A Prospective Observational Study on Post-Operative Major Surgical Patients Developing Silent Deep Vein Thrombosis at Hospital Universiti Sains Malaysia

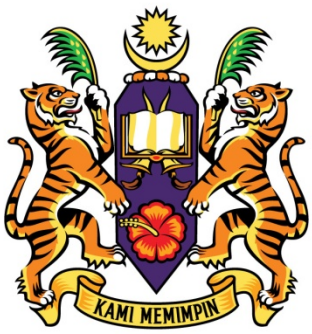
by

Dr Wong Pak Kai (Michael)

MBChB (Sheffield)

Dissertation Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Medicine

M.Med (Surgery)



2014

A Prospective Observational Study on Post-Operative Major Surgical Patients Developing Silent Deep Vein Thrombosis at Hospital Universiti Sains Malaysia

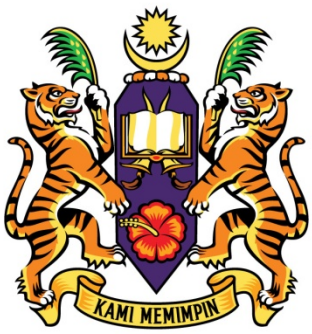
by

Dr Wong Pak Kai (Michael)

MBChB (Sheffield)

Dissertation Submitted in Partial Fulfillment of the Requirement for the Degree of Master of Medicine

M.Med (Surgery)



2014

ACKNOWLEDGEMENTS

This dissertation would not have been possible without the guidance and the help of several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this study.

First and foremost, I would like to express my sincere gratitude to my supervisor, Mr Mohd Nor Gohar Rahman, the Head of Department of Surgery, School of Medical Sciences, USM, for his continuous support, for his patience, motivation, enthusiasm, and immense knowledge. His guidance has helped me in all the time of research and writing of this thesis.

This thesis would not have been possible without the help of my co-supervisor, Mr Zaidi, who has contributed tremendously in this study with his genuine ideas, suggestions and inputs in the effort of initiation of this study and his never ending encouragements and supports.

This thesis would be left incomplete without the dedicated radiologists, Dr. Rohsila Muhammad, Associate Professor Dr. Mohd Shafie Abdullah and Dr. Juhara Haron, for their utmost dedications in performing the ultrasonographic scans; they have to come in to perform even on public holidays and at wee hours with not even a sigh or grudge. Thank you so much.

Many thanks also forwarded to Pn. Anis Kausar and immense gratitudes to Dr Muhammad Irfan Abdul Jalal who helped me through with the difficult statistical analysis part of this project and his valuable timeless statistical consultations.

To my family, my beloved wife Dr Wong Mung Seong and my two beautiful daughters, Tiffany and Charlotte Wong, who have been very patience and steadfast during this difficult period, for which I am truly grateful. To my parents, Mr. Wong Liong Yew and Madam Ting Leng Ching, who bore me, raised me, educated me, and not to mention fully supported and loved me. For they have sacrificed with all their endless effort to make me a better person, to endure my future and provide me opportunity to pursue my dream and destiny. To them I dedicate this thesis.

Many gratitudes to my fellow colleagues, especially Dr Rusli and Dr Bazli who has helped me in many ways. We have shared invaluable moments and fruitful experiences during our years in master program especially during the hardship in facing the exit examinations.

And one above all of us, the omnipresent God Almighty, Creator of Heaven and Earth; for answering my prayers, for surplus me the strength at the time I was weak and despair. “but those who hope in the LORD will renew their strength. They will soar on wings like eagles; they will run and not grow weary, they will walk and not be faint.” (Isaiah 40:31). Thank you, LORD.

Dr Michael Pak Kai WONG

TABLE OF CONTENTS

CONTENTS **PAGE**

CONTENTS **PAGE**

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CVA	Central Venous Access
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
IJV	Internal Jugular Vein
IQR	Interquartile range
NICE	National institute of clinical excellence
PCC	Intermittent Pneumatic Calf Compression Pumps
PS	Power and sample size
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
STATA	Statistics & Data
TDS	Graduated Compression Stocking / Thrombo-Deterrent Stockings
VTE	Venous Thromboembolism

LIST OF SYMBOLS

%	percentage
/	or
:	ratio
<	less than
=	equal to
>	more than
®	trademark registered
1-β	statistical power
m	ratio of control / cases
n	number of subjects
p_{stat}	p value
q^{stat}	1-prevalence
™	trademark unregistered
vs	versus
α	type 1 error
Δ	precision

ABSTRAK

KAJIAN PROSPEKTIF DIKALANGAN PESAKIT SURGERI YANG MENGALAMI TROMBOSIS PADA VENA DALAM SECARA "SENYAP" DI HOSPITAL UNIVERSITI SAINS MALAYSIA

Pengenalan: Trombosis vena dalam berbentuk senyap adalah salah satu komplikasi yang mengancam nyawa pesakit-pesakit surgeri. Setakat ini, hanya satu kajian yang telah melaporkan kes-kes baru (insiden) thrombosis pada vena secara senyap di Malaysia. Selain daripada itu, tiada usaha setakat ini untuk menilai penggunaan model penilaian risiko Caprini untuk mengenalpasti subjek yang memerlukan pencegahan thrombosis pada vena dalam secara senyap (DVT).

