



Cohort Study

Predictive risk factors for venous thromboembolism in neurosurgical patients: A retrospective analysis single center cohort study

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ABSTRACT

Background: Venous thromboembolism (VTE) has a major effect on morbidity and mortality in neurosurgical patients. However, identifying risk factors that may be useful in practice is a challenge. The purpose of this study was to investigate the incidence and determine the predictors of VTE in patients undergoing neurosurgery.

Materials and methods: This retrospective, single-center cohort study was conducted on adult patients admitted to a private hospital for a primary elective neurosurgical procedure between January 2015 and December 2020. Univariate analysis was used to examine clinical factors, and multivariable regression analysis was used to identify predictors of VTE. The area under the receiver-operating characteristic (AUROC) curve demonstrated the fitting model and discrimination power.

Results: A total of 350 patients who underwent neurological surgery were identified. There were 26 patients (7.4%) with VTE. The final predictors were found to be statistically significant in the multivariate binary logistic regression analysis, including non-Asian populations (p value < 0.001, odds ratio [OR]: 6.11, 95% confidence interval [CI] = 2.20–16.89), lack of postoperative ambulation (p value = 0.009, OR: 9.25, 95% CI = 1.17–48.83), and septic shock complication (p value = 0.001, OR: 5.36, 95% CI = 1.46–19.62). The AUROC was 0.708 (95% CI 0.61–0.80).

Conclusion: Although the incidence of VTE in patients receiving neurosurgery is minimal, it is also higher in non-Asian patients, those who lack of postoperative ambulation, and patients with septic shock complications. This approach may be useful to predict thromboembolism in neurosurgical patients. External validation of the prognostic model requires more investigation.

1. Introduction

Venous thromboembolism (VTE) includes pulmonary embolism (PE) and deep vein thrombosis (DVT), which are major postoperative complications especially after surgery of the nervous system. These complications can be a major cause of morbidity and even death in neurosurgical patients [1]. The risks of mortality within 1 month after DVT and PE are 6% and 12%, respectively [2]. Furthermore, in these patients, VTE is associated with longer hospital stays and higher health care costs.

Virchow's triad mechanism, which includes flow stasis, intravascular vessel wall injury, and the presence of a hypercoagulable state, indicates the development of a VTE condition in neurosurgical patients [3]. Venous stasis can be affected by the anesthesia and paralysis used during

surgery and postoperative care with fluid therapy. In addition, blood transfusions can cause vascular damage, resulting in tissue factor over release and blood hypercoagulability, which is most typically seen in neurosurgical patients with traumatic brain injury [4]. Limited postoperative mobility or delayed ambulation is another cause of VTE events [3]. It is difficult to estimate the actual number of VTE problems experienced by patients after neurosurgery. Some studies have reported a VTE incidence of 1%–5% in patients receiving prophylaxis [5–7]. On the other hand, rates ranging from 13% to 50% might include those who do not receive prophylaxis after surgery; therefore, caution is needed when interpreting the data [7,8]. Following elective neurosurgery, standard therapy includes mechanical devices (compression stockings, intermittent/sequential compression devices, intermittent pneumatic compression) and pharmacoprophylaxis with heparin,

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low-molecular-weight heparin, or other anticoagulants, but the most appropriate prophylaxis in patients undergoing neurosurgical interventions remains unclear [9–11]. The decision to administer pharmacological prophylaxis is determined based on the patient's category of risk, and the varying clinical practices of neurosurgeons has an effect on postoperative VTE prophylaxis after elective neurosurgery [9]. Although many physicians avoid using pharmacological prophylaxis for any reason, some emergencies require a return to the operating room, which raises concerns about the risk for intracranial hemorrhage [12, 13].

Although mechanical prophylaxis does not increase the risk of bleeding, it has a limited benefit in reducing thrombosis prophylaxis. Despite this, the optimal VTE prevention strategies in neurosurgical patients remain unknown [7,14]. Identifying risk factors is the most critical aspect in the management of these patients [15,16]. Several studies have demonstrated the factors that contribute to VTE after neurosurgery, but the evidence is primarily derived from Western populations. In Asian patients, there is diversity across regions [17,18], and identified risk factors vary depending on the study site, which allows us to provide guidance on how to manage VTE prophylaxis in a way that is appropriate for each individual. Here, we sought to define the incidence and determine predictors of thromboprophylaxis in neurosurgical patients.

2. Materials and methods

This was a retrospective cohort study. We analyzed the records of neurosurgical patients admitted to a private tertiary care hospital, single center, between January 1, 2015, and December 31, 2020. The Institute Ethics Committee at Bangkok Hospital in Chonburi Province, Thailand, authorized our research (IRB No. 04–2564). The study was done in accordance with the Declaration of Helsinki's ethical guidelines.

2.1. Participants

For this analysis, all patients who underwent any type of neurosurgical procedure were selected. Inclusion criteria were (1) 18 years of age or older and (2) evidence of neurosurgical process. Patients were excluded if they had undergone a previous neurosurgical intervention, were referred from another hospital, required a neurosurgery operation that lasted more than 24 h, or had an incomplete electronic medical record. There were 350 patients included.

2.2. Sample size

The sample size was determined by using G*Power program base on logistic regression analysis. We estimated sample size of 350 neurosurgical patients, with VTE events from previous study, to give 80% power at the 5% significance level (two-sided) and 5% margin of error.

2.3. Variables and outcomes of interest

The following clinical factors were recorded and analyzed: gender, age, race, comorbidities, body mass index (BMI), previous medication use (steroid, antiplatelet, anticoagulant), smoking, functional status, previous VTE, type of neurosurgery (brain or spine), surgery procedure (craniotomy, craniectomy), surgery time, intubation tube, blood transfusion (estimated blood loss), length of stay, ambulation, complications after surgery, American Society of Anesthesiologists (ASA) classification, and Caprini score.

The outcome of interest was the occurrence of VTE (PE and DVT) during acute hospitalization. Clinical symptoms with a physician's diagnosis or objectively verified symptoms such as DVT ultrasonography, D-dimer test, imaging confirmation, or chest computed tomography scans were used to identify VTE. Other variables included the duration of VTE occurrence, location of VTE, and methods of VTE

prophylaxis (pharmacological or mechanical prophylaxis).

2.4. Statistical analysis

Demographic characteristics with continuous data were presented as mean and standard deviation for variables with a normal distribution and as median and interquartile range for variables with nonnormal distribution. Categorical variables were presented by chi-square test or Fisher's exact test as appropriate.

Prediction factors were calculated by multivariable logistic regression models. The variables from the univariate analysis were converted to binary variables and included in the model to identify clinical factors associated with VTE (p value < 0.2). Significant factors including clinical significance were interaction tests for multicollinearity using a variance inflation factor of < 10 . Predictors of VTE development were identified using backward stepwise regression analysis with p value < 0.05 to determine variables. The Hosmer–Lemeshow test was used to assess the fit of the multivariate regression model to the data; p value > 0.05 indicates a model that fits the data well. All statistical analyses were performed using IBM SPSS 23 software.

2.5. Unique identifying number is: researchregistry7632

The processes were established in accordance with STROCSS 2021 guidelines [19].

3. Results

A total of 350 neurosurgical patients were admitted to the hospital and underwent VTE screening. Table 1 summarizes the patients' demographic data, including gender, age, race, length of stay, postoperative characteristics, and other variables.

Twenty-six patients (7.4%) experienced VTE following a neurosurgical procedure. There were 12 cases of PE (3.4%) and 11 cases of DVT (3.1%). All 24 patients were men, 88.5% were White, and the median time to event was 13 days. Pneumonia and acute respiratory failure were the most common complications after surgery. VTE prevention was provided to 24 patients (mechanical prophylaxis in 23 cases and pharmacological prophylaxis in 1 case).

Factors associated with VTE in the univariate analysis were selected for the multivariable regression analysis, including gender, age ≥ 65 years, race, BMI, history of smoking, intubation tube, ambulation, complications after surgery, and Caprini score (Table 2).

In neurosurgical patients, non-Asian populations (odds ratio [OR] 6.09; 95% confidence interval [CI] 2.20 to 16.87; p value < 0.001), postoperative ambulation (odds ratio [OR] 9.17; 95% confidence interval [CI] 1.74 to 48.41; p value = 0.009), and septic shock complication (odds ratio [OR] 5.31; 95% confidence interval [CI] 1.45 to 19.44; p value = 0.012) were found to be independently associated with VTE (Table 3).

The discriminating capability of our model was 0.708 (95% CI: 0.61–0.80), as measured by the receiver-operating characteristic curve.

4. Discussion

VTE complication in a neurosurgery patient causes suffering. In addition, these patients experience a reduction in quality of life as well as adverse effects [7,20]. The management of VTE is particularly difficult, because the risks and benefits must be balanced [16]. The rate of VTE in our analysis, which included 350 cohorts, was 7.4%, which is within the range of previously reported neurosurgery-related VTE rates of 3.3%–23%. The high prevalence in previous study was observed in patients with tumor/malignancy (28%–43%), craniotomy (25%), and traumatic brain injury (20%) [7,21]. Similar to what we observed in our study, most craniotomy patients (60%) developed VTE. Among the 26 VTE patients, two patients did not receive prophylaxis because they

Table 1
Baseline characteristics of neurosurgical patients (n = 350).

Characteristic	n (%)
Age (years), mean ± SD	55.0 ± 17.8
Male	257 (73.4)
Race	
Asian	202 (57.7)
Non-Asian White	148 (42.3)
BMI (kg/m ²)	
<25	203 (60.2)
25	134 (39.8)
Comorbidity	
No	103 (29.4)
Yes	247 (70.6)
Hypertension	169 (48.3)
Heart disease	61 (17.3)
Diabetes mellitus	50 (14.3)
Previous steroid use	154 (44.0)
Smoking	35 (10.0)
Type of neurosurgery	
Brain	302 (86.3)
Spine	48 (13.7)
Surgery time (hours), median (IQR)	2 (1.7)
ICU length of stay, median (IQR)	2 (5)
Estimated blood transfusion (unit), mean ± SD	2.8 ± 1.3
Postoperative ambulation	
Yes	343 (98.0)
No	7 (2.0)
Complication	
No	194 (55.5)
Yes	156 (44.5)
Acute respiratory failure	82 (23.4)
Pneumonia	73 (20.9)
Anemia	51 (14.4)
Septic shock	16 (4.6)
Meningitis	7 (2.0)
ASA classification	
Class 1	3 (0.9)
Class 2	42 (12.2)
Class 3	146 (42.4)
Class 4	149 (43.3)
Class 5	4 (1.2)
Caprini score	
1–2	6 (1.7)
3–4	123 (35.1)
≥5	221 (63.1)
VTE	
PE	12 (3.4)
DVT	11 (3.1)
DVT and PE	3 (0.9)
VTE prophylaxis	
Mechanical prophylaxis	23 (88.5)
Mechanical with pharmacological prophylaxis	1 (3.8)

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; DVT, deep vein thrombosis; ICU, intensive care unit; IQR, interquartile range; PE, pulmonary embolism; SD standard deviation; VTE, venous thromboembolism.

were classified as low risk according to available guidelines. However, VTE can arise as a result of septic shock and pneumonia. Only one patient received both mechanical and pharmacological prophylaxis. That patient was non-Asian, had a Caprini score of 6 (high risk), suffered septic shock as a consequence, and stayed 42 days in the ICU. Despite proper thromboprophylaxis, some patients still develop VTE as a result of many risk factors [20]. Several studies have demonstrated that White race, gender, age, BMI, cigarette smoking, prior VTE, time of surgery, ICU length of stay, non-ICU length of stay, intubation tube status, lack of postsurgery ambulation, postsurgery complications (i.e., septic shock, pneumonia, acute respiratory failure, anemia, delirium, meningitis), a high ASA classification, and high Caprini score can increase the risk of VTE [11,15,20–26]. Although many studies have examined the factors related to VTE, few have examined prediction models [11]. The studies by Smith et al., Kaewborisutsakul et al., Nunno et al., Cote et al., Juhua et al., and Missios et al. found that age, gender, surgery time, history of

Table 2
Univariate analysis in neurosurgical patients with VTE.

Factor	Odds ratio	95% Confidence interval	p value
White race	6.51	2.41–17.75	<0.001
Age >60 years	2.11	0.95–4.72	0.068
BMI (kg/m ²)	3.13	1.35–7.25	0.008
Previous steroid use	0.93	0.41–2.09	0.864
Smoking	3.08	1.15–8.29	0.026
Surgery time	2.01	0.77–5.30	0.156
Postoperative ambulation	10.53	2.23–49.90	0.003
Postoperative complication	2.14	0.94–4.85	0.069
Pneumonia	2.62	1.14–6.05	0.024
Acute respiratory failure	2.21	0.96–5.09	0.061
Septic shock	4.77	1.42–16.02	0.011
Meningitis	5.37	0.99–29.13	0.052
ASA classification 3–5	4.13	0.52–30.27	0.179
Caprini score (high risk)	3.49	1.18–10.37	0.024

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

Table 3
Multivariable logistic regression analysis.

Factor	Adjusted OR (95% CI)	p value
Non-Asian population	6.09 (2.20–16.87)	<0.001
Postoperative ambulation	9.17 (1.74–48.41)	0.009
Septic shock	5.31 (1.45–19.44)	0.012

Abbreviations: CI, confidence interval; OR, odds ratio.

VTE, ICU length of stay, ASA classification, blood transfusion, intubation tube, BMI, ambulation, sepsis complication, new-onset postoperative motor deficits, hyperglycemia, hypertension, higher postoperative D-dimer, lower Glasgow Coma Scale score, and Hispanic ethnicity were independent predictors of VTE after neurosurgery. Similar to our study, ambulation, postsurgery septic shock, and non-Asian race were also revealed to be predictive for VTE [11,23,24,26].

Postoperative immobility is considered to be a significant risk factor for VTE. Our investigation revealed that patients who were unable to ambulate after neurosurgery had a 9.25-fold risk of a VTE event, which is similar to the findings of Kristopher et al. and Joeky et al. [15]. Many guidelines recommend early ambulation to prevent VTE [2,6,9,27,28]. The benefits of ambulation are obvious. Previous studies have shown that early ambulation is associated with a decreased risk of VTE. In addition, ambulation has been correlated with a reduced length of stay, earlier discharge from rehabilitation, and lower incidence of readmission for spine surgery [2,29]. However, ambulation alone is not sufficient to discontinue VTE pharmacologic prophylaxis during a patient’s hospital admission [30].

In neurosurgical patients, septic shock was also a significant risk factor related to VTE [15,23,26,31]. According to our analysis, the risk of VTE in patients with septic shock was 5.36-fold higher than in those without this complication. A variety of mechanisms have been proposed. Septic shock is commonly related to alterations in hemostasis that cause blood to coagulate (hypercoagulability). The inflammatory pathway stimulates the production of cytokines, which causes platelet activation via the activated microthrombotic pathway, resulting in acute disseminated intravascular coagulation [31].

Non-Asian race was found to be another predictor of VTE. Caucasian and African populations were associated with a higher incidence of VTE than Asian populations. According to many ethnic comparison studies, the incidence appears to be 2.5- to 4-fold lower among Asian Americans and Asian Pacific Islanders than among Caucasians [17,18]. Although the reason for the lower frequency of VTE in the Asian population is unknown, it might be due to a lower incidence of primary hypercoagulable disorder, Factor V Leiden mutation, which can lead to VTE [32,33]. This mutation increases the risk of blood clots, which are the most common prothrombotic variation in young and middle-aged individuals

[34,35]. Prior studies have suggested that Asian populations have a lower incidence of Factor V Leiden mutation (0.5%) than Caucasians do (5%) [32,33]. In Thailand, the prevalence of Factor V gene mutations is quite low [33].

Our study has several limitations. First, the study was not designed to evaluate the prognostic factor of VTE biomarkers. The Factor V Leiden gene mutation is biomarker of hereditary thrombophilia. The heterozygous mutation has been found in the White population of the United States and Europe (with a prevalence ranging from 3% to 8%), but it is less common in other ethnic groups. However, in Thailand, the identification process was restricted to detection because of a shortage of resources. Furthermore, in Thai patients, screening for the Factor V Leiden gene mutation is of limited benefit and may not be cost effective [33–35]. Another laboratory value of interest was blood glucose level. According to the study by Kaewborisutsakul et al., hyperglycemia has been found to be a risk factor for thrombosis [24]. We did not collect any information on blood glucose, because there is only a weak association between VTE and hyperglycemia, and many studies have reported only hyperglycemia caused by diabetes. In addition, research on the impact of the risk of VTE appears to be contradictory [36–38].

Second, this was a single-center, retrospective study. Our study had a small sample size, and the records also contained incomplete data, resulting in a small number of VTE events and an underestimation of the association. Finally, we found that when all reasons for cranial and spine surgeries were considered, most neurosurgical patients (80%) underwent cranial surgery. There may be a need to evaluate and apply the findings of this study to different specific types of surgical procedures.

Nonetheless, there are also some strengths to this study. To our knowledge, this study, we have a model for predicting this problem in specific individuals in real practice.

5. Conclusion

Using a multivariate analysis, our investigation revealed the predictive factors for VTE in neurosurgical patients. According to the model, non-Asian race, postsurgery ambulation, and septic shock complications are substantial predictors of VTE. The use of this model to predict the probability of VTE could be part of a valuable management strategy for patients undergoing elective neurosurgery. Further steps are needed to external validation of prognostic model.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Ethical approval

The Institute Ethics Committee at Bangkok Hospital in Chonburi Province, Thailand, authorized our research (IRB No. 04–2564).

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Authors' contributions

All authors contributed to the inception, design, analysis, interpretation, and drafting of the research manuscript and approved final version to be submitted.

Consent

This study was exempt from the IRB because it did not require consent form.

Registration of research studies

Name of the registry: <http://www.researchregistry.com>.

Primary investigator Porntip Parmontree.

Title of research “Predictive risk factors for venous thromboembolism in neurosurgical patients: A retrospective analysis single center cohort study”.

Unique Identifying number or registration ID: researchregistry7632.

Hyperlink to your specific registration (must be publicly accessible and will be checked):

<https://www.researchregistry.com/register-now#home/registrationdetails/62068b149278b2001e3a3fb4/>

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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