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ORIGINAL ARTICLE

Low incidence of deep vein thrombosis in critically ill medical patients in Thais: a prospective study

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Abstract

Background: Critically ill medical patients face a heightened risk of developing venous thromboembolism. In Thailand, routine thromboprophylaxis is not employed. The incidence of deep vein thrombosis (DVT) in the medical intensive care unit (ICU) has not been elucidated in the Thai population.

Objectives: The aims were to evaluate the incidence of DVT and identify associated risk factors in critically ill medical patients.

Methods: A single-center, prospective cohort study was conducted from 2019 to 2020. Consecutive patients underwent screening for proximal DVT by duplex ultrasound of both legs.

Results: A total of 200 patients were enrolled, with 115 being male (57%). The mean (SD) age was 66.5 (16.4) years. The mean (SD) Acute Physiology and Chronic Health Evaluation II score was 27 (8). The cumulative incidence of DVT over 5 days was 7% (95% CI, 3.4%-10.6%). No clinically or radiologically diagnosed pulmonary embolism occurred in patients with DVT. No independent risk factor associated with DVT was identified. Hospital mortality in those with and those without DVT was 42.9% and 32.3%, respectively. There was no significant difference in the length of ICU or hospital stay or inpatient mortality between those with and those without DVT.

Conclusion: Without thromboprophylaxis, the incidence of DVT in the Thai population remains low. A strategy of screening ultrasound 5 to 7 days after admission to the ICU may be a suitable alternative to anticoagulant prophylaxis in critically ill Thai patients without symptoms of venous thromboembolism.

KEYWORDS
critical care, deep vein thrombosis, Doppler ultrasound, intensive care unit, mortality

Essentials

- Incidence of deep vein thrombosis (DVT) in Asian critically ill medical patients remains unclear.
- A prospective study screening DVT in Thai medical intensive care units was conducted.
- Without thromboprophylaxis, DVT incidence was relatively lower than those in Western countries.
- No independent risk factors associated with DVT were identified.

1 | INTRODUCTION

Critically ill medical patients are at high risk for developing deep vein thrombosis (DVT). Several risk factors including immobilization, central venous catheterization, or underlying disease—such as malignancy—contribute to DVT incidence. Patients with DVT reportedly experience a longer stay in intensive care unit (ICU) and a prolonged duration of mechanical ventilation compared with those without DVT [1]. Additionally, DVT increases the risk of in-hospital mortality [2]. In Western countries, the estimated incidence of DVT detected by screening ultrasound in critically ill patients ranges from 13% to 30% [3,4]. However, evidence from Asian countries is limited. It is perceived that the risk of venous thromboembolism (VTE) is lower in Asian populations. Studies have demonstrated a lower incidence of VTE in Asians than in Western populations [5,6]. However, whether this is definitively true remains to be elucidated.

Several studies have shown that the use of heparin or low-molecular-weight heparin is associated with a lower risk of DVT in ICU patients [7]. In Western countries, pharmacologic thromboprophylaxis was used in 33% to 100% of critically ill patients [3,4]. The American College of Physicians' guidelines recommend that critically ill patients receive anticoagulant prophylaxis if they have a low risk of bleeding [8]. However, in Asians, anticoagulant prophylaxis in critically ill medical patients is not routinely used [9]. Concerns about bleeding associated with anticoagulants often outweigh the benefits of preventing unforeseen thrombosis.

Although several risk stratification scores for VTE have been proposed to identify those at high risk who need thromboprophylaxis [10,11], the implementation of these scores is low due to limited validation in Asians. A previous study in Thailand demonstrated independent risk factors associated with DVT in medical ICU patients such as femoral venous catheter [12].

Given the limited evidence in the current literature, this study aims to demonstrate the incidence of DVT in medically critically ill patients and to externally validate previously identified risk factors in the Thai population.

2 | METHODS

2.1 | Study design

A single-center, prospective observational study of medical critically ill patients was conducted at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, from October 2019 to May 2020.

Consecutive adult patients admitted to the medical ICU for ≥48 hours were included. Indications for medical ICU in our hospital are patients with hemodynamic instability, severe acute respiratory distress syndrome, high-risk postoperative complication, requirement for extracorporeal support, and after cardiac arrest. Patients were excluded if they had contraindications for duplex ultrasound such as open leg wounds or amputation. According to previously published risk factors in Thai medical ICUs, patients were defined as "at-risk" if they had at least 1 of the following conditions at the time of enrollment or during admission [13]: 1) female sex, 2) age >50 years, 3) femoral venous catheter, and 4) requiring platelet transfusion.

