-5% of people suffer DVT during their lives (Farzamnia et al., 2010). DVT, which is a common condition, can occur in either hospitalized or outpatient. In those hospitalized for a general medical condition, it is estimated that up to 26% will develop DVT, with a higher prevalence in patients with conditions such as stroke, shock, myocardial infarction, congestive heart failure and malignancy (Haas, S., 2002). Hospitalized patients such as patients who just undergone surgery or trauma, spinal cord injury, and conditions related to obstetrics/gynecology are associated with up to 100% probability of developing DVT. Meanwhile, for outpatients/patients who come to hospital due to a chief complain of DVT, the risks of developing DVT might be due to inherited coagulation disorders or prolonged limb dependency (airplane travel) (Haas, S., 2002). It is proven that there is a small exponential increase of incidence with travelling time (Lapostolle, F., & Doggen, C. J., 2004). DVT was initially dubbed 'economy class syndrome', first recognized half a century ago (Emonson, D., 1997). It was subsequently called 'traveller's thrombosis'.

In most cases, DVT arises in the region of lower extremities but may also occur in the arms, cerebral sinuses, and viscera. Calf veins restricted DVT is associated with smaller clots and fewer long-term sequelae (Bates, S. M., & Ginsberg, J. S., 2004). Meanwhile, proximal DVT usually involves the popliteal, femoral, or iliac veins (Zhu, T., & Matsuhisa, 2011). Although most DVT cases resolve spontaneously without complication (Bates, S. M., & Ginsberg, J. S., 2004), there are certain untreated DVT cases which later lead to pulmonary embolism (PE) causing as many as 300,000 deaths annually in the United States (Tapson, V. F., 2008).

2.3 RISK FACTORS OF DEEP VEIN THROMBOSIS

Risk factors associated with deep vein thrombosis can be divided into three which are environmental, acquired and inherited factors (Deitcher, 2000; Goodnight, 2001).

2.3.1 ENVIRONMENTAL FACTORS

Environment factors are linked to transient conditions that may result from surgery, immobilization, pregnancy, and therapeutic complications associated with oral contraceptives, hormone replacement therapy and chemotherapy (Furie, 2008; Goodnight, 2001). Other than that, increasing age is also a risk factor to develop DVT. Only 5 out of every 100,000 children suffer the problem, meanwhile the rate increases to 400 out of every 100,000 in people over 80 years old (White, R. H., 2003).

2.3.1.1 Hormone replacement therapy, oral contraceptive therapy, pregnancy

Oral contraceptive therapy and pregnancy might cause acquired antithrombin deficiency. Deficiencies of AT is associated with recurrent thrombosis in the vein.

Pregnant women show the highest risk of developing pathological thrombosis (Dickson, B., 2004) during third trimester of pregnancy and first 6 weeks after delivery. This is because during pregnancy, the risk of developing thrombosis is also influenced by the presence of pro-thrombotic abnormalities, which involved 30 to 50 fold of common pro-thrombotic genetic variants (Sanchez, O., Planquette, B., & Meyer, G., 2009).

2.3.1.2 IMMOBILIZATION

Weakened lower limb muscles due to absence of long term mobilization might disrupt the movement of blood flow back to the heart. Reduced contraction by these muscles might cause a backflow of the blood thus causing the blood to accumulate backward. This event will also cause the accumulation of activated platelets, clotting factors and thrombin which later promotes thrombus formation (Ufuk, C., 2012).

2.3.2 ACQUIRED RISK FACTORS

Acquired risk factors are associated with conditions that hinder normal haemostasis such as cancer, nephritic syndrome, vasculitis, antiphospholipid antibodies, myeloproliferative disease, hyperviscosity syndrome and others (Deitcher, S. R., 2000).

2.3.2.1 CANCER

A cancer free person has a lower risk of developing DVT and PE compared to a cancer patient. A large population-based study was conducted among patients diagnosed with cancer to determine the incidence of PE. 1.6% from 235,149 cancer

patients were diagnosed symptomatic PE within 2 years. All the hematological and solid tumor types are associated with PE but vary among the types of cancer. Highest risk of PE related to the age and sex are among patients with hematological malignancies, lung cancer and gastrointestinal cancer (Rosendaal, F., 2005). They become significant predictor of death during the first year for all cancer types (Sanchez et al., 2009). Patient with persistent risk factors such as cancer have a significantly higher risk of recurrent thrombosis (Zhu, T., & Matsuhisa, 2011).

2.3.3 INHERITED FACTORS

Inherited risk factors are associated with genetic mutation that result in deficiency of naturally occurring inhibitors such as protein C, protein S, antithrombin (AT) or clotting factors resistant to anticoagulant activities of physiological inhibitors as in activated protein C resistance (APCR) (Dickson, B., 2004).

2.3.3.1 ANTITHROMBIN DEFICIENCY

Antithrombin(AT) deficiency was first discovered in 1965 (Deitcher, S. R., 2000). This disorder is inherited as an autosomal dominant disorder. It has been reported that 1 in 600 people have AT deficiencies: type I and type II. Type I is a quantitative disorder in which there is a reduction in the concentration of AT. Type II is a qualitative disorder in which concentration of AT is normal but the molecule is functionally abnormal (Stein et al., 2007). Deficiencies of AT is associated with recurrent venous thrombosis, which may include every vein site (Deitcher, S. R., 2000). The thrombotic event may be primary (absence of triggering factors) or may

be followed by another risk factor such as pregnancy. Acquired AT deficiencies may be associated with DIC, liver disease, nephritic syndrome, oral contraceptives and pregnancy.

2.3.3.2 PROTEIN C AND PROTEIN S DEFICIENCY

Protein C is a vitamin K dependant protein made in the liver (Dickson, B. (2004).

Protein S which acts as a cofactor functions to activate protein C (Deitcher, S. R., 2000). Active protein C will exert its inhibitory effects against the clotting factors.

Therefore, deficiencies of proteins C and S are associated with thrombosis (Dickson, B., 2004).

2.4 PATHOPHYSIOLOGY OF DVT

DVT occurs primarily in lower limb extremity (Zhu, T., & Matsuhisa, 2011). The modern era of understanding the etiology of thrombosis began with pathologist Virchow, who in the mid 1800s postulated three major causes of thrombosis: (1) venous stasis (2) hypercoagulable and (3) venous endothelial damage (Dickson, 2004; Rosendaal, 2005). These factors favor clot formation by disrupting the balance of the opposing coagulative and fibrinolytic system (Line, B. R., 2001).

2.4.1 VENOUS STASIS

Venous stasis is usually caused by immobility associated with prolonged bed rest or sitting, obesity, neurologic disease or old age. But it also can be caused by pregnancy, congestive heart failure, sickle cell disease and systemic lupus

erythematosus. Venous stasis inhibits clearance or dilution of activated coagulation factors (Bates, S. M., & Ginsberg, J. S., 2004) thus favoring coagulation process.

2.4.2 HYPERCOAGULABILITY

Hypercoagulability may result from inherited or acquired coagulation disorders of the blood, malignancy or oral contraceptive use. Common inherited clotting disorders include Factor V Leiden mutation, thrombin mutation, deficiencies of antithrombin III, protein C or protein S (Goldhaber, S. Z., & Elliott, C. G., 2003) may also cause development of DVT because these factors function to promote coagulation (Bates, S. M., & Ginsberg, J. S., 2004).