Objektif: Tujuan kajian ini adalah untuk menentukan insiden trombosis vena dalam secara "senyap" dan menilai potensi kepenggunaan model penilaian risiko Caprini dalam mengenalpasti pesakit yang memerlukan pencegahan DVT.

Metodologi: Ini adalah kajian prospektif kohort yang melibatkan 55 orang pesakit surgeri di HUSM yang mempunyai risiko tinggi untuk mengalami thrombosis vena dalam secara senyap. Setiap subjek telah menjalani pemeriksaan ultrabunyi dupleks bagi sistem vena dalam sebelum dan selepas pembedahan yang dijalankan oleh dua orang pakar radiologi. Skor risiko Caprini dikira untuk setiap subjek dan pemberian pencegahan DVT kemudiannya dibuat berdasarkan keputusan pakar klinikal yang bertanggungjawab terhadap pesakit tersebut, yang tidak mengetahui skor risiko Caprini. Hubungkait antara skor risiko Caprini dan pemberian pencegahan DVT di analisa secara statistik dengan menggunakan

kaedah regressi linear dan logistic mudah. Nilai p yang kurang daripada 0.05 dianggap mempunyai kesan yang ketara dari segi analisa statistik.

Keputusan: Tiada subjek mengalami trombsis vena dalam (kadar insiden = 0% (n=0)). Terdapat hubungkait yang ketara antara pencegahan DVT dan skor Caprini (nisbah ganjil 8.16 (95% selang keyakinan: 1.01, 68.74), nilai p = 0.016). Selain itu, penggunaan keteter vena utama juga mempunyai hubungkait yang ketara dengan pencegahan DVT (nisbah ganjil 6.34 (95% selang keyakinan 1.62, 24.80), nilai p = 0.008). Menariknya, penggunaan keteter pada vena utama menyebabkan peningkatan skor risiko Caprini sebanyak 4 unit (purata kenaikan : 4.186 (95% selang keyakinan 3.164, 5.207, nilai p <0.001) berbanding sebanyak 2 skor yang pada kebiasaannya diberikan terhadap faktor risiko ini.

Kesimpulan: Trombosis pada vena dalam secara "senyap" secara nyatanya tidak wujud dalam kajian ini. Penggunaan pencegahan DVT secara berhemat yang berpandukan penggunaan skor risiko Caprini secara tidak langsung sepanjang praktis klinikal harian mungkin boleh menerangkan ketiadaannya thrombosis pada vena dalam secara "senyap" semasa kajian ini. Walaubagaimanapun, kajian lanjut adalah diperlukan untuk mempercirikan penggunaan skor risiko Caprini untuk meramalkan kewujudan thrombosis vena dalam secara "senyap" di persekitaran kajian ini.

ABSTRACT

A PROSPECTIVE OBSERVATIONAL STUDY ON POST-OPERATIVE MAJOR SURGICAL PATIENTS DEVELOPING SILENT DEEP VEIN THROMBOSIS AT HOSPITAL UNIVERSITI SAINS MALAYSIA

Introduction: Silent deep vein thrombosis (DVT) is one of the life-threatening complications affecting surgical patients. So far there is only one study documenting the incidence of silent DVT in Malaysia. Besides, no efforts have been made to evaluate the use of Caprini risk assessment model to identify subjects who are in need of prompt DVT prophylaxis.

Objectives: The aims of this study are to determine the incidence of silent DVT and evaluate the potential utility of Caprini risk assessment model to target high risk subjects for DVT prophylaxis.

Methods: This is a prospective cohort study involving 55 HUSM surgical subjects who are at risk of silent DVT. Each subject had a preoperative and postoperative compression ultrasound complemented by duplex venous ultrasonography of deep venous system performed by two separate radiologists. Caprini risk assessment scores were calculated for each study participants and the decision on the administration of DVT prophylaxis was made based on the clinical judgement of the clinicians in charge without knowing the calculated Caprini risk scores. The association between DVT prophylaxis and Caprini risk scores were analysed using simple logistic regression. Any p value that is less than 0.05 is considered statistically significant.

Results: Not a single subject developed DVT (incidence rate of silent DVT = 0%, n=0). There is a significant association between DVT prophylaxis and Caprini risk scores (OR 8.16 (95% CI: 1.01, 68.74), p value = 0.008). Besides, the use of central venous catheter is also significantly associated with the use of DVT prophylaxis (OR 6.34 (95% CI: 1.62, 24.80), p value = 0.016). Interestingly the use of central venous catheter resulted in more than 4 point increment of Caprini risk scores (mean increment: 4.186 (95% CI: 3.164, 5.207), p value <0.001) instead of the usual 2 points allotted to this risk factor.

Conclusion: Silent DVT is virtually non-existent in this study setting. The judicious use of DVT prophylaxis, which is guided by the inadvertent use of Caprini risk score during day-to-day practice, may explain the effective prevention of silent DVT at this setting. Nevertheless, further studies are warranted to further characterize the utility of Caprini risk assessment scores for the prediction of silent DVT in this setting.

