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Clinical Study

# Incidence and risk factors associated with in-hospital venous thromboembolism after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Our purpose was to determine the incidence and risk factors associated with in-hospital venous thromboembolism (VTE) in patients with aneurysmal subarachnoid hemorrhage (aSAH). The Nationwide Inpatient Sample database was queried from 2002 to 2010 for hospital admissions for subarachnoid hemorrhage or intracerebral hemorrhage and either aneurysm clipping or coiling. Exclusion criteria were age <18, arteriovenous malformation/fistula diagnosis or repair, or radiosurgery. Primary outcome was VTE (deep vein thrombosis [DVT] or pulmonary embolus [PE]). Multivariate logistic regression was used to assess association between risk factors and VTE. Secondary outcomes were in-hospital mortality, discharge disposition, length of stay and hospital charges. A total of 15,968 hospital admissions were included. Overall rates of VTE (DVT or PE), DVT, and PE were 4.4%, 3.5%, and 1.2%, respectively. On multivariate analysis, the following factors were associated with increased VTE risk: increasing age, black race, male sex, teaching hospital, congestive heart failure, coagulopathy, neurologic disorders, paralysis, fluid and electrolyte disorders, obesity, and weight loss. Patients that underwent clipping *versus* coiling had similar VTE rates. VTE was associated with pulmonary/cardiac complication (odds ratio [OR] 2.8), infectious complication (OR 2.8), ventriculostomy (OR 1.8), and vasospasm (OR 1.3). Patients with VTE experienced increased non-routine discharge (OR 3.3), and had nearly double the mean length of stay ($p < 0.001$) and total inflation-adjusted hospital charges ($p < 0.001$). To our knowledge, this is the largest study evaluating the incidence and risk factors associated with the development of VTE after aSAH. The presence of one or more of these factors may necessitate more aggressive VTE prophylaxis.



## 1. Introduction

In the USA, there are between 16,000 and 30,000 patients with aneurysmal subarachnoid hemorrhage (aSAH) per year [1,2]. Patients with aSAH frequently have a prolonged hospital course since multiple neurologic and medical complications may arise. This puts patients at higher risk for venous thromboembolism (VTE). The occurrence of VTE can have a major impact on outcome. Little research exists regarding the incidence, prevention and detection of VTE after aSAH as reflected in the most recent 2012 American Heart Association/American Stroke Association Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [3].

Much of our current knowledge has been extrapolated from the general neurosurgical population [4–17]. Difficulties in extrapolating incidence and risk factors include (1) neurosurgery covers a wide spectrum of disease, so that patients undergoing elective spine surgery, brain tumor resection, or functional procedures might be expected to have discordant VTE incidence, and (2) the disease processes associated with aSAH bring a new set of potential risk factors that may influence VTE risk. Decision-making for the use of chemical prophylaxis in patients after aSAH is complex, as one must account for multiple factors, including aneurysm status (secured or not), whether a craniotomy is performed, presence of intