Venous Thromboembolism Risk Assessment and Prophylaxis Modalities in Critically Ill Patients

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ABSTRACT

Venous thromboembolism (VTE) is a common complication observed among critically ill patients and is associated with significant mortality and morbidity. Thus, this prospective study was conducted to assess VTE and bleeding risk factors, and prophylaxis modalities were given for critically ill patients. A total of 80 patients admitted for >2 days in the Intensive Care Unit (ICU) of a tertiary care hospital, aged >18 years old were included in this study. Patients' demographic data, VTE risk, bleeding risk factors, and VTE prophylactic methods were reviewed from the patients' medical records. Among the 80 patients, 65 (81.3%) had high VTE risk and 15 (18.8%) had moderate VTE risk. A total of 64 (80%) patients were at high risk of bleeding and 16 (20%) were at low bleeding risk. The most common risks observed were advanced age, male, severe renal impairment, and active bleeding. A total of 45 (56.25 %) patients received VTE thromboprophylaxis. Thromboembolic deterrent (TED) stocking was the most commonly used prophylactic method (n = 15, 33.33%) followed by unfractionated heparin (UFH) (n = 6, 13.33%). Overall, appropriate VTE prophylaxis was given (63.7%; p = 0.0188) based on VTE and bleeding risks during the study period. In conclusion, there is a significant risk for VTE among critically ill patients. This study outlines the need to implement both VTE and bleeding risk stratification strategies in all critically ill patients and highlight the need to provide adequate thromboprophylaxis when indicated.

Key Words: *venous thromboembolism, prophylaxis, intensive care.*

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INTRODUCTION

Thrombus formation in the deep veins is a common complication observed in critically ill patients as a result of immobilization and their presenting medical conditions such as sepsis, trauma, and also the surgical procedures they underwent [1, 2]. Furthermore, critically ill patients while in the intensive care undergo various invasive tests and procedures such as central venous catheterization, which increases this complication [3, 4]. Venous thromboembolism predisposes critically ill patients to develop pulmonary embolism (PE) and post-thrombotic syndrome leading to major morbidity and mortality [5, 6]. In the general medical, surgical, and intensive care unit (ICU) population, the occurrence of deep venous thrombosis (DVT) varies from 28% to 32% [7]. In some cases, DVT may reach up to 60% in the case of trauma patients and 70% in acute ischemic stroke patients [8]. Moreover, 1- 2% of DVT cases may face a fatal PE [8, 9]. The complexity of venous thromboembolism (VTE) lies in the difficulty in diagnosis as well as treatment. This is particularly true for patients in the ICU as their common symptoms that suggest VTE are often masked by their clinical status (intubation, sedation, altered mental status). Furthermore, 95% of VTEs are asymptomatic [10]. Once VTE is diagnosed, many patients in ICU are at comparatively higher bleeding risk, making the initiation

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of therapy with anticoagulant riskier. These two drawbacks above emphasize the importance of efficient protective approaches in preventing DVTs in this setting [11].

In view of this, the American College of Chest Physicians (ACCP) has developed prevention guidelines against VTE to lessen its risk, keeping in view the high occurrence of VTE in the ICU population. These guidelines highlight the significance of its prevention as well as the need to weigh the risk-benefit ratio of thromboprophylaxis in the high-risk group [12]. In Asia, fewer incidences are observed on this preventable fatal disease but utilization of DVT prophylaxis should not be much different from those of Western patients [13]. In general, however, the occurrence of DVT was observed to be very high in ICU patients, specifically in patients given no DVT prophylaxis (25% to 31%), in comparison to the patients who were given some form of prophylaxis (11 to 16%) [7, 14].

VTE is an important aspect of critical care that can be prevented. However, there is a lack of data looking at the measures taken in high-risk patients in the local population. Therefore, we aimed to investigate the occurrence of VTE risks using a VTE risk assessment tool and the various prophylactic modalities used in critically ill patients in the local setting. It is with the hope that this study will shed light on the appropriateness of prophylactic measures taken in high-risk patients.

METHODS

Study design

This was a cross-sectional study performed in critically ill patients in a local tertiary hospital. Following ethical approval from the local research ethics committee (UKM 1.5.3.5/244/NF-007-2015), subjects were selected. Patients admitted for a minimum of 2 days in the ICU, aged ≥18 years old, were included in the study. Patients that were admitted solely for VTE treatment were excluded. As we used convenient sampling, we took into consideration the limited population size. The size of the target population was estimated at 100 patients so the sample size based on calculation was 80 [15]. Data collection was done by reviewing patient medical records prospectively.

Risk assessment

DVT risk was assessed using Caprini's risk stratification scorecard [16]. This scorecard consists of four different sections of risk factors. Each section carries increasing points (1, 2, 3, and 5) for each risk factor with increasing weight. The sections in which 5 points are given to each factor include less than a one-month history of stroke, multiple trauma, acute spinal cord injury, and fracture of hip, pelvis, or leg, and undergoing elective major lower extremity arthroplasty. Summation of each section subtotal points equates to a total risk factor score indicating the DVT risk. A score of '0' indicates 'very low' risk, '1-2' 'low' risk, '3-4' 'moderate' risk, and '5 or more' 'high' risk of DVT.

The probability of bleeding was evaluated using the IMPROVE bleeding risk assessment tool [17]. This assessment consists of 13 risk factors attributed by scores between 1 and 4.5 each with active gastro-duodenal ulcer the only risk factor appointed score of 4.5. The addition of the scored risk factors totaling seven or more indicates higher bleeding risk.

When pharmacological DVT prophylaxis was initiated, it was based on our ICU anticoagulant prescribing guide [18]. It was used as a reference for dosing of heparin, enoxaparin, and fondaparinux administered subcutaneously. The dosing was based on the patient's body weight, the degree of renal function, and/or obesity. The choice of the anticoagulant prescribed was determined by the treating ICU physician.

Appropriateness of DVT prophylaxis regimens was determined based on the DVT total risk factor score, IMPROVE bleeding score, and the local prescribing guide for anticoagulants. DVT prophylaxis regimen was considered appropriate when the following criteria were met: when the IMPROVE bleeding score indicated a high risk for bleeding, mechanical prophylaxis was instituted (regardless of the DVT total risk factor score); when DVT risk was moderate or high and bleeding risk was low, the patient received combination prophylaxis with pharmacological and mechanical prophylaxis. Whereas, if the patient had low or very low DVT risk and low risk of bleeding then it was considered appropriate for the patient to receive either mechanical or pharmacological prophylaxis.

Statistical analyses

Statistical Package for the Social Sciences version 22 (SPSS, Chicago, IL) was used to perform all statistical analyses. Descriptive statistic for categorical variables (gender, race, age group, risk level of DVT, bleeding risk, DVT prophylactic modalities used, and appropriateness of DVT regimen) was expressed in absolute values and percentage. For continuous variables (age and body weight), mean ± standard deviation was performed. A Chi-square test was used for non-parametric data. Categorical variables were compared using the Chi-square test or Yates' correction where necessary. All statistical tests were two-tailed. A p-value of <0.05 denoted statistical significance.

RESULTS

Eighty patients were recruited in the study. Demographic data, reasons for ICU admissions, level of DVT risk, and bleeding risk are summarized in Table 1. The most

common risk factor observed was immobilization in all patients for more than 72 hours followed by having central venous access (n = 78, 97.50%) and thirdly, age ≥40 years (n = 58, 72.50%). Other risk factors that were detected increasing the risk of DVT were sepsis (n = 45, 56.30%), serious lung disease including pneumonia (<1 month) (n = 39, 48.80%), major surgery >45 minutes (n = 29, 36.30%), obesity (n =24, 30%) and malignancy (n = 14, 17.5%). Table 2 illustrates the association between the level of DVT risk and patients' demographic data.

Table 1: Demographic data, reason for ICU admissions, level of DVT risk, and bleeding risk. Values presented as mean ± standard deviation or number and percentage in parentheses where appropriate.

Variables	Values (n = 80)
Age, years	54.43 ± 17.506
Weight, kg	74.28 ± 17.818
Gender	
Female	28 (35.0)
Male	52 (65.0)
Race	
Malay	43 (53.8)
Chinese	22 (27.5)
Indian	15 (18.8)
Reasons for ICU admission	
Respiratory disease	13 (16.3)
Sepsis	11 (13.8)
Cardiovascular disease	14 (17.5)
Neurological disease	11 (13.8)
Gastrointestinal disease	19 (23.8)
Trauma	7 (8.8)
Others	5 (6.3)
Level of DVT risk	
Low risk (0 to 2 score)	0 (0)
Moderate risk (3 to 4 score)	15 (18.8)
High risk (5 or more score)	65 (81.3)
Bleeding risk	
Low risk (< 7 score)	16 (20.0)
High risk (≥ 7 score)	64 (80.0)

Table 2: Association between DVT risk level and patients' demographics. Values are expressed as numbers and percentages in parentheses.

Patient`s Demographics	Risk level of DVT		Statistics
	Moderate risk (3- 4 score)	High risk (5 or more score)	
Gender			
Male	5 (9.6)	47 (90.4)	$\chi^2 = 8.138$
Female	10 (35.7)	18 (64.3)	**p = 0.004**
Age group (years)			
≤40	10 (45.5)	12 (54.5)	
41-60	5 (21.7)	18 (78.3)	*Yates* $\chi^2 = 14.475$
61-74	0 (0.0)	25 (100)	**p = 0.002**
≥75	0 (0.0)	10 (100)	

Race			
Malay	8 (18.6)	35 (81.4)	***Yates*** χ^2 **= 9.9**
Chinese	0 (0.0)	22 (100)	**p = 0.007**
Indian	7 (46.7)	8 (53.5)	

χ^2 = Chi-square test
Yates χ^2 = Yates chi-square test
p-value <0.05 is statistically significant
Abbreviation: DVT (Deep Vein Thrombosis)

Bleeding risk was high in 64 (80%) patients, and low in 16 (20%) patients. Overall, advanced age (40-84 years) was the most common bleeding risk factor observed (n = 58, 72.5%) followed by male (n = 52, 65%), severe renal failure (creatinine clearance <30ml/min, n = 29, 36.3%), active bleeding (n = 24, 30%), thrombocytopenia and current cancer (n = 14, 17.5%), liver failure with INR >1.5 (n = 12, 15.0%), and active gastro-duodenal ulcer (n = 2, 2.5%). There was no association between bleeding risk and patients' demographics as shown in Table 3.

Table 3: Association between bleeding risk and patients' demographics. Values are expressed as numbers with percentages in parentheses.

Patient's Demographics	Bleeding Risk		Statistics
	High risk (≥7 score)	Low risk (<7 score)	
Gender			
Male	41 (78.8)	11 (21.2)	χ^2 **= 0.124**
Female	23 (82.1)	5 (17.9)	**p = 0.725**
Age group (years)			
≤40	16 (72.7)	6 (27.3)	
41-60	16 (69.6)	7 (30.4)	***Yates*** χ^2 **= 4.543**
61-74	24 (96.0)	1 (4.0)	**p = 0.208**
≥75	8 (80.0)	2 (20.0)	
Race			
Malay	33(76.7)	10 (23.3)	***Yates*** χ^2 **= 1.24**
Chinese	20 (90.9)	2 (9.1)	**p = 0.53**
Indian	11 (73.3)	4 (26.7)	

χ^2 = Chi-square test
Yates χ^2 = Yates chi-square test
p-value <0.05 is statistically significant
Abbreviation: DVT (Deep Vein Thrombosis)