A PROSPECTIVE OBSERVATIONAL STUDY ON POST-OPERATIVE MAJOR SURGICAL PATIENTS DEVELOPING SILENT DEEP VEIN THROMBOSIS AT HOSPITAL UNIVERSITI SAINS MALAYSIA

Dr Wong Pak Kai (Michael)

MMed Surgery

Department of Surgery,

School of Medical Sciences, Universiti Sains Malaysia

Health Campus, 16150 Kelantan, Malaysia

Introduction: Silent deep vein thrombosis (DVT) is one of the life-threatening complications affecting surgical patients. So far there is only one study documenting the incidence of silent DVT in Malaysia. Besides, no efforts have been made to evaluate the use of Caprini risk assessment model to identify subjects who are in need of prompt DVT prophylaxis.

Objectives: The aims of this study are to determine the incidence of silent DVT and evaluate the potential utility of Caprini risk assessment model to target high risk subjects for DVT prophylaxis.

Methods: This is a prospective cohort study involving 55 HUSM surgical subjects who are at risk of silent DVT. Each subject had a preoperative and postoperative compression ultrasound complemented by duplex venous ultrasonography of deep venous system performed by two separate radiologists. Caprini risk assessment scores were calculated for each study participants and the decision on the administration of DVT prophylaxis was made based on the clinical judgement of the clinicians in charge without knowing the calculated Caprini risk scores. The association between DVT prophylaxis and Caprini risk scores were analysed using simple logistic regression. Any p value that is less than 0.05 is considered statistically significant.

Results: Not a single subject developed DVT (incidence rate of silent DVT = 0%, n=0). There is a significant association between DVT prophylaxis and Caprini risk scores (OR 8.16 (95% CI: 1.01, 68.74), p value = 0.008). Besides, the use of central venous catheter is also significantly associated with the use of DVT prophylaxis (OR 6.34 (95% CI: 1.62, 24.80), p value = 0.016). Interestingly the use of central venous catheter resulted in more than 4 point increment of Caprini risk scores (mean increment: 4.186 (95% CI: 3.164, 5.207), p value <0.001) instead of the usual 2 points allotted to this risk factor.

Conclusion: Silent DVT is virtually non-existent in this study setting. The judicious use of DVT prophylaxis, which is guided by the inadvertent use of Caprini risk score during day-to-day practice, may explain the effective prevention of silent DVT at this setting. Nevertheless,

further studies are warranted to further characterize the utility of Caprini risk assessment scores for the prediction of silent DVT in this setting.

Dr Mohd Nor Gohar Rahman: Supervisor

Dr Zaidi bin Zakaria: Co-Supervisor

A.Prof Mohd Shafie Abdullah: Co-Supervisor

Dr Rohsila Muhamad: Co-Supervisor

CHAPTER ONE

INTRODUCTION

1.1 SCIENTIFIC BACKGROUND OF VENOUS THROMBOEMBOLISM

Venous thromboembolism imposed a great impact on the mortality of the surgical and medical patients. It is the most preventable cause of death in surgery. Venous thromboembolism is a broad term used to describe deep vein thrombosis and also pulmonary embolism. The natural history of venous thromboembolisms are resolution, propagation, recanalization and embolization. The pathogenesis of venous thromboembolism is multifactorial. Up to date, there is still no single independent predicting factors that have a direct relationship with increase occurrence of deep vein thrombosis. Rudolf Virchow, a German Pathologist, made famous as the Father of Pathologist in his era postulated the pathogenesis of the formation of thrombus through the classical Virchow's triad: endothelial injury, blood stasis and hypercoagulability. With the presence of any of the components in the triad, there would be increased risk of thrombus formation. Efforts have been made over the years to study its pathogenesis and also to device a tool to predict its coming and outcome. Post-operative venous thromboembolism is reported as one of the most preventable hospital morbidity and mortality in today's practice of the anti-thomboprophylaxis agent.

1.2 EPIDEMIOLOGY OF DEEP VEIN THROMBOSIS

In an International Multicentre trial on antithrombotic prophylaxis, they documented the clinical deep vein thrombosis in post-operative period to be as high as 31% (211/667) whilst in those with prophylaxis heparin is 8.5% (53/667). They also

reported that the time of onset of the clinical deep vein thrombosis is highest from the third to the sixth days post operative period in both control and heparinized groups (Kearon, 2003; Kakkar *et al.*, 1975). Wilasusmee *et al*. (2009) reported the prevalence of 10.5% of their patients admitted to ICU with presence of deep vein thrombosis and in this setting, the investigators did not give routine thromboprophylaxis to all their patients. Chua *et al.* (2008) reported an incidence of 5.01% (21/251) for clinical deep vein thrombosis among admissions for neuro-rehabilitation (median of 14 days post-events) in a Singaporean setting. They used D-Dimer assay as the markers to select the groups of patient going for Duplex venous ultrasound scan. From their 251 patients, they have 247 patients who have elevated D-Dimer assay of more than 0.34µg/mL and among these patients; only 21 patients have positive findings of deep vein thrombosis at either proximal or distal deep vein systems. Therefore, they concluded that in asian neurorehabilitation admission in Singapore, the asymptomatic lower limb DVT is uncommon with the possible genetic or ethnic protective factors, early walking initiation and the timing of the admission which is during the decline of the maximal thrombotic risk (Chua *et al.*, 2008).

In United States, the deep vein thrombosis is affecting about 145 per 100,000 individuals per year whilst the pulmonary embolism reported as 69 per 100,000 individuals per year in the general population (Caprini and Arcelus, 2006; Silverstein *et al.*, 1998). The venous thromboembolism accounted for 150,000 to 200,000 deaths per year and one third of the venous thromboembolism related deaths occur following surgery (Gould *et al.*, 2012).

In 2007, the epidemiological model was constructed to estimate the number of venous thromboembolism per annum within the six European Union countries; France, Germany, Italy, Spain, Sweden and United Kingdom. The estimated symptomatic

venous thromboembolism events per annum was 465,715 cases of deep vein thrombosis, 295,982 cases of pulmonary embolism and 27,473 venous thromboembolism related deaths (Cohen *et al.*, 2007).

In an American study by Harris *et al.* (1997), they screened for asymptomatic deep vein thrombosis in surgical intensive care patients. They yield an incidence of 7.5% of proximal deep vein thrombosis which is asymptomatic. Based on the natural history of the proximal deep vein thrombosis, 40% of asymptomatic deep vein thrombosis will become symptomatic and the rest remain undiagnosed. From the undiagnosed thrombosis, 50% will develop pulmonary embolism and 30% will succumb to the disease (Harris *et al.*, 1997).

In the United Kingdom, it has been reported in 2005 through The House of Commons Health Committee that an estimation of 25,000 deaths resulted from preventable hospital-acquired venous thromboembolism per year (NICE, 2010). Prophylaxis was concluded to be underuse. However, most of the study subjects are Caucasian, it would only be unfair to extrapolate their epidemiology to the Asian.

There is a similar study conducted in our hospital in 2004 looking at the incidence of deep vein thrombosis in post operative general surgery patients. All the study subjects were not given any forms of thromboprophylaxis as it was not within the hospital policy and it was strongly believed that the Asian has a low incidence of developing deep vein thrombosis by the treating clinicians. From their results, they noted an incidence of 2.2 percent which is comparatively low when compared to the Caucasion populations (Tun *et al.*, 2004).

1.3 SILENT DEEP VEIN THROMBOSIS

Silent deep vein thrombosis also known as asymptomatic deep vein thrombosis is formation of thrombus within the deep vein system with no clinical manifestations such as the swollen tender limbs seen in symptomatic deep vein thrombosis. In the thrombosis research efforts were made in detection of early thrombus formation in the attempt to halt the propagation of the thrombus that may eventually lead to venous thromboembolic event such as pulmonary embolism. Repeated statements were made over the years that venous thromboembolism is the most preventable hospital morbidity and mortality. Hence, strong advocation for the usage of thromboprophylaxis especially from the pharmacological giants. However, not all the centres have the financial luxury to supply the thromboprophylaxis agents to all the patients. Hence, it driven the effort of my study to detect silent deep vein thrombosis in an effort to justify the use of thromboprophylaxis agents either it is a mechanical or pharmacological agents.

1.4 CAPRINI RISK ASSESSMENT SCORES

The venous thromboembolism is a common cause of preventable death in surgical patients (Gould *et al.*, 2012). Efforts have been made over the years to reduce the risk and prevent the venous thromboembolism. There are multiple risk assessment models proposed over the years to risk stratify the patients. My predecessors were using Salzman and Hirsh predictive models (Salzman and Hirsh, 1994; Tun *et al.*, 2004) in the risk stratifications of their patients. However, I found that it is lack of details and the stratification may occasionally become a subjective overview of the patient's risk, hence, leading to bias of risk stratifications. I choose to use Caprini Risk Assessment Model as it is more clinician friendly and less burden when applied at a busy referral

centre such as ours. It is simple scoring systems which can be performed by just ticking the boxes by the house officers on admissions. Knowing the risks enable us to be more vigilant in the preventive efforts.

CHAPTER TWO

LITERATURE REVIEW

The post operative patients have significant increase risk of Deep Vein Thrombosis (DVT) due to late mobilization or exposure to thrombin generating procedures such as central venous catheterization and surgical procedures. Most of the epidemiological data regarding silent and clinical venous thromboembolisms are reflective of the western population. There are scanty data on our region to support and justify the use of anti-thromboprophylaxis agents in our post operative patients.

Most of the studies are focused on clinical venous thromboembolism. However, little was done to detect silent or asymptomatic venous thromboembolism. It may be due to the unawareness of the impact that silent deep vein thrombosis to the financial burden of our health care system. Silent deep vein thrombosis may resolve spontaneously or may progress to symptomatic DVT and life threatening Pulmonary Embolism (PE). It is the most preventable death in post-operative surgical patients.

Deep vein thrombosis is the formation of thrombus within the deep vein system of the lower limbs which manifest clinically as painful and swollen calf. Silent Deep Vein Thrombosis is defined as the formation of thrombus within the deep vein system of the lower limbs without any clinical manifestations. It is also described in the literature as asymptomatic deep vein thrombosis. Venous Thromboembolism imposes a great morbidity and mortality to post operative patients. It is the most preventable mortality in surgical patients (Gould *et al.*, 2012).

In a Japanese prospective clinical trial, they observed the incidence of asymptomatic deep vein thrombosis to peak on the post operation day 4. In their study, they have recruited 101 patients undergoing either total hip or knee replacement

surgery. All their patients received prophylactic injection of Fondaparinux on the post operation day 1 onwards up to day 14. They noticed in the total hip replacement surgery group, the incidence of the asymptomatic deep vein thrombosis was 0% on the day of surgery, 13.6% on day 1, 27.1% at day 4 and 11.9% at day 14. In the total knee replacement group, they noticed the incidence of asymptomatic deep vein thrombosis was 50% on day 1, 58.3% at day 4 and 20.8% at day 14 (Yamaguchi *et al.*, 2010). In our daily observations, most of our patients undergoing major abdominal surgery are discharged at the average of post operation day 4. Hence, we arranged for the ultrasound duplex of the venous system on day 4 or on the day before their discharge.

The Venous duplex ultrasound with venous compression ultrasonographic assessment is used to detect the deep vein thrombosis. Although the sensitivity of the above examination is still debatable and controversial in terms of detecting asymptomatic deep vein thrombosis, it is still the easiest and least invasive compared to the contrast venography (Quenet *et al.*, 2012). The compression ultrasonography is highly accurate method for detecting proximal deep vein thrombosis with slightly poor sensitive in detecting calf deep vein thrombosis (Jongbloets *et al.*, 1994). The sensitivity and specificity of compression ultrasonography in detecting proximal deep vein thrombosis reported as 91% and 99%, respectively (Lensing *et al.*, 1989; Weinmann and Salzman, 1994). Contrast venography is sensitive and specific to detect DVT. However, it imposes the patients to the risks to contrast related side effects and may not be possible in several groups of surgical patients (Jongbloets *et al.*, 1994).

Bilateral ultrasonography of the lower extremity is performed with colour flow duplex imaging of the major proximal veins including the common femoral, superficial femoral and popliteal veins. The routine used probes are the linear probes of 9-3MHz or curved probes of 5-2MHz. The compressibility is evaluated at 1cm intervals. The

diagnosis of deep vein thrombosis is deemed when the venous segment was not fully compressible, the presence of thrombus in the vein, absence of flow or abnormal flow.(Harris *et al.*, 1997, Pennell *et al.*, 2008, Kume *et al.*, 2010)

2.2 A BRIEF COMPARISON ON VARIOUS TYPES OF DVT RISK STRATIFICATION SYSTEMS

So far, only one local study which utilized DVT risk stratification systems for the selection of study subjects (Tun *et al.*, 2004). The investigators utilized the modified version of Salzman and Hirsh (Salzman and Hirsh 1994) for risk stratifying subjects who were at risk of DVT. This system classified to three risk strata (low, moderate and high risk groups) based on the age of the subjects, types and duration of surgery, medical comorbidities (major or minor medical illnesses), presence of lower limb paralysis and lower limb amputation. However, this risk-stratification system is overly simplified since it excludes other significant DVT risk factors such as family history of thrombophilia, specific types of surgery and others. Besides, the stratification system is also too subjective which makes it operator-dependant. This will result in variable predictive outlook given to the same subset of subjects by different operators. Consequently, Salzman and Hirsh's risk stratification system becomes a less accurate tool for predicting the occurrence of DVT in general surgical setting. The full details on Salzman and Hirsh's DVT risk classification system is summarized in figure 2.1.

Figure 2.1: Modified version of Salzman and Hirsh's risk stratification system for DVT based on Tun *et al.* (2004).

	Deep Vein Thrombosis	Fatal Pulmonary Embolism
Low risk groups	<10%	0.01%
Moderate risk groups	10-40%	0.1-1%
High risk groups	40-80%	1-10%
Low risk groups	Minor surgery (<30 min); no risk factor other than age groups Major surgery (>30 min); age <40 years; no other risk groups Minor trauma or medical illness	
Moderate risk groups	Major general, urological, gynaecological, cardiothoracic, vascular or neurological surgery; age >40 years or other risk factors Major medical illness, heart or lung disease or cancer, inflammatory bowel disease Major trauma or burns Minor surgery, trauma or illness in patients with previous deep vein thrombosis, pulmonary embolism or thrombophilia	
High risk groups	Fracture or major orthopaedic surgery of pelvis, hip or lower limb Major pelvic or abdominal surgery for cancer Major surgery, trauma or illness in patients with previous deep vein thrombosis, pulmonary embolism or thrombophilia Lower limb paralysis (hemiplegia, stroke or paraplegia) Major lower limb amputation	

(Tun *et al.*, 2004, with permission)

To address the weaknesses of Salzman and Hirsh's system, another competing DVT risk stratification system was developed. Caprini's risk assessment model was originally developed in 1991 by a group of researchers from Northwestern University (Arcelus *et al.* 1991). The investigators classified the risks associated with DVT into two broad categories; primary (mostly inherited deficiencies or disorders of key players in coagulation systems, for instance antithrombin III deficiency, disorders associated with plasminogen, dysfibrinogenemia and others) and secondary risk factors (old age, use of oral contraception, malignant diseases, pregnancy and others). As the knowledge of the pathophysiological process of DVT burgeons, Caprini's risk assessment model for DVT was revised and upgraded, culminating in an improved version called

Caprini's risk assessment model version 2005 (Caprini 2005). This new, upgraded versionof Caprini's risk assessment model has been validated in various surgical settings such as general surgery and plastic and reconstructive surgery, for the prediction of 30 and 60-day mortality secondary to deep vein thrombosis and these studies found that the Caprini's risk assessment model accurately predicted the development DVT in both general and plastic and reconstructive surgical populations (Bahl *et al.,* 2010, Pannucci *et al.,* 2011). Nevertheless, this DVT risk stratification system received a further upgrade when Caprini (2010) published the 3rd version of the Caprini's risk assessment model. The differences between the 2nd and 3rd version of the DVT risk stratification tool is summarized in figure 2.2 (adapted from Pannucci *et al.,* 2012).

Figure 2.2: Comparison between the 2nd and 3rd version of Caprini's risk assessment models

	2005 Caprini Model			2010 Caprini Model	
Operative Time	0-44 min ≥ 45 min	1 point 2 points		0-59 min 60-119 min 120-179 min ≥ 180 min	1 point 2 points 3 points 5 points
Body Mass Index (kg/m^2)	≥25	1 point		≥30 and <40 ≥40 and <50 ≥50	1 point 2 points 3 points
SVT	Not as risk factor	-		History of SVT	3 points
Cancer	History of cancer Current cancer	2 points 2 points		History of cancer Current cancer	2 points 3 points

Issues have been raised about which of the versions fare better in terms of accurately stratifying the subjects who are at risk of developing DVT. To provide definite answers to this information lacuna, Pannucci and associates (2012) validated both versions of Caprini's risk assessment model in a surgical setting. The authors found that the 2005 version of Caprini's risk assessment model is the better tool in

identifying subjects who are at increased risk of DVT. As a result, it is now gaining a rapid rise in popularity due to its simplicity (it is in a checklist format), excellent validity, and high applicability across the multitude of surgical disciplines. Nevertheless, no local studies so far have endeavoured to assess the validity of the Caprini's risk assessment model for DVT risk stratification. Therefore, an attempt to do so is therefore highly applaudable.

2.3 JUSTIFICATION OF THE STUDY

The venous thromboembolism is a common cause of preventable death in surgical patients (Gould *et al.*, 2012). Efforts have been made over the years to reduce the risk and prevent the venous thromboembolism. There are multiple risk assessment models proposed over the years to risk stratify the patients. The simplest being a classification by Clagett *et al.* (1988) who classified the level of venous thromboembolism risk to low, moderate, high and highest. This classification is lack of details hence, the level of classification may vary from a clinician to another. However, when it is too detail, it became unpopular as it purposed a clinical burden to remember the scoring systems. In the previous studies, Salzman and Hirsh predictive models were used in risk stratifying their patients (Salzman and Hirsh, 1994; Tun *et al.*, 2004. However, it lacks details and the stratification may occasionally become a subjective overview of the patient's risk. There are two widely adapted detailed risk assessment models – Rogers' Risk Assessment Model from the Patient Safety in Surgery Study and Caprini Risk Assessment Model (Gould *et al.*, 2012). In my study, I choose to use Caprini Risk Assessment Model as it is more clinician friendly and it is not as detailed as the Rogers' Risk Assessment Model. The aim of this study is to see whether the

Caprini Risk Assessment Model in relationship to asymptomatic DVT. All the subjects of the study will be risk stratified according to Caprini Risk Assessment Model and classify them to low, moderate, high and highest risks. Based on the Risk Assessment Model, the comparison made to see the group and the presence of silent deep vein thrombosis via ultrasound duplex of the venous system. If this should be a negative finding, I would look at the risk score from the model in proportion to the patient being scanned.

CHAPTER THREE

OBJECTIVES

3.1 GENERAL OBJECTIVES

To determine the incidence of silent deep vein thrombosis (DVT) and validate the utility of Caprini's risk assessment model in identifying those who are in need of DVT prophylaxis .

3.2 SPECIFIC OBJECTIVES

1) To determine the incidence of silent deep vein thrombosis in post operative surgical patients at HUSM.

2) To determine the association between the use of DVT prophylaxis and the Caprini risk score groups.

3.3 RESEARCH QUESTIONS?

1) What is the incidence of silent deep vein thrombosis among post operative surgical patients at HUSM?

2) Is there any significant association between the use of DVT prophylaxis and Caprini risk score groups?

3.4 RESEARCH HYPOTHESES

1) **Null hypothesis:** The incidence of silent deep vein thrombosis is 2.2% (Tun *et al.* 2004)

Alternative hypothesis: The incidence of silent deep vein thrombosis is more or less than 2.2% (two-sided hypothesis)

2) **Null hypothesis:** There is no significant association between the use of DVT prophylaxis and Caprini risk score groups.

Alternative hypothesis: There is a significant association between the use of DVT prophylaxis and Caprini risk score groups.