2.4.3 VESSEL DAMAGE

Besides that, clot formation also proceeds if vessel damage occurs, as in traumatic injury, surgery or spontaneous rupture (cerebrovascular accidents). This is because vessel damage will prevent endothelium from undergoing coagulation and initiating local fibrinolysis (Bates, S. M., & Ginsberg, J. S., 2004).

All of the above factors may cause accumulation of clotting factors and platelets which leads to thrombus formation in the vein, often near the venous valve. Inflammation around the thrombus promotes further platelet aggregation and the thrombus propagates or grows proximally. This inflammation may cause local symptoms but because the vein is deep in the leg, it is usually not accompanied by clinical symptoms or signs (McCane, K. L., & Huether, S. E., 2006). If the thrombus creates significant obstruction to venous blood flow, increased pressure in the vein behind the clot may lead to edema of the

extremity. Most thrombi will eventually dissolve without treatment but untreated DVT is associated with high risk of embolization of a part of the clot (pulmonary embolism) and may lead to persistent venous outflow obstruction and post thrombotic syndrome (McCane, K. L., & Huether, S. E., 2006).

2.5 COMPLICATIONS

Among the most important complications of DVT are PE, death, disease recurrence, post-thrombotic syndrome, excessive bleeding due to coagulant medications, encompassing chronic venous hypertension causing limb pain, swelling, hyperpigmentation, dermatitis, ulcers, venous gangrene, and lipodermatosclerosis (Tovey, C., & Wyatt, S., 2003).

2.5.1 PULMONARY EMBOLISM (PE)

The most serious complication of DVT so far is PE, which is an occlusion of portion of the pulmonary vascular bed by an embolus (McCane, K. L., & Huether, S. E., 2006).

An embolus can either be blood clot, tissue fragments, lipids/ fats or an air bubble. Thrombi dislodged from deep veins in the thigh are the most common form of emboli. This is termed venous thromboembolism. Symptomatically, PE occurs in approximately 30% of cases of untreated DVT and has an estimated incidence of 100,000 to 300,000 cases per year in the United States (White, 2003; Anderson, 2003, Kearon, 2003, Stratmann, 2003).

2.5.2 POST THROMBOTIC SYNDROME (PTS)

Meanwhile, post thrombotic syndrome (PTS) is also a frequent complication of DVT and is characterized by chronic, persistent pain, swelling and ulceration of the affected limb

(Kahn, S. R., & Ginsberg, J. S., 2004). The high incidence risk of DVT recurrence (Farzamnia et al., 2011) after the first attack has a multifactorial pathogenesis and its probability is related with the number and severity of risk factors (Tovey, C., & Wyatt, S., 2003). The sequel of DVT varies from either complete resolution of the clot without any complication or death due to pulmonary embolism or post thrombotic syndrome (Bates, S. M., & Ginsberg, J. S., 2004).

2.6 INVESTIGATION

The approach to the diagnosis of DVT has evolved over the years. A fast, reliable, noninvasive, and inexpensive screening test is needed that can be performed immediately on attendance at hospital (Brandjes et al., 1997). But before those investigations are performed, the person's clinical probability of developing DVT has first to be evaluated by using Well's criteria.

2.6.1 PRE-CLINICAL TESTING

Originally developed in 1995, the Wells DVT criteria are used to determine a patient's pre-test probability of having a DVT. These criteria have since been refined and included in an algorithm to guide diagnostic evaluation for DVT using D-dimer testing and venous ultrasonography. Well's score uses Well's criteria as the reference in order to categorize the patients into either low risk group (Score ≤ 0 ; Group 1), moderate risk group (Score = 1 or 2; Group 2) or high risk group (Score ≥ 3 ; Group 3) (Williams, A., Lee, P., & Kerr, A. 2002).

2.6.2 SCREENING TEST

2.6.2.1 D-DIMER TEST

In D dimer test, it measures the D dimer level in the blood. It can be used as an excellent marker for fibrinolytic activity that occurs in our circulation (Ufuk, C., 2012). D-dimer, which is a fibrin degradation product (FDP), is a small protein fragment present in the blood after a blood clot is degraded through fibrinolysis process. It is named because it contains two cross linked D fragments at the fibrin protein (Adam et al., 2009). Plasma D-dimers are specific cross linked derivatives of fibrin, produced when fibrin is degraded by plasmin (Aschwanden, M., Lab, K. H., Jeanneret, C., Gehrig, A., & Jeager, K. A., 1999). D-dimers are not normally present in human blood plasma, except when the coagulation system has been activated, for instance when there is the presence of thrombosis or disseminated intravascular coagulation (Adam et al., 2009). The D-dimer assay depends on the binding of a monoclonal antibody to a particular epitope on the D-dimer fragment.

Numerous clinical studies have shown that measurement of plasma D-dimer to be useful as a thrombosis exclusion test but have to be evaluated against the criterion standard, venography. This is due to the low specificity of D dimer test. A normal result from a highly sensitive D-dimer test effectively rules out DVT among patients classified as having either low or moderate clinical probability of DVT. Table 2.1 shows the Well's criteria used in evaluating the clinical probability of a person to suffer from DVT. The pre-test probability (Well's criteria for DVT) is best assessed using a clinical practice guide (CPG). For instance, a 'negative' D-dimer test result

when using a highly sensitive assay can ‘rule out’ DVT using the Wells’ clinical prediction (Scarvelis, D., & Wells, P. S., 2006).

Table I: Well’s Pre-test Probability for DVT	
Clinical Features	Well’s score
Active cancer (treatment ongoing, within previous 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for > 3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the DEEP venous system	1
Entire leg swollen	1
Calf swelling > 3 cm when compared with the asymptomatic leg*	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (non-varicose)	1
Alternative diagnoses as likely as or greater than that of DVT	2
Source: (Hargett, C. W., 2008)	TOTAL
Total marks of every patient will be calculated. Min mark:0, max mark:3;	
High pretest probability (>3 points)	
Moderate pretest probability (1-2 points)	
Low pretest probability (zero or negative points)	

Several detection kits of D- dimer tests are commercially available; all of them rely on a different monoclonal antibody against D-dimer (Adam et al., 2009). There are two types of D-dimer test which are either qualitative or quantitative. Different types of assay have varying sensitivities and specificities and are not standardized. But D-dimer tests have generally had high sensitivity and negative predictive value for the presence of thrombus in patients with low pre-test probabilities. Furthermore, different laboratories may use different 'cut-offs' for what constitutes a positive or negative result would be depending on what type of D-dimer assays being used.

The characteristic of the available D-dimer assay will affect their performance and its use in clinical decision-making. For example the HemosIL DD HS assay which is the 'second generation' latex agglutination D-dimer, is highly sensitive. This has similar presentation with the ELISA assay unlike 'first generation' latex agglutination assay. The HemosIL DD HS using the 'cut offs' of 230 ng/mL and its data are:

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

Several D-dimer assays are used clinically. Two of the most extensively studied are the laboratory based VIDAS enzyme linked immunosorbent assay (ELISA) and the SimpliRED whole blood agglutination test (Pittet et al., 1996). The SimpliRED test provides a qualitative result (positive or negative) within 10 minutes and is suitable for near patient testing. Some evidence exists that D-dimer concentrations

should be measured after the end of the anticoagulation period, to determine the risk of re-thrombosis (Palareti et al., 2002).

Although this test is particularly sensitive for venous DVT, high concentrations of D-dimers are insufficiently specific for making a positive diagnosis of DVT. This is because high level of D dimer not only occur in DVT but as well as in other disorders such as malignancy, pregnancy, trauma and post surgery (Aschwanden et al., 1999) leading to false positive result of the test. While false negative readings can occur if the sample is taken either too early after thrombus formation or if testing is delayed for several days (Vanes et al., 2012).

2.6.2 DIAGNOSTIC TEST

Investigations used for the definitive diagnosis of DVT are by visualizing the thrombus. Examples of these investigations include contrast venography, ultrasonography, computed tomography, and magnetic resonance imaging (Ebell, M., 2001).

2.6.2.1 DOPPLER ULTRASOUND (DUS)

Ultrasonography is considered to be the best non-invasive diagnostic method and has been evaluated against venography in many studies, showing an average sensitivity and specificity of 97% for proximal deep vein thrombosis (Scarvelis, D., & Wells, P. S., 2006). However, ultrasonography cannot be relied on to diagnose calf vein thrombosis and the sensitivity for symptomatic calf vein thrombosis has been reported to be as low as 75%.

The technique of colour coded Doppler ultrasonography (colour Doppler) is identical to duplex ultrasonography. In colour flow sonography, pulsed Doppler signals are used to produce the images. When a Doppler shift is recognised, it is assigned a colour (red or blue) according to its direction towards or away from the probe. Therefore colour Doppler results in a display of flowing blood as a colour overlay to the grey scale ultrasound image, which makes it easier to identify the veins.

Ultrasonography was performed with a high-resolution 5- or 7.5-MHz linear-array transducer. The deep veins were evaluated for compressibility at 1-cm intervals from the common femoral vein to the point where the popliteal vein joins the calf veins. In patients with no history of DVT, DVT is diagnosed if the vein is not compressible. In patients with a history of DVT, DVT was diagnosed if there was a new noncompressible site or if the diameter of a clot had increased by at least 4 mm from a previous measurement (Sidhu, S., & Alikhan, R., 2007).

Physicians cannot rely on signs and symptoms to make the diagnosis of DVT and must depend on imaging studies to guide treatment. DUS is currently the technique of choice for the diagnosis of DVT in symptomatic patients. This is because it has been proven safe and cost-effective, with a very high sensitivity and specificity (96% and 98%, respectively) for the diagnosis of proximal DVT (Gantini, D., 2006). Thus, bilateral DUS examination of lower limb veins should be performed as the initial examination in the workflow of DVT only in patients with risks of DVT (Gaitini, D., 2006)

DUS examination is non-invasive, rapidly obtained, and it can be performed serially. However, DUS is insensitive to calf vein thrombosis and to asymptomatic DVT occurring after surgery (Line, B. R., 2001).

2.6.2.2 VENOGRAPHY

Venography, is a rarely-used diagnostic test that produces X-ray images of the veins and blood flow through them. Veins are not normally visible on an X-ray image, so a special dye is injected into the blood to make it visible. Venography is usually performed only after other tests have failed to find the clot. For example, an ultrasound may fail to find a clot, but a positive D-dimer test may indicate there is a clot somewhere. In these cases, venography can be used to try to locate a clot the ultrasound may have missed. In women with a suspected PE, CT venography may be added to the standard CT angiogram to try to find the source of the clot. However, there is controversy concerning whether the benefit of finding vein clots in these women is worth the extra radiation exposure (Stein et al., 2007).

Of the diagnostic procedures for DVT, venography is the only invasive test of proven value (Line, B. R., 2001). Nevertheless, it is the gold standard for establishing the diagnosis of deep vein thrombosis. However, this procedure is invasive, not always technically possible, and it carries a small risk of an allergic reaction or venous thrombosis.

2.7 CORRELATION BETWEEN D-DIMER AND DOPPLER ULTRASOUND

In some centers, compression ultrasound imaging of the proximal veins of the leg is combined with a D-dimer test. It has been suggested that patients with a low clinical probability and a normal ultrasound scan can be safely discharged without serial ultrasonography (Anderson et al., 1999).

2.8 TREATMENT

DVT is the main cause of death in hospitalized patients and thromboprophylaxis is believed to be the only way to prevent these deaths through active monitoring of the drug given (Bottaro et al., 2012). The goal of the therapy in treating DVT for short term is to prevent the extension of thrombus and PE meanwhile for the long term is to prevent recurrent events (Scarvelis, D., & Wells, P. S., 2006). Short term anticoagulant drugs such as heparin are administered by intravenous infusion or subcutaneous injection. Long term anticoagulant drugs such as Coumadin are orally administered (Dickson, B., 2004). Interventions such as thrombolytic drugs (streptokinase) and placement of inferior vena cava filters are reserved for special situations. Meanwhile streptokinase which is used to dissolve the thrombus is not frequently used because of the risk of bleeding complications is three times greater (Tovey, C., & Wyatt, S., 2003).

2.8.1 HEPARIN

Heparin is present in human tissues as naturally occurring highly sulfated glycosaminoglycan. Heparin sulfate is a heparin-like-substance made by the vascular

endothelium. The anticoagulant activity of heparin is enhanced by binding to AT. Heparin-AT complex inactivates thrombin and factor Xa (Dickson, B., 2004).

2.8.2 LOW MOLECULAR WEIGHT HEPARIN (LMWH)

LMWH is derived from UFH via enzymatic digestion to produce smaller and low molecular weight glycosaminoglycan molecules. LMWH has a higher half-life and does not require monitoring (Dickson, B., 2004). High efficacy and easy administration LMWH (anticoagulation therapy) make this the preferred anticoagulant, whether given on an outpatient or an inpatient basis. In a meta-analysis comparing the effectiveness of LMWH at a fixed dose with unfractionated heparin at an adjusted dose, significantly fewer deaths, major hemorrhage and recurrent venous thromboembolism occurred with the LMWH (Dongen, C. J., Bellet, A. G., Prins, M. H., & Lensing, A. W., 2004). Thus, the current standard of care is to administer weight-adjusted LMWH once daily for 5–7 days as initial treatment and treatment should not be discontinued until the international normalised ratio has been in the therapeutic range for two consecutive days (Dongen, et al, 2004). LMWH adverse effect includes bleeding.

2.8.3 COUMADIN

Coumadin is a vitamin K antagonist drug that inhibits the vitamin K dependant coagulation factors. Warfarin is a Coumadin derivative that is widely used which inhibits carboxylation of vitamin K dependant factors (II, VII, IX, X) as well as vitamin K dependant anticoagulant proteins such as protein C and protein S. Warfarin is given orally as long term anticoagulant (Dickson, B., 2004).

2.8.4 FONDAPARINUX SODIUM

Fondaparinux sodium, which is a synthetic pentasaccharide that inhibits activated factor X is also used as a treatment for DVT. This drug has recently been used for prophylaxis of venous thromboembolism in patients having major orthopaedic surgery of the legs (Tovey, C. & Wyatt, S., 2003). Other than that, inferior vena cava filters are inserted as one of the treatment of DVT to reduce the rate of pulmonary embolism. The indications for their use include pulmonary embolism with contraindication to anticoagulation and recurrent pulmonary embolism despite adequate anticoagulation (Tovey, C. & Wyatt, S., 2003). Besides that, this treatment is also used temporarily and is removed three weeks after the period during which the risk of embolisation is greatest. A small proportion of patients with deep vein thrombosis develop recurrent venous thromboembolic complications or bleeding during anticoagulant treatment. These complications may occur more frequently if these patients have concomitant cancer. These risks correlate with the extent of cancer (Prandoni et al., 2002).

2.9 MANAGEMENT

^{99m}Tc-radiolabeled peptides that target the molecular biology of thrombosis should aid in the management of the disease, particularly in asymptomatic patients at high risk, in patients (Brandjes et al., 1997) with recurrent symptoms, in patients with active DVT in the calf and/or pelvis, and in patients with intermediate- or low-probability lung scans (Line, B. R., 2001). Wearing compression stockings is also suggested as the rate of post thrombotic syndrome may be reduced.

CONCEPTUAL FRAMEWORK

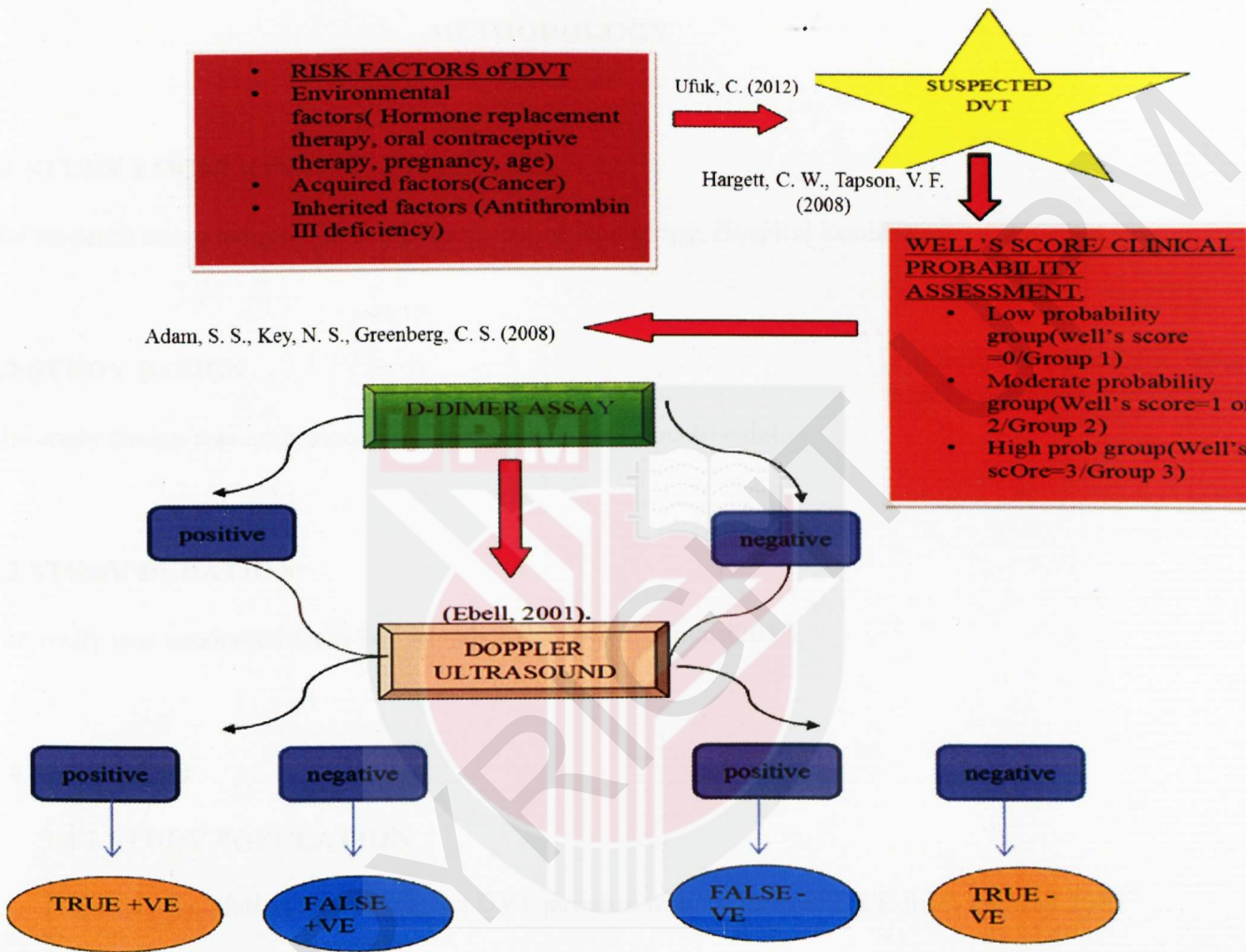


Figure 2.2 Conceptual framework of the research.

CHAPTER 3

METHODOLOGY

3.1 STUDY LOCATION

The research was conducted in the Department of Radiology, Hospital Serdang.

3.2 STUDY DESIGN

The study design was across-sectional study using retrospective data.

3.3 STUDY DURATION

The study was conducted from 26th March 2013 until 6th August 2013.

3.4 SAMPLING

3.4.1 STUDY POPULATION

The study population was suspected DVT patients who underwent DUS from January 2012 until July 2013 in Hospital Serdang.

3.4.2 SAMPLING POPULATION

3.4.2.1 INCLUSION CRITERIA

The inclusion criteria were patients aged between 20 to 80 years old suspected with DVT from January 2012 until July 2013 in Hospital Serdang.

3.4.2.2 EXCLUSION CRITERIA

The inclusion was patients with no D-dimer assay.

3.4.3 SAMPLING FRAME

The sampling frame was a list of medical records of patients who were identified based on their admission registration. All of them were suspected DVT patients who underwent DUS in Hospital Serdang.

3.4.4 SAMPLING UNIT

The sampling unit was a medical record of suspected DVT patient who underwent DUS for DVT in Hospital Serdang.

3.4.5 SAMPLING METHOD

Convenient sampling method was used to choose samples from the lists of medical records of suspected DVT patients who underwent DUS that matched our inclusion and exclusion criteria.

3.4.6 SAMPLE SIZE ESTIMATION

The sample size estimation was calculated based on the formula:

$$n = \frac{Z_{1-\alpha/2}^2 \times P(1-P)}{d^2} = \frac{(1.96)^2 \times 0.07(1-0.07)}{(0.05)^2}$$

$$= 100.035 \approx \mathbf{100 \text{ patients}}$$

z = confidence level at 95% (standard value of 1.96)

α = level of significance

P = prevalence (Tun M et al, 2001)

d = margin of error at 5% (standard value of 0.05)

3.5 DATA COLLECTION

3.5.1. STUDY INSTRUMENT

The study instrument was a pro-forma used to collect the information from the medical record.

3.5.2 DATA COLLECTION TECHNIQUE

The data were collected from the Patients and Laboratory Information System by the researchers.

3.5.3 QUALITY CONTROL

The standardized pro-forma was used to collect the data from each subject. Data collection was monitored by supervisor.

3.6 DATA ANALYSIS

The sensitivity, specificity and the positive-predicting value, and negative predictive value of D-dimer test were calculated.

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.

- 1) Sensitivity : $\text{true positive} / (\text{true positive} + \text{false negative})$
- 2) Positive predictive value : $\text{true positive} / (\text{true positive} + \text{false positive})$
- 3) %False negative : $[\text{false negative} / (\text{false negative} + \text{true positive})] \times 100$
- 4) Specificity : $\text{true negative} / (\text{true negative} + \text{false positive})$
- 5) Negative predictive value : $\text{true negative} / (\text{true negative} + \text{false negative})$
- 6) %False positive : $[\text{false positive} / (\text{false positive} + \text{true negative})] \times 100$
- 7) The association between D-dimer test and DUS in different Well's score groups is obtained by using McNemar test.

3.7 STUDY ETHICS

Ethical approval was obtained from

- A) Ethical Committee of Faculty of Medicine and Health Sciences, University Putra Malaysia (UPM)
- B) Ministry of Health of Malaysia
- C) Director of Hospital Serdang, Serdang, Selangor

The ethics forms were submitted to UPM and Ministry of Health. The approval letter was forwarded to the Director of Hospital Serdang. All the information obtained from the subject was kept confidential. The information was used strictly for our research only.

3.8 STUDY VARIABLES

3.8.1 DEPENDENT VARIABLE

The dependent variable was deep vein thrombosis patient who were identified by using D-dimer test and DUS.

3.8.2 INDEPENDENT VARIABLE

Demographic factors (gender, age and race)

3.9 DEFINITION OF TERM

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

Deep Vein Thrombosis (DVT): DVT is diagnosed to be present when the DUS (diagnostic investigation of DVT) shows positive result. DUS shows positive result when there is a clot/thrombus found in the vein of the suspected DVT patients. The DVT status of the patients was obtained from the result of DUS which was performed by the radiologist of Hospital Serdang. The information was obtained from the medical record.

D-dimer level: D-dimer test is used as a screening tool to diagnose patients with DVT. The value of the D-dimer level was obtained from the medical record. The D-dimer level shows positive result when the level is $>0.5\mu\text{g/dL}$ and vice versa.

Doppler ultrasound (DUS): DUS is the diagnostic test to diagnose patients with DVT in Hospital Serdang. A positive DUS result shows that the patient suffers from DVT meanwhile a negative DUS result excludes DVT. The result of DUS was obtained from the medical record written by the attending physician.

Well's score: Well's score is a score given to a person to evaluate the clinical probability of that person to suffer from DVT. It uses Well's criteria as the reference in order to categorize the patients into either low risk group (Score ≤ 0 ; Group 1), moderate risk group (Score = 1 or 2; Group 2) or high risk group (Score ≥ 3 ; Group 3). The minimum score is 1 meanwhile the highest score is 3. The higher the score, the higher the probability of that person to suffer from DVT. The score is given by the researchers based on the medical note of the patients written by the clinician.

CHAPTER 4

DATA ANALYSIS

4.1 RESPONSE RATE

Our initial study population was patients with suspected DVT who went for DUS from August 2012 until July 2013. The total number of patients during this period was 130 people. Out of 130 patients, 48 of them had no D-dimer assay done, 2 of the patients did not undergo DUS test meanwhile 1 of them was below 20 years old. So, from August 2012 until July 2013, there were only 79 patients eligible to be included in our study meanwhile 51 patients had to be excluded. Since there were 21 more patients needed to meet our sample size requirement (100 patients), we had to extend our study population period. A total of 100 patients were managed to be obtained after extending the study population period from January 2012 until July 2013. Between those periods, there were a total of 213 suspected DVT patients. Out of that, 108 of them had no D-dimer assay done, 4 patients did not undergo DUS meanwhile 1 patient had to be excluded because he did not fulfill the age requirement (below 20 years old). Thus, within those periods, 100 samples were finally achieved but a total of 113 patients had to be excluded. Therefore, since we managed to fulfill our sample size requirement, our response rate was 100%.

4.2DEMOGRAPHIC CHARACTERISTIC OF RESPONDENTS

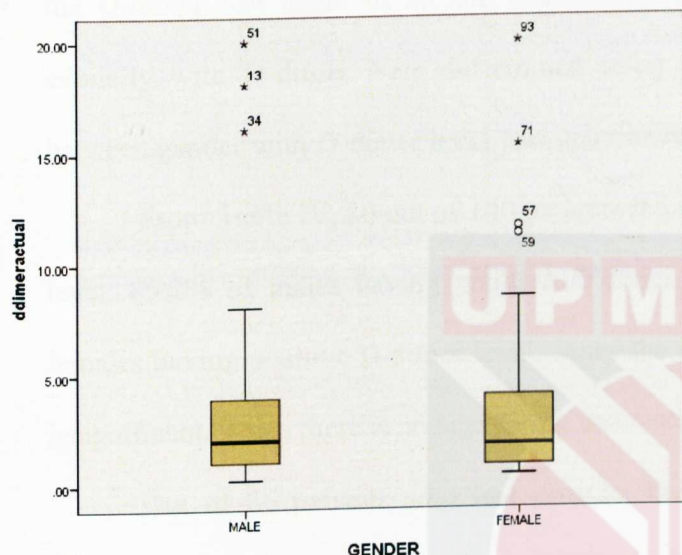
Table II shows the distribution of demographic characteristics of 100 patients of samples that had been collected. Among 100 patients, male (54%) is more than female(46%). The age of the patients was normally distributed. From all the patients, most of them were from the age group of 50 until 80, that was about 62%. The data for age of the patients was normally distributed. Thus mean is used to interpret the data. Mean of age was 53.29~53 years old (standard dev. =14.81). From the view of ethics, Malay (59%) was the majority among the sample,then was Chinese(22%) and last was Indian(19 %).

Table II: Distribution of respondents by demographic characteristics.

Demographic characteristics	Frequency	Percentage
Age		
20-≤50	38	38
50-≤80	62	62
Gender		
Male	54	54
Female	46	46
Race		
Malay	59	59
Chinese	22	22
Indian	19	19

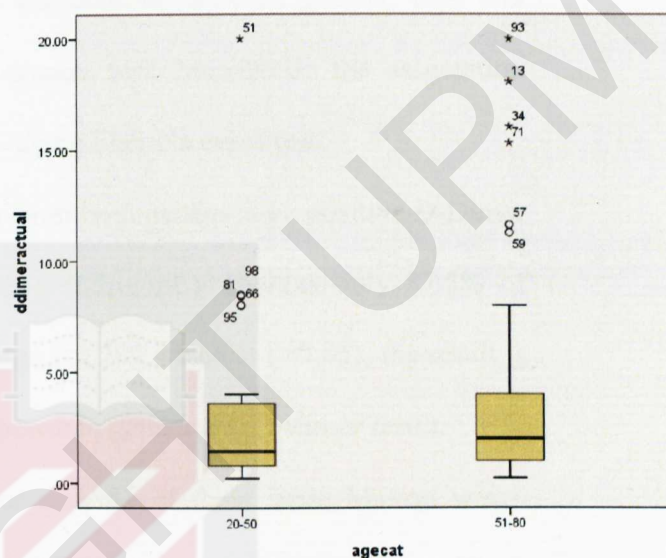
4.3 D-dimer level by demographic characteristics and Well's score group among all respondents.

Figure 1: Boxplot of D-dimer level in both gender.



The D-dimer level in males was found to be higher.

Figure 1: Boxplot of D-dimer level in different age groups.



The D-dimer level was found to be slightly higher in 50-80 years old age group compared to 20-50.

Table III shows the D-dimer level of respondents in different Well's score group. From Table III, it was found that most of the respondents were in moderate risk group of patients and the D-dimer level was found to be the highest in high risk group patients.

Table III: The D-dimer level of respondents in different Well's score group.

Well's score	Frequency	Percentage	D-dimer level	
			Median	IQR
Risk of DVT				
Low	37	37%	2.73	3.22
Moderate	60	60%	1.85	2.88
High	3	3%	2.75	-

4.4 Associations between demographic factors and Well's score group with the D-dimer level.

Table IV shows the association between gender, age, race and Well's score group with the D-dimer test result of all the respondents. The associations between gender, race and ethnicity with D-dimer were determined using Chi-square test. Meanwhile the association between gender with D-dimer level was determined by using Fisher's exact test.

From Table IV, 86 out of 100 patients (86.0%) from both gender have positive D-Dimer level. 85.2% of males having positive D-dimer level ($>0.5\mu\text{g/mL}$) whereas only 87.5% of females having positive D-dimer level. Since the p value is 0.799 which is (>0.05), the result is insignificant. Thus, there is no significant association between gender and D-dimer result.

Out of 86 patients who had positive D-dimer test, 51 of them were Malays which account for 59%. Since the p value is 0.539 which is (>0.05), the result is not significant. Thus, there is no significant association between race and D-dimer result. Meanwhile it is observed that the D-dimer positive result was found to be higher in age group 51-80 years old. But this result is insignificant because the p value is more than 0.05. Thus, there is no significant relationship between age and the D-dimer level.

From the table, all patients who are in high risk group (Well's score = 3) have positive result in both D-dimer and DUS. Since the p value is 0.761 which is (>0.05), the result is not significant. Thus, there is no significant association between Well's score and D-dimer result.

Table IV: Associations between (gender, age and race) and D-dimer test result.

		D-dimer result		Total	P value
		Positive	Negative		
Gender	Male	46	8	54	0.799
	% within gender	85.2%	14.8%		
	Female	40	6	46	
	% within gender	87.0%	13.0%		
Age	20-50	34	4	38	0.558*
	% within age	89.5%	10.5%		
	51-80	52	10	62	
	% within gender	83.6%	16.4%		
Race	Malay	51	8	59	0.539
	% within race	86.4%	13.6%		
	Chinese	20	2	22	
	% within race	90.9%	9.1%		
	Indian	15	4	19	
	% within race	78.9%	21.1%		
Well's score group	0	32	5	37	0.761
	% within group	86.5%	13.5%		
	1-2	51	9	60	
	% within group	85.0%	15%		
	3	3	0	3	
	% within group	100%	0%		

* uses Fisher's exact test

4.5 Sensitivity and specificity of the D-dimer test.

Table V shows the result of a screening test (D-dimer test) and DUS in suspected DVT patients.

From Table V, the sensitivity and specificity of the D-dimer test can be calculated. The calculation is shown below:

$$\text{Sensitivity} = \frac{(\text{True Positive/TP})}{(\text{True Positive/TP}) + (\text{False Negative/FN})} \times 100$$

$$= \frac{23}{23+1} \times 100$$

$$= 95.8\%$$

The sensitivity calculated is 95.8% which is very high. As the sensitivity of the test increases, the number of people with the disease DVT who are missed by being incorrectly classified as negative (false negative) will decrease.

$$\text{Specificity} = \frac{(\text{True Negative/TN})}{(\text{True Negative/TN}) + (\text{False Positive/FP})} \times 100$$

$$= \frac{13}{13+63} \times 100$$

$$= 17.1\%$$

The specificity of the D-dimer assay used is 17% which is considered to be very low. This may suggest a high number of false positive results. In the research, we had 100 respondents.

Among of 100 patients, 86 were positive in D-dimer while 14 were negative. However , there are only 23 patients were positive in DVT in the group of positive D-dimer , and 1 patient positive in DVT who was negative in D-dimer. Sensitivity of D-dimer test was 95.8% while the specificity was 17%. This shows that the D-dimer test has high sensitivity and very low specificity. D-dimer test will provide many false positive.

Table V: Result of D-dimer and DUS done on all suspected DVT patients.

		DUS result		Total
		Positive DUS	Negative DUS	
D-dimer result	Positive D-dimer	23	63	86
	Negative D-dimer	1	13	14
Total		24	86	100

4.6 The concordance between the D-dimer and DUS test among the low, moderate and high risk group of patients.

Table VI shows the result of D-dimer test and DUS in low, moderate and high risk group patients. From Table VI, for low risk group, since p value is <0.001 (<0.05), the result is significant. Thus, in the McNemar test used, therefore there is no concordance between D-dimer test with Doppler ultrasound in low risk group patients. The difference in percentages of DVT detected between D-dimer and Doppler ultrasound is 83.8% $[(32-1)/37 \times 100=83.8\%]$ in low risk group. Thus, D-dimer is more likely to wrongly diagnose by 83.8%.

Meanwhile, for moderate risk group, since the result is significant, therefore there is also no concordance between D-dimer tests with DUS. The difference in percentages of DVT detected between D-dimer and DUS is 51.7% $[(51-20)/60 \times 100=52\%]$. Thus, D-dimer is more likely to wrongly diagnose by 51.7%.

Table VI: D-dimer and DUS result in different Well's score group.

Risk of DVT	D-dimer result	Doppler Ultrasound result		Total	P value
		Positive	Negative		
Low Risk group (Well's score : 0)	Positive	1	31	32	<0.001
	Negative	0	5	5	
Total		1	36	37	
Moderate Risk Group (Well's score : 1 or 2)	Positive	19	32	51	<0.001
	Negative	1	8	9	
Total		20	40	60	
High Risk group (Well's score : 3)	Positive	3	0	3	0.578
	Negative	0	0	0	
Total		3	0	3	

Meanwhile, Table VII shows the result of sensitivity, specificity, positive predictive value/PPV and negative predictive value/NPV of patients in different Well's score group (low, moderate or high risk group). From Table VII, in low risk group patients, the sensitivity of the D-dimer test is 100%. Meanwhile the NPV of D-dimer test is 1. This means, in low risk group patients, a negative D-dimer test patient would have 100% chance of obtaining a negative DUS result, thus having no DVT. In moderate risk group patients, the NPV is quite high (0.89). Meanwhile, for high risk group patients, the sensitivity is 100% and the PPV is 1. This means, in high risk group patients, a positive D-dimer test patient would be 100% likely to have a positive DUS result, thus having a positive DVT status.

Table VII: Sensitivity, specificity, positive predictive value/PPV and negative predictive value/NPV of patients in different Well's score group (low, moderate or high risk group).

Risk groups of DVT	Low risk group	Moderate risk group	High rik group
Sensitivity	$= [1/(1+0)] \times 100$ $= 100\%$	$= [19/(19+1)] \times 100$ $= 95\%$	$= [3/(3+0)] \times 100$ $= 100\%$
Specificity	$= [5/(5+31)] \times 100$ $= 13.9\%$	$= [8/(8+32)] \times 100$ $= 20\%$	$= [0/(0+0)] \times 100$ $= 0\%$
PPV	$= 1/(1+31)$ $= 0.03$	$= 19/(19+32)$ $= 0.37$	$= 3/(3+0)$ $= 1$
NPV	$= 5/(5+0)$ $= 1$	$= 8/(8+1)$ $= 0.89$	$= 0/(0+)$ $= \text{undefined}$

CHAPTER 5

DISCUSSION

5.1 Demographic characteristics of respondents

5.1.1 Gender

In our study involving suspected DVT patients, male (54%) was found to be more than female (46%). Our result was supported by the study done by White, R. H., Dager, W. E., Zhou, H., Murin, S., 2006. Men have been reported to have a higher incidence of recurrent DVT than women. The findings of this study confirmed the results from prior studies that have reported that women are less likely than men to develop recurrent DVT. A study done by Kyrle et al, showed that the patient's sex is not a major determinant of recurrent DVT after an initial episode of spontaneous DVT.

5.1.2 Age

From all the patients, most of them were from the age group of 50-≤80 years old, that was about 62 %. The mean of age in our study was 53 years old. From a study done by Nordstrom, M., Lindblad, B., Bergqvist, D., & Kjellstrom, T., it was found that the mean age of patients with suspected DVT was 64 ± 17 years old. This finding might be hypothesized based on several factors which state that aging is associated with an increase in D-dimer level due to a number of autoimmune, degenerative and vascular diseases (Pieper et al, 2000).

5.1.3 Race

From the view of ethnics, Malay (59%) was the majority among the sample, then was Chinese (22%) and last was Indian (19%). From the previous study that was done in North Carolina, it was found that the number of suspected DVT cases reported were higher in Blacks, (Black: 52.98; non Black: 47.02%) (Pieper et al., 2000). However, there were no Malay, Chinese and Indian in USA. Hence, we cannot compare the previous study with our study.

5.2 D-dimer level by demographic characteristics and Well's score group among all respondents.

5.2.1 Gender

From our study, it was found that the D-dimer level was found to be higher in males; with a median value of D-dimer of 2.00. However, our finding contraindicated with a study done by Pieper et al which stated that mean log of D-dimer level was found higher in female. This might be because there were 57 pregnant ladies participated in the study. Meanwhile, in our study, there were only 5 pregnant ladies. Pregnant women show the highest risk of developing pathological thrombosis (Dickson, B., 2004). Thus, that might be the factor that leads to the difference in the finding. However Pieper et al also found that gender was a non-significant factor that can affect the D-dimer level.

5.2.2 Age

In our study, it was found that the median of D-dimer level in elderly ($50 \leq 80$ years old) was higher than those in age group of $20 \leq 50$ years old. This is consistent with several previous reports showing high D-dimer levels in elderly subjects (Hager K, & Platt D, 2000).

5.2.3 Well's score

From our study, it was found that patients who are in high risk group has the highest median of D-dimer level of $2.75 \mu\text{g/dL}$. Meanwhile, for low risk group is $2.73 \mu\text{g/dL}$ and low risk group is $1.65 \mu\text{g/dL}$. This result is supported by the previous study which showed that the highest D-dimer level is found in high risk group $6.8 \mu\text{g/dL}$. (Douma, et al, 2010)

5.3 Association between demographic characteristic and Well's score with D-dimer result.

5.3.1 Gender

This study indicated that there was no significant association between gender and D-dimer level. The previous study also supported our findings. Study done by Pieper et al., found that gender was a non-significant predictor, but somehow women demonstrated slightly lower values of D-dimer. This study was done in Duke's University and it was reported that there was no significant association between gender and D-dimer level with a p-value of 0.2555. The reason was probably because our sample was small. Since we only had 100 samples, thus the result may be affected since we do not have enough data to prove the significance of the result.

5.3.2 Age

In our study, it was found that there was no significant relationship between age and the D-dimer level. Hence, there was no association between age and D-dimer level. The present study contraindicates with the findings of the previous study. In the previous study done by Pieper et al, age was positively correlated with high D-dimer levels ($p = 0.0001$) by the Kruskal-Wallis test. Aging is associated with an increase in D-dimer level due to a number of autoimmune, degenerative and vascular diseases (Pieper et al, 2000). With the reason that the sample size in our study was small, which is only 100 patients, compared to 1727 samples in the previous study, thus the data collected is insufficient to prove that there is a significant association between age and D-dimer level.

5.3.3. Ethnicity

This current study indicated that there was no significant association between ethnics and D-dimer level. In our study, there were three main ethnics; Malay, Chinese, Indian. These three ethnics were not equal in ratio. Hence, we cannot compare the three ethnics with D-dimer level. From the previous study that was done in United State states, there was different among white man and non-white man in USA (Flack, J. M., Ferdinand K. C., & Nasser, S. A., 2003). However, there were no Malay, Chinese and Indian in USA. Hence, we cannot compare the previous study with our study.

5.3.4 Association between Well's score and D-dimer level

Patients who were in moderate risk group (Well's score = 1 or 2) has the highest number of people who have positive D-dimer test (59.3%). All patients who were in high risk group (Well's score = 3) have positive result in both D-dimer and DUS. Since the p value is 0.761 which is (>0.05), the result is not significant. Thus, there was no significant association between Well's score and D-dimer result. However, in the previous study, there was a significant association between Well's score and D-dimer level (Douma, 2010). The reason our finding was found to be not significant might be due to the present study only used information obtained through medical record and pro-forma (secondary data), there could be some information bias involved. This is because the information obtained is purely dependant on the information written by the physician (eg: risk factor, clinical signs and symptoms). Thus, any discordance done by the physician would indirectly affect our result.

5.4 Sensitivity and specificity of the D-dimer test

Sensitivity of D-dimer test was 95.8% in the diagnosis of DVT while the specificity was 17%. This shows that the D-dimer test used in Hospital Serdang was highly sensitive but very low in specificity. Thus, D-dimer test may provide many false positive results. However, in the comparison with the previous study, the D-dimer test showed a high sensitivity and moderate specificity. The VIDAS D-dimer assay showed a sensitivity of 98.2%, but specificity was 40.7% (Dempfle et al., 2006). The sensitivity of D-dimer test in our study still preserved quite high sensitivity when compared to previous study (95.8% vs 98.2%). However, when viewing into the specificity of the D-dimer, it had a mere 23.6% which is much lower from previous work (Dempfle et al., 2006).

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 some of the female patients. The results might also be affected by the number of sample size we had, that was only 100 patients. In the comparison with previous study, the sample size of the study was 560 patients (Dempfle et al., 2006). Hence, a large sample size would provide a more accurate result. Besides, high concentrations of D-dimers are insufficiently specific for making a positive diagnosis of DVT. This is because a high level of D-dimer not only occurs in DVT but also as well as in other disorders such as malignancy, pregnancy, trauma and post surgery (Aschwanden et al., 1999) leading to a false positive result of the test.

5.5 The concordance between the D-dimer and DUS test among the low, moderate and high risk group of patients

There is no concordance between D-dimer test with DUS in low and moderate risk group patients. Meanwhile, D-dimer test and DUS only show concordance in the high risk group. However, previous study showed that Well's criterion is useful. The pre-test probability (Well's criteria for DVT) is best assessed using a clinical prediction guide (CPG). A low pre-test probability of DVT plus a negative D-dimer result can be combined in a Bayesian fashion to effectively rule out DVT (Hargett, C. W., & Tapson, V. F., 2008).

However, when we calculated the sensitivity and specificity of D-dimer test separately in different risk groups, in a low risk group (Well's score of 0), the negative predictive value (NPV) was 100%, thus showed that a Well's score of 0 or less, combined with a normal D-dimer test, is thought to lower the risk of misdiagnosing DVT and make diagnostic lower leg ultrasonography unnecessary (Goodacre, S., Sutton, A. J., & Sampson, F. C., 2005). This would

be more cost effective at a long run as unnecessary examinations can be avoided. In the research conducted by Goodacre et al, a normal D-dimer result is proven to be able to rule out DVT in low risk group patients. Meanwhile, in high risk group patients (Well's score of 3), D-dimer test showed 100% sensitivity and positive predictive value (PPV) of 1.



CHAPTER 6

CONCLUSION

D-dimer assay used in Hospital Serdang has a high sensitivity value (95.8%) meanwhile a very low specificity (17%). Thus there might be a lot of patients to be wrongly diagnosed to suffer from DVT. Next, there is also no concordance between D-dimer test and DUS (diagnostic test used to diagnose patients with DVT in Hospital Serdang) in low and moderate risk group. The presence of concordance is only proven in the high risk group with 100% sensitivity and PPV of 1. Hence, the high risk patients (Well's score of 3) who are suspected with DVT can directly proceed with DUS without D-dimer test. However, in low risk patients, with NPV of 1, a negative D-dimer result may be able to exclude presence of DVT thus obviates the need for further imaging test.

LIMITATION OF THE STUDY

The limitations present in this study were small sample size and non probability sampling method. Convenient sampling method is a type of non probability sampling method. 85 patients had to be excluded from the study due to absence of D-dimer assay result. Thus, we had to use the convenient sampling method in which we had to extend the sampling frame period. Non probability sampling method had affected the sample size indirectly. Non probability method does not represent the population as a whole compared to other sampling methods. Bias may present in the study because non probability sampling method is not random. Small sample size had affected the sensitivity and specificity of the D-dimer test. Small sample size also restricted the comparability between the D-dimer test and DUS.

Besides that, since the present study only used information obtained through medical record and pro-forma (secondary data), there could be some information bias involved. This is because the information obtained is purely dependant on the information written by the physician (eg: risk factor, clinical signs and symptoms). Thus, any discordance done by the physician would indirectly affect our result.

Next, Hospital Serdang physicians do not use Well's criteria to estimate the pre-test probability of a patient who suffer from DVT. Meanwhile, Well's criteria is used in our pro-forma to obtain the Well's score in order to categorize the patients into either low, moderate or high risk group of developing DVT. Thus, we have to refer on the clinical note written by the attending physician and give score to the patients on our own. There might be some error during scoring the patients which may cause us to miscategorise the patients. This will finally affect our result on the association between Well's score and D-dimer level.

RECOMMENDATION

We would like to suggest that the attending physicians dealing with suspected DVT cases to score the patients and group them into either low, moderate or high risk groups prior to proceeding to other diagnostic tests. A prospective study using Well's score with D-dimer level coupled with Doppler ultrasound is needed to further validate our study. This would ease the future researchers to categorize the patients by using the Well's score and thus enable them to obtain a more accurate result.

In our opinion, the low risk group patients may not require further imaging with DUS if their D-dimer result shows negative since the NPV of D-dimer test is 1. This would be more cost effective at a long run as unnecessary examinations (DUS) can be avoided.

Meanwhile, for high risk group patients, since the PPV is 1, they may not have to undergo D-dimer test since DUS (diagnostic test to rule out DVT in Hospital Serdang) still needs to be performed in order to rule out DVT despite the patients having either positive or negative D-dimer result. This too would be more cost effective at a long run as unnecessary examinations (D-dimer) can be avoided.

Lastly, we would like to suggest the clinicians in Hospital Serdang to use Well's criteria as a pre-clinical test to evaluate the suspected DVT patients. Well's criteria has been proven to be best assessed using a clinical prediction guide (CPG) to effectively rule out DVT (Hargett, C. W., & Tapson, V. F., 2008).

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APPENDIX 1: GANTT CHART

		2012											
		PHASE I				PHASE II							
	Weeks	1	2	3	4	17	18	19	20	21	22	23	24
1	Preparation of draft proposal												
2	Submission of draft proposal												
3	Preparation, submission and presentation of final proposal												
4	Preparation of ethical approval and permission letters to organizations												
5	Data collection and analysis												
6	Submission of data analysis and presentation												
7	Preparation of project report and scientific article												
8	Submission of project report and scientific article												
9	Preparation of final presentation												
10	Final presentation												
11	Correction of final report												
12	Submission of final report, scientific article												

Research team**Supervisor**

Dr Suraini bt Mohamad Sani

Co-supervisors

Dr Hasyma bt Abu Hassan

Members

Siti Hajar bt Darussalam

Jacky Tein Fuwen

Budget planning

No	Items	Estimated cost
1.	Printing	RM 50.00
2.	Hard cover	RM 200.00
3.	Photocopy	RM 100.00
4.	Binding	RM 10.00
5.	Transportation	RM 80.00
	Total	RM 440.00

Pro Forma

SD No:

Suspected DVT: ☐ Yes ☐ No

Age : Date of birth:

Gender :

D-dimer level :

Race :

DUS result: ☐ Yes ☐ No

If present	Score
Risk factors	
Active cancer (treatment ongoing or within previous 6 months or palliative)	(1)
Recently bedridden more than 3 days or major surgery within 4 weeks	(1)
Clinical Signs	
Localized tenderness along the distribution of the deep venous system	(1)
Entire leg swollen	(1)
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	(1)
Pitting odema confined to symptomatic leg	(1)
Collateral superficial veins (non-varicose)	
Alternative diagnosis as likely or greater than that of DVT	(-2)

High probability- more than 3 marks

Moderate probability-1 to 2 marks

Low probability -0 mark