Table 4 outlines the appropriateness of the thromboprophylaxis applied. Fifteen patients were at a moderate risk to develop DVT. Out of that, only seven patients received prophylaxis. Among 65 patients, 38 patients at high risk for DVT received prophylaxis. A total of 45 (56.25 %) patients received DVT thromboprophylaxis. Out of that, 15 patients were at moderate risk of DVT and 7 (15.6%) patients received prophylaxis. Thirty-eight (84.4 %) patients with a high risk of DVT received prophylaxis and 'thromboembolic deterrent (TED) stocking' (n = 15, 18.8%) was the commonest prophylactic modality used and the second most common prophylactic method was 'unfractionated heparin' (UFH) (n = 6, 7.5%). Pharmacological prophylaxis was administered to 11 (13.8 %) patients. Among 11 patients, UFH was prescribed to 6 (7.5%) patients while 4 (5.0%) patients received low-molecular-weight heparin (LMWH) enoxaparin. Mechanical prophylaxis was given to 20 (25.0 %) patients. Among 20 patients, 15 (18.8%) patients received TED stockings, while 6 (7.5%) patients received sequential compression device (SCD). The total number of patients who received both pharmacological and mechanical prophylaxis was 14 (17.5 %). Among these, 'UFH and SCD' (n = 5, 6.3%) was the most commonly used combination prophylaxis followed by combination prophylaxis of 'UFH and TED stockings' (n = 3, 3.8%).

Table 4: Appropriateness of DVT prophylaxis. Values are expressed as numbers and percentages in parentheses.

DVT risk and Bleeding risk	Appropriateness of prophylactic regimen			
	Appropriate	Inappropriate	Total	*p*-value

High DVT risk	Low bleeding risk	5 (9.8)	5 (17.2)	10 (12.5)	>0.05
	High bleeding risk	37 (72.5)	18 (62.1)	55 (68.8)	
Moderate DVT risk	Low bleeding risk	5 (9.8)	1 (3.4)	6 (7.5)	>0.05
	High bleeding risk	4 (7.8)	5 (17.2)	9 (11.3)	
Overall		**51 (63.7)**	**29 (36.3)**	**80 (100)**	0.0188

Yates χ^2 = Yates chi-square test
p-value <0.05 is statistically significant
Abbreviation: DVT (Deep Vein Thrombosis)

The most commonly used thromboprophylaxis when patients were at high risk of bleeding was TED stockings (n = 14, 31.11%) followed by SCD (n= 6, 13.33%) and UFH (n= 4, 8.89%). On the other hand, patients at low risk of bleeding received combination prophylaxis such as most commonly used 'UFH and SCD' (n=3, 6.7%), followed by 'UFH and TED stockings' and UFH (n= 2, 4.44%). The pattern between bleeding risk and prophylactic modalities is shown in Figure 1.

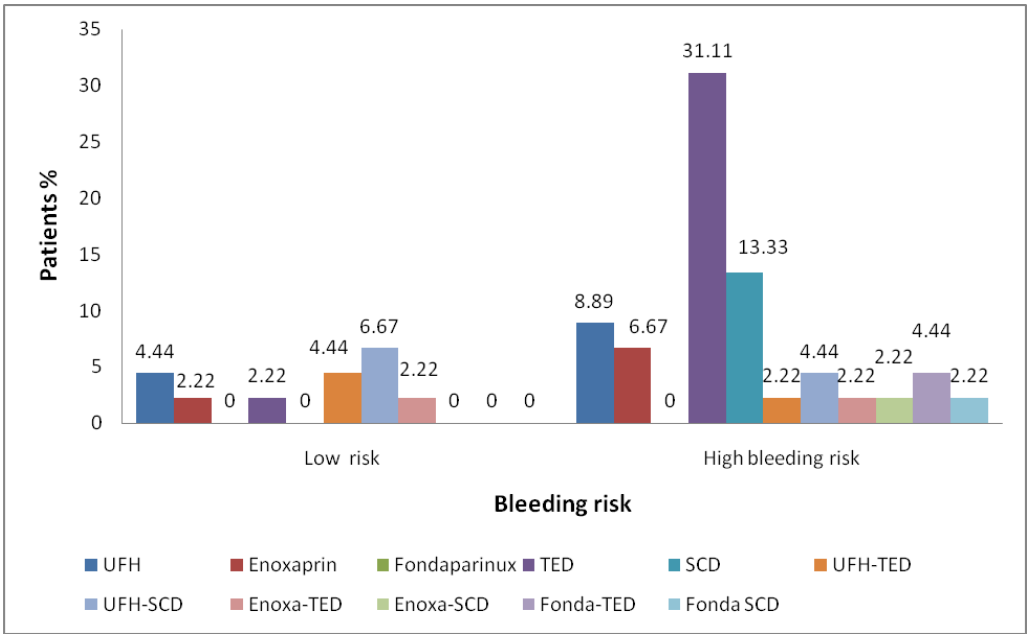

Figure 1: Pattern between bleeding risk and prophylactic modalities. UFH = unfractionated heparin; TED = thromboembolic deterrent stocking; SCD = sequential compression device; Fonda = fondaparinux; Enoxa = enoxaparin.

There was a significantly higher overall appropriate prophylaxis given (n=51, 63.7%; p= 0.0188) during the study period. There was no significant association between the level of DVT risk/bleeding risk and appropriateness of the prophylactic regimen as shown in Table 4. Out of 80 patients, 10 (12.5%) patients were categorized as high VTE risk/low bleeding risk. Among these, the percentage of appropriate and inappropriate prophylaxis being given was equal in both groups (n = 5, 50%). On the other hand, 55 (68.9%) patients were categorized as high VTE risk/high bleeding risk and the percentage of appropriate prophylaxis being given was 67.3% (n = 37). Patients categorized as moderate VTE risk/low bleeding risk were 6 (7.5%) in total and 5 (83.3 %) patients among these received appropriate prophylaxis. Patients categorized as moderate VTE risk/high bleeding risk were 9 (11.3%) in total and 4 (44.4%) received appropriate prophylaxis.

DISCUSSION

In critically ill patients, there is an increased risk and occurrence of VTE, which is associated with significant morbidity and mortality [11]. The diagnosis of VTE usually requires prompt treatment with anticoagulants at therapeutic doses. Although treatment of VTE with anticoagulant is largely effective, the risk of bleeding remains a major setback [19]. One of the major concerns is the occurrence of hemorrhage and identifying risk for bleeding tendencies is of utmost importance. Although the risk of VTE is largely performed, due to the need for early management, a detailed approach in reviewing bleeding

tendencies is usually overlooked in clinical practice [20]. To address concerns of risk of VTE, risk of bleeding, and prophylactic modalities being given, the present study was performed in an attempt to improve patient outcomes was successfully achieved.

The risk of VTE varies considerably in critically ill patients. This is similarly observed in the present work in which multiple risk factors are associated with VTE [21, 22]. Among these, the most commonly observed VTE risk factors were patients confined to bed for >72 hours (immobilization), followed by central venous access and advanced age (≥40 years). Similar findings were also demonstrated in previous work conducted in medical patients [23]. Patients admitted in the ICU are generally bedridden with prolonged immobilization acquired from sedation, use of vasopressors, mechanical ventilation, and are hemodynamically compromise. All these conditions increase the risk of thrombosis, due to stasis of blood flow in the venous system [24]. Interestingly, this current work also demonstrated that ethnicity, age, and gender were also VTE risk factors. In terms of ethnicity, the percentage of Malay was found to be the highest, which is, however reflective of the current local population according to Malaysian Statistics, 2014. There has been no data to suggest other reasons behind this, although further work may be required to determine this. Age has been most consistently associated with an increased risk of VTE and is sharply increased after 45 years of age [25]. However, the reason for an increased VTE risk with age is not understood, but it may be related to the presence of other illnesses that predisposes the patient to thrombosis such as immobility [25]. Previous studies performed to assess the role of gender as a risk factor for VTE show conflicting results. Some studies reported no significant differences in the incidence of DVT between males and females [26, 27]. However, after the age of 50, men are at a greater risk than women [28]. A higher incidence of metabolic syndrome or other cardiovascular risk factors is the possible reason for males to have a higher risk for VTE in the current study.

Balancing the risk of thrombosis and risk of bleeding is a difficult challenge as hemorrhagic risk runs parallel to thrombotic risk [29]. Most critically ill patients have a high bleeding risk with multiple bleeding factors. This is mainly due to concomitant acute conditions such as sepsis, multi-organ failure, or massive blood loss secondary to surgery or trauma. Among common bleeding risk factors are advanced age, male, severe renal failure, active bleeding, thrombocytopenia, and current cancer [19], similarly observed in the present work. However, in this present work, further assessment demonstrated that gender, age, and ethnicity had no association with increased bleeding risk. Association between gender, in particular, have been contentious with the IMPROVE study demonstrating a greater risk of bleeding for male, whereas other works show that male is a weaker risk factor [19]. However, the association for males as a risk factor for bleeding and its relation is yet to be established especially in the local setting. Indeed, the reason for assessing both bleeding risk and VTE risk together was due to the similar risk factors shared by both VTE and bleeding risk [19], such as admission into ICU/CCU, advanced age, central venous access, and current cancer.

According to the current guidelines, routine VTE prophylaxis with UFH or LMWH is recommended for critically ill patients admitted to the ICU with a high VTE risk. Mechanical prophylaxis is recommended for those who are at a high risk of major bleeding [30]. Unfortunately, VTE prophylaxis rates of critically ill patients in Asia are not well studied as compared to the Western population. The use of VTE prophylaxis remained low in the current study at approximately 60%, with combined modalities selected for only 8.9% of overall high VTE risk/low bleeding risk patients. The relatively low rate of thromboprophylaxis used may be associated with the belief of low prevalence of VTE among Asians, fear of bleeding complications such as contraindications to anticoagulants, lack of awareness for the necessity of giving thromboprophylaxis, concerns for cost of thromboprophylaxis, and lack of institutional guidelines to be implemented. Underuse of DVT prophylaxis in hospitalized medical patients despite ACCP recommendations [14, 30] have also been previously reported. The TED stocking was the preferred mechanical prophylactic modality in both high VTE risk and high bleeding risk patients in ICU, similarly observed in another work [31]. However, routine mechanical thromboprophylaxis in critically ill patients is still significantly underused. Similarly, there was a low rate of pharmacological prophylaxis used in the current work that may reflect reluctance on physicians in the use of anticoagulants in ICU. The most common prescribed pharmacological prophylaxis was UFH, which could be due to its lower cost compared to enoxaparin [31]. LMWH is more effective than UFH in critically ill trauma patients [32] as it is less likely to produce hematomas, HIT and osteoporosis than UFH [17]. Despite this, the use of UFH reduces the rate of VTE by 50% when compared with no prophylaxis [3].

CONCLUSION

This study has highlighted several important findings that would improve the risk assessment of VTE, bleeding, and utilization of thromboprophylaxis in critically ill patients. Nevertheless, the generalization of the results should be done with caution due to several limitations of the study. Factors that influence the decision making of physicians in

thromboprophylaxis methods were not assessed. Our sample size could also be a limiting factor in predicting an actual prevalence of VTE risk in critically ill patients. Patients were also not followed up after discharge or during their stay in the hospital. Despite this, our results showed that both VTE and bleeding risk is high among critically ill patients in the local setting. Furthermore, underutilization of effective prophylaxis is observed to a large extent. This confirms the need for improved implementation of appropriate thromboprophylaxis guidelines in critically ill patients in the local hospital that uses both VTE risk and bleeding risk assessments. This will ultimately help in the successful management of VTE and prevent the associated morbidity and mortality.

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