CHAPTER FOUR

METHODOLOGY

4.1 STUDY DESIGN AND PERIOD OF THE STUDY

This is a prospective cohort study involving post operative HUSM surgical patients who are at risk of developing silent DVT. This study was conducted from December 2013 until May 2014 for a total period of 6 months.

4.2 STUDY AREA

This study was performed at the General Surgical Wards of HUSM, a main centre of referral for surgical patients who are in need of specialized surgical care. On the average, this centre received 1080 surgical patients per annum (90 subjects / month). The number of potential subjects who are at high risk of silent DVT is estimated at 80 cases per month.

4.3 REFERENCE POPULATION

All general surgical subjects who are at high risk of postoperative silent DVT in Kelantan

4.4 SOURCE POPULATION

All general surgical subjects who are at high risk of postoperative silent DVT and hospitalized at HUSM, Kubang Kerian, Kelantan.

4.6 SAMPLING FRAME

General surgical subjects who have fulfilled inclusion and exclusion criteria and undergone surgical treatment in the surgical wards of HUSM, Kubang Kerian, Kelantan.

4.7 STUDY PARTICIPANTS

All surgical subjects who have met the prerequisites selections as mentioned above and consented to study participation.

4.8 INCLUSION AND EXCLUSION CRITERIA

4.8.1 Inclusion criteria

All the subjects are aged 18 and above, who underwent surgical operations involving general or regional anaesthesia for more than 45 minutes and has consented to participate in the study.

4.8.2 Exclusion criteria

Any subjects who were already diagnosed or on treatment for any form of venous thromboembolism and those who meet the inclusion criteria but refused to participate in the study for whatsoever reasons.

4.9 SAMPLING METHOD

Convenient sampling method was chosen due to the scarcity of potential study participants secondary to last-minute cancellation of the planned surgical procedures and for not fulfilling the inclusion and exclusion criteria of this study.

4.10 SAMPLE SIZE CALCULATION

Sample size was calculated using single proportion formula for the first objective and Power and Sample Size (PS) software version 3.0.4.3 (Vanderbilt University, Nashville, Tennessee, USA; 2011) for objective 2. For objective 1, two estimates of the incidence of silent DVT were used, which were based on the studies by Tun *et al.* (2004) and Harris *et al.* (1997). Based on these two estimates, the calculated sample size for objective 1 will be as follows:

Objective 1: Incidence of silent DVT in postoperative surgical patients (using estimates from Harris *et al.* (1997))

$$n= \left(\frac{z}{\triangle}\right)^2 p(1- p)$$

z =1.96

$\triangle$= precision =0.06

p = Incidence of silent DVT = 7.5% (Harris *et al.* 1996)

$n = (1.96/0.06)^2\ 0.075(1-0.075)$

n = 74 subjects

Drop out rates = 10%

n_{final} = 82 subjects

Objective 1: Incidence of silent DVT in postoperative surgical patients (using estimates from Tun *et al.* (2004))

$$n= \left(\frac{z}{\triangle}\right)^2 p(1- p)$$

z =1.96

$\triangle$= precision =0.05

p = Incidence of silent DVT = 2.2% (Tun *et al.* 2004)

$n = (1.96/0.05)^2\ 0.022(1-0.022)$

n = 33 subjects

Drop out rates = 10%

n_{final} = 37 subjects

For this objective, the sample size calculated using the estimate from Tun *et al.* (2004) was chosen since it was based on local estimate of silent DVT, which reflects the number of new cases of silent DVT encountered during the day-to-day surgical practice in HUSM.

Objective 2: The association between the use of DVT prophylaxis and Caprini risk score.

For this objective, the sample size was calculated using the parameter estimate obtained from Bahl *et al.* (2009) for P_o (the prevalence of DVT prophylaxis in Caprini low risk group (4 or less)). For P_1 (the prevalence of DVT prophylaxis in the Caprini high risk group (Caprini score >4) is set at 0.01 based on expert opinion. Therefore the calculated sample size was as follows:

α (Type I error rate, level of significance) = 0.05

Power of the study (1-β) = 0.80

P_0 = 0.01 (clinical expert opinion)

P_1 = 0.32 (Bahl *et al.* 2009)

m = ratio of controls to cases = 1

n = 21 subjects per group

Attrition rate = 10%

Total number of subjects needed = [21 + 21(10)] x 2

n_{final} = 48 subjects (24 per group).

4.11 STUDY PROTOCOLS AND OPERATIONAL DEFINITIONS

4.11.1 Study protocols

The subjects who were consented to participate in the study will first be risk stratified according to the Thrombosis Risks Factor Scoring system proposed by Caprini and Arcelus (2006).Each subject who consented to participate in the study had a pre-operative duplex ultrasound of the deep venous system of bilateral lower limbs and followed by a post-operative ultrasound duplex of the deep venous system of bilateral lower limbs on post operative day four.