The study was approved by the Ethical Research Committee of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (approval number MURA2019/642). Written informed consent was obtained from patients or their immediate family members.

After careful counseling regarding the study protocol, patients were screened for proximal DVT by duplex ultrasound within 48 hours of ICU admission. Serial duplex ultrasounds were performed at days 5 and 7 and then weekly (or earlier if clinically indicated) until discharge from ICU.

The duplex ultrasound screening was performed using a Sonosite M-Turbo portable ultrasound system (SonoSite Inc) and a 10- to 15-MHz probe. The extended compression ultrasound protocol, the compression ultrasound from the common femoral vein through the popliteal vein up to the calf veins confluence, was performed [14]. The diagnosis of DVT was made if the veins were noncompressible or in case of direct visualization of intraluminal thrombus.

The duplex ultrasound of the legs was performed by the pulmonary and critical care fellows who were trained by a radiologist (T.P.). All measurements were recorded and reviewed by an experienced radiologist (T.P.). If a proximal DVT was detected and confirmed on the ultrasound, the decision to start a therapeutic anticoagulant was made by the primary care team. In addition, repeated duplex ultrasounds were performed in patients who were diagnosed with proximal DVT at a similar schedule. The evolution of thrombus was categorized into stable thrombus, thrombus progression, and thrombus regression.

2.2 | Data collection

Electronic medical records were reviewed. Data on the following variables were collected: 1) demographic characteristics including age, sex, body mass index, Acute Physiology and Chronic Health Evaluation (APACHE) II score, active malignancy, immobilization for >72 hours, history of malignancy, known thrombophilia, recent major surgery,

previous oral anticoagulant, sepsis, and respiratory or cardiac failure (the detailed definitions are available in the Supplementary Definitions); 2) treatment and interventions including vasopressor use for >48 hours, central venous catheter insertion, blood component transfusion, renal replacement therapy, mechanical ventilation for >48 hours, and sedation used; and 3) outcomes including prevalence and incidence of DVT, length of ICU stay, and ICU and in-hospital mortality. Causes of death were adjudicated based on the recorded International Classification of Diseases Tenth Revision (ICD-10) and clinical progress notes of the attending physicians.

The primary outcomes were the prevalence and incidence of DVT in medically critically ill Thai patients. The secondary outcomes were external validation of previously identified risk factors associated with DVT in the Thai population and all-cause mortality.

2.3 | Statistical analysis

Demographic data are presented as descriptive statistics. Categorical variables are presented as counts and percentages. Continuous variables are presented as means and SDs. Characteristics between patients in the at-risk group and those in the low-risk group were compared by using the independent *t*-test for continuous variables and the chi-square test for categorical variables. Prevalence and incidence of DVT are presented as percentages with calculated 95% CIs by Wald interval method. The incidence of DVT between the at-risk and low-risk groups was compared by using the 2-sample test of proportion. Risk factors for DVT were demonstrated by using logistic regression. Odds ratio and their 95% CIs were analyzed. *P* value <.05 was considered statistically significant. All statistical analyses were performed using Stata statistical software version 16.1 (StataCorp).

The sample size calculation was based on the prevalence and incidence of DVT in a previous prospective observational study in critically ill Thai medical patients. From that study, the prevalence and incidence of proximal DVT were 14.1% (95% CI, 9.6%-20.15%) and 8.82% (95% CI, 5.4%-14.0%), respectively [12]. The study required 186 or 124 patients to estimate the prevalence or incidence, respectively, with an acceptable error of 5%.

3 | RESULTS

Over 1 year, 289 patients were admitted to the medical ICU. Eighty-nine patients were excluded, as 54 (18.6%) patients had limited ultrasound screening because of cellulitis, thrombophlebitis, or amputation. Thirty-five patients (12.1%) had ICU stays ≤48 hours (Supplementary Figure S1).

A total of 200 patients were enrolled in this study. Among all patients, the mean (SD) age was 66.5 (16.4) years, and 115 were male (57%). The mean body mass index was 21.6 kg/m^2, and the mean (SD) APACHE II score was 27 (8). One hundred seventy (85%) patients were mechanically ventilated, and 32 (16%) were previously on therapeutic anticoagulation due to an underlying disorder (atrial fibrillation, VTE, coronary disease, pulmonary hypertension, and mechanical valve replacement). Forty-five patients (22.5%) had active cancer. Baseline demographics and clinical characteristics are presented in Table 1. Main diagnoses for ICU admission are presented in Supplementary Table S1.

During ICU admission, 2 patients (1%) received anticoagulant prophylaxis, and 2 patients (1%) received mechanical prophylaxis. Among the 32 patients previously on anticoagulation, 15 patients (7.5%) received therapeutic anticoagulation for thromboprophylaxis.

All ultrasounds were performed as scheduled. Three patients had evidence of postthrombotic change on the screening ultrasound indicating preexisting DVT at the time of ICU admission. During ICU admission, 14 out of 200 patients (7%) had evidence of acute proximal DVT. In 9 patients, DVTs were discovered within 48 hours, and on day 5 in the other 5 patients. The median time to DVT diagnosis was 48 hours. This translates to a cumulative incidence of DVT over 5 days of 7% (95% CI, 3.4%-10.6%) and a prevalence of 8.5% (95% CI, 4.6%-12.4%). The locations of the incident DVT were on the left and right sides of 8 and 6 legs, respectively. The left popliteal and right common femoral veins were the most frequent sites. All patients had no clinical symptoms of DVT during the ICU stay. Of the 14 DVT patients, all had computed tomography (CT) angiography of the chest and none showed evidence of pulmonary embolism (PE).

Of the 3 patients with prior DVT on ICU admission, no progression of DVT was observed despite the absence of prophylactic anticoagulation. These patients did not receive anticoagulant prophylaxis due to a high perceived risk of bleeding. Of the 14 incident DVTs, 11 (78%) received therapeutic anticoagulation. For these DVTs, the extents of the thrombus remained stable on follow-up ultrasounds. Three patients with incident DVT did not receive anticoagulant therapy for the following reasons: massive upper gastrointestinal hemorrhage, disseminated intravascular coagulation, and high risk of intracranial bleeding. One of these patients died due to sepsis before the next scheduled follow-up ultrasound. In the other 2 patients who did not receive anticoagulant treatment, follow-up duplex ultrasounds of the legs were performed. One had a stable thrombus at 1 week, and 1 had regression of thrombus at 2 weeks. No bleeding complications occurred in those who received anticoagulant therapy.

Overall, death occurred in 66 (33%) patients, with sepsis being the most common cause. No VTE-related deaths were observed. There was no significant difference in mortality between those with and those without DVT (42.9% and 32.3%, respectively; *P* = .42).

According to the prespecified risk criteria, 82 (41%) patients were in the at-risk group and 118 (59%) patients were in the low-risk group. There was no significant difference in the incident DVT incidence between the at-risk and low-risk groups (6.1% vs 7.6%; *P* = .67).

Among patients with incident DVT, the percentages of those with a history of malignancy, red blood cell transfusion, plasma transfusion, renal replacement therapy, and sedation requirement were numerically higher than the percentages of those without DVT. However, there was no statistically significant difference between the 2 groups. We performed univariate and multivariate analyses including age, gender, femoral catheterization, and platelet transfusion as

TABLE 1 Baseline characteristics of patients with incident DVT and no DVT.

Characteristics	Total (*N* = 200)	Incident DVT (*n* = 14)	No DVT (*n* = 186)	*P* value
Age (y), mean (SD)	66.5 (16.4)	63.9 (15.2)	66.8 (16.5)	.53
Male sex, *n* (%)	115 (57.5)	9 (64.3)	106 (57)	.59
BMI, mean (SD)	21.6 (3.8)	22.2 (2.5)	21.6 (3.9)	.55
APACHE II, mean (SD)	27 (8)	27.9 (8.3)	27 (8)	.68
Active malignancy, *n* (%)	45 (22.5)	5 (35.7)	40 (21.5)	.22
Immobilization for >72 h, *n* (%)	193 (96.5)	14 (100)	179 (96.2)	.46
History of malignancy, *n* (%)	48 (24)	5 (35.7)	43 (23.1)	.29
Family history of malignancy, *n* (%)	13 (6.5)	1 (7.1)	12 (6.5)	.92
Known thrombophilia,[a] *n* (%)	3 (1.5)	0	3 (1.6)	.63
Recent major surgery, *n* (%)	16 (8)	0	16 (8.6)	.25
Previous oral anticoagulants, *n* (%)	32 (16)	0	32 (17.1)	.09
History of DVT, *n* (%)	3 (1.5)	0	3 (1.6)	.63
End-stage renal disease, *n* (%)	38 (19)	3 (21.4)	35 (18.8)	.81
Sepsis, *n* (%)	155 (77.5)	11 (78.6)	144 (77.4)	.92
Respiratory or cardiac failure, *n* (%)	175 (87.5)	11 (78.6)	164 (88.2)	.29
Vasopressor used for >48 h, *n* (%)	162 (81)	12 (85.7)	150 (80.7)	.64
Mechanical ventilator use for >48 h, *n* (%)	170 (85)	11 (78.6)	159 (85.5)	.48
Sedation, *n* (%)	45 (22.5)	5 (35.7)	40 (21.5)	.22
Central venous catheter insertion, *n* (%)	112 (56)	9 (64.3)	103 (55.4)	.52
RBC transfusion, *n* (%)	51 (25.5)	6 (42.8)	45 (24.2)	.12
Plasma transfusion, *n* (%)	7 (3.5)	1 (7.1)	6 (3.2)	.44
Platelet transfusion, *n* (%)	21 (10.5)	2 (15.4)	19 (10.2)	.55
Renal replacement therapy, *n* (%)	39 (19.6)	4 (28.6)	35 (18.9)	.38

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; DVT, deep vein thrombosis; RBC, red blood cell.
[a]One patient had protein S deficiency; 2 patients had antiphospholipid antibody syndrome.

prespecified risk factors; there were no significant risk factors associated with DVT. The hospital mortality, length of hospital stays, and length of ICU stay were not affected by the presence of DVT (Table 2).

4 | DISCUSSION

Our study evaluated the incidence of DVT in patients admitted to the medical ICU and identified the factors associated with DVT. We categorized patients into at-risk and low-risk groups according to the previously identified risk factors in the Thai medical ICU [13]. We screened for proximal DVT using duplex ultrasound in patients admitted to the medical ICU. Our study revealed that the incidence of DVT was 7% (95% CI, 3.4%-10.6%). Most DVTs occur within 48 hours, and there were no symptoms or signs suggestive of DVT. It is noted that symptoms and physical examination might not accurately indicate DVT, especially in critically ill patients who are intubated and sedated [15]. Our figure was comparable with that reported in another study

TABLE 2 Outcomes of patients with DVT or without DVT.

Outcomes	Total (*N* = 200)	Incident DVT (*n* = 14)	No DVT (*n* = 186)	*P* value
Length of stay in ICU (d), mean (SD)	10.7 (10.7)	13.6 (9.2)	10.5 (10.8)	.31
Length of stay in hospital (d), mean (SD)	31.3 (37.3)	27.9 (15.6)	31.5 (38.4)	.73
Death, *n* (%)	66 (33)	6 (42.9)	60 (32.3)	.42

DVT, deep vein thrombosis; ICU, intensive care unit.

of medical ICU from a tertiary care hospital in Thailand, which was 10.1% [12].

In Western countries, the incidence of DVT detected by screening ultrasound ranges from 13% to 30 % in medical-surgical critical patients without thromboprophylaxis and 5.1% to 15.5% in those with pharmacologic thromboprophylaxis [16]. In Asia, the estimated incidence of all VTEs in ICU is 6.6% to 10% [6] without pharmacologic prophylaxis [9]. However, there are limited data on the incidence of DVT in critically ill medical patients. A study of 80 medical ICU patients in Hong Kong demonstrated a proximal DVT incidence of 7.5% [17]. In this study, they excluded patients with femoral catheterization or a history of previous VTE. Another study in a Thai medical ICU reported the incidence proportion of proximal DVT of 10.1%. In both studies, DVT was screened by compression ultrasound, and no routine anticoagulant prophylaxis was given; hospital mortality was not affected by the presence of DVT [12]. Though we did not find a significant difference in hospital mortality in our study, the number of deaths was numerically higher in patients with DVT than in those without DVT (42.9% and 32.3%).

The question of whether DVT detected by ultrasound screening results in worsened outcomes, including mortality or PE, is controversial. In our study, all patients who had DVTs detected by ultrasound screening underwent a chest CT due to other respiratory conditions, and no concurrent PE was observed. It is noted that we did not evaluate asymptomatic PE. In 1 patient with DVT who did not receive anticoagulation, spontaneous regression of the thrombus was detected in week 2. In addition, our findings indicate that DVT was not associated with mortality or length of ICU or hospital stay.

In our study, we screened for proximal but not distal DVT. Proximal DVT is associated with a higher risk of thrombus progression and embolization than distal DVT [18]. Although the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines state that inpatient status is a risk factor for thrombus extension in patients with isolated distal DVT, suggesting they should receive anticoagulant treatment [19], the clinical importance and management of isolated distal DVT in critically ill settings have not been adequately addressed in clinical trials. Furthermore, by serially screening the proximal veins, we could detect the extension of the distal thrombus to the proximal veins.

The ICUs included in this study primarily admitted medically critically ill patients, most of whom had sepsis with respiratory failure. Although our ICUs have limited capacity, the complexity of cases is comparable with that of larger hospitals. This is evidenced by the mean (SD) APACHE II score in our study, which was 27 (8). In comparison, the mean (SD) APACHE II score in multicenter sepsis trials in the United States and Canada was 25 (7.8) [20].

We were unable to identify any risk factors associated with DVT. When we categorized patients by prespecified risk factors for DVT, no significant difference in the incidence of DVT was demonstrated between the at-risk and low-risk groups. This could be attributed to several factors. Firstly, femoral catheterization was not routinely performed in our center. As femoral catheterization is a well-known risk factor for DVT [21], all central venous catheterizations were conducted through the internal jugular vein. This might result in different settings and risk factors compared with those in the previous study in Thailand. Secondly, admission criteria in our medical ICU primarily involved respiratory failure and sepsis. Patients with active cardiac conditions [22] or acute stroke [23] were admitted to specialized ICUs, potentially contributing to the lower risk of DVT. Lastly, in 16% of our cohort, patients had received therapeutic anticoagulants before ICU admission. This might have contributed to the lower incidence of DVT in our population.

We did not specify in advance the collection of data regarding the IMPROVE VTE risk score, the score that predicts 3-month risk of VTE in hospitalized patients [10]. According to the score, all patients admitted to the ICU were considered high-risk, and it is recommended that they receive anticoagulant prophylaxis. However, when calculating the IMPROVE VTE score based on the available data (excluding concurrent limb paralysis and defining immobilization as >72 hours), 74% of patients had a score of ≥3, indicating high-risk status. There was no significant association between these high-risk patients (as defined by the IMPROVE VTE risk score) and the occurrence of DVT (P = .70).

As we collected baseline characteristics during the hospital course, we acknowledge that some factors might not occur within 48 hours, potentially leading to immortal time bias. No patients had a femoral catheter insertion and all the platelet transfusions occurred within 2 days of ICU admission except for 1 patient without DVT who received a platelet transfusion 3 days after ICU admission.

To address the potential for immortal time bias, we performed a sensitivity analysis excluding patients with platelet transfusion more than 48 hours after ICU admission. The results of this sensitivity analysis were similar to those of our primary analysis, with patients classified as at-risk and low-risk at 40.7% and 59.3%, respectively. The incidence of DVT was also similar to that in the primary analysis, suggesting that our findings are robust and not significantly impacted by this bias (6.17% and 7.62% in the at-risk and low-risk groups, respectively). In addition, immortal time bias can occur when analyzing outcomes such as length of stay in ICU/hospital and mortality based on the occurrence of DVT. To mitigate this bias, we excluded patients with incident DVT diagnosed for more than 48 hours, and the results of this sensitivity analysis were similar to those of our primary analysis. Length of stay in ICU and hospital and mortality were not significantly different in patients with or without DVT.

The study has several strengths. 1) This is a prospective cohort study. 2) Consecutive eligible patients admitted to medical ICU were included. 3) Duplex ultrasound was performed by critical care and pulmonary fellows who were trained by a radiologist. 4) All results were independently reviewed and confirmed by a radiologist. 5) All DVT patients underwent CT of the chest to evaluate for concurrent PE. 6) Follow-up ultrasounds were conducted to demonstrate the history of thrombus extension in patients with DVT.

We acknowledge the following limitations: although the duplex ultrasound was conducted by well-trained fellows, it was operator-dependent. However, all DVT cases were reviewed and verified by a radiologist. We did not follow the patients after their discharge from ICU or the hospital; therefore, DVT occurrences at a later date were not recorded. The sample size of this study was calculated to allow a precise estimate of the proportion. Therefore, the number is limited for comparison of outcomes between groups. Although we performed a multiple logistic regression, the number of events was low, which could lead to an imprecise estimate. Finally, we were unable to demonstrate the natural history of incident DVT in those not receiving anticoagulant treatment, as follow-up ultrasounds were performed in only a few patients.

In conclusion, we found that the incidence of proximal lower limb DVT among critically ill medical Thai patients was 7% (95% CI, 3.4%-10.6%). No risk factor associated with DVT was identified. The rate of pharmacologic thromboprophylaxis in our ICU remains low. A strategy of screening ultrasound 5 to 7 days after admission to the ICU may be a suitable alternative to anticoagulant prophylaxis in critically ill Thai medical patients without symptoms of VTE.

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AUTHOR CONTRIBUTIONS

S.A. collected data, performed the study, and wrote the first draft of the manuscript. Y.S. designed the study, led the study, and provided critical revision to the manuscript. T.P. trained the fellows to perform duplex ultrasound, reviewed imaging, and provided critical revision to the manuscript. P.T. designed the study and provided critical revision to the manuscript. P.A. provided critical revision to the manuscript. K.B. designed the study, analyzed the data, and wrote the final version of the manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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