For the purpose of perfoming venous ultrasonograph, Siemens Acuson X300 Premier Edition ultrasound machine (Siemens, Washington DC, USA) was used. Two different radiologists were tasked to perform the ultrasound to ensure the reliability of the results. The ultrasonography of bilateral lower extremities was performed with colour flow duplex imaging of the major veins including the common femoral, superficial femoral and popliteal veins. Thrombi present in these veins were recorded as deep vein thrombosis. Ultrasound probes of various frequencies were selected to optimize imaging according to the patient's body habitus. The routine used probes are the linear probes of 9-3MHz or curved probes of 5-2MHz. The compressibility is evaluated at 1cm intervals. This examination is then repeated with duplex ultrasound of the venous system to look for any other evidence of abnormal flow. The diagnosis of deep vein thrombosis is deemed present when the venous segment was not fully compressible, the presence of thrombus in the vein, absence of flow or abnormal flow. The inter-rater agreement of the results were excellent (Cohen's kappa =1 (95% CI of kappa (not applicable).

4.11.2 Operational definitions

Table 4.1 : Operational definitions of variables used in this study

Risk factors	Operational definitions (references)	SPSS codings
Age	Age of study participants at the time of inclusion into the study	Recorded as continuous variable
Gender	Male and female	0 = female 1 = male
Ethnicity	The race of subjects included in this study	0 =Malays 1 = Non-malays
BMI	BMI = kg/(m)^2 (WHO 2004)	0 = High 1= Low
Use of central venous catheter	The use of central venous catheter during the surgical admission	0 = No 1 = Yes
Types of central venous catheter	The location where the CVC was placed	0 = Nil 1 = Internal Jugular Vein 2 = Femoral vein 3 = Subclavian vein
DVT prophylaxis	The use of any form of DVT prophylaxis during the hospitalization for surgery	0 = No 1 = Yes
Types of DVT prophylaxis	The types of DVT prophylaxis used during the period of hospitalization	0 = Nil 1 = Pneumatic calf compression 2= Thromboembolic deterrent stocking 3 = Subcutaneous Heparin 4 = Fundaparinux 5 = Combined modes
Silent DVT	The presence of venous thrombosis in the limb of an asymptomatic patients (Pennell , Mantese and Westfall 2008)	0 = Not present 1 = Present

4.12 ETHICAL ISSUES

Since this study involves direct contact with human subjects, it thus requires ethical approval from the local ethical review board. An ethical clearance was obtained from USM Human Research Ethics Committee on 10th February 2014; FWA Registration Number 00007718 and IRB Registration Number 00004494**.** Moreover, the whole principles of ethics on human research as laid down by the Declaration of Helsinki (18th World Medical Association General Assembly, 1964) was thoroughly followed during the conduction of this study.

Voluntary written informed consent was obtained from each participant of the study. Their rights to withdraw from the study at any stage and for any reason without jeopardizing their subsequent medical care were adequately informed to them. The confidentiality of information on each subject was preserved by not documenting the patient's name or any other forms of identification on the data collection sheet. Each subject was given a random number and only the study investigator knew how to break the random code. Besides, the data collection sheet were kept by the principal investigator at a secure place and the SPSS file, in which all the information was stored, was password-protected to prevent any accidental or intentional breach of participant's confidentiality.

4.13 STATISTICAL ANALYSES

Data analyses were performed using IBM Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) and STATA version 11 (StataCorp. 2009.

Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.). Simple linear and logistic regression analyses were used for the purpose of analyses.

The data was firstly inspected for any inaccuracies and missing values. Any subject who is missing of more than 20% of the data was excluded from the analyses. No remedial measures for missing data were performed due to the unavailability of the SPSS add-on required for the execution of such statistical procedures.

The data was then descriptively analysed in mean and percentage or median and interquartile range for continuous data, whilst for categorical data, frequency and percentage were used. The nonparametric Kruskall-Wallis test was then used to compared the differences in the outcome variable (Caprini risk score) between factors which have more than groups (eg types of DVT prophylaxis, choice of central venous catheter used). Besides that, simple logistic and linear regression analyses were employed to obtain the model that is accurately predictive of DVT prophylaxis (using Caprini risk score groups, CVA as the predictors, age, gender ethnicity and BMI) and Caprini risk scores (the same predictors used). The nominal level of significance were set at the nominal 0.05 (two sided) and any p value that is less than this threshold is considered to be statistically significant.

CHAPTER FIVE

RESULTS

5.1 GENERAL FEATURES OF THE STUDY SUBJECTS

In total, 55 subjects were included in the study. The mean age of the study participants was 51.3 years (SD 15.18). More females were recruited than males (54.5% vs 45.5%), but nevertheless the ratio between the gender was still maintained at 1:1. The study sample was predominantly composed of individuals of Malay ethnicity whilst only 5% of study samples were of Chinese (94.5% vs 5.5%). Nearly two third of the subjects did not use any form of central venous access (63.6%) whilst among those who have it, internal jugular vein (IJV) catheter placement was the main type of central venous access (80%).

With respect to DVT prophylaxis, more than three fourth (76.5%) of the subjects did not receive any mode of DVT prevention. Among those who received it, thromboembolic deterrent stocking was the main form of DVT prophylaxis (46.2%). Apart from that, the mean body mass index (BMI) of the study participants was 25.7 (SD 4.62).

In regard to Caprini risk assessment score for venous thromboembolism (VTE), the mean score was 6.0 (SD 2.72). The range of the Caprini score recorded from the study participants is from 3 to 13. More than two thirds of study participants belonged to the high Caprini risk score group (Caprini score more than 4). Further information is presented in Table 5.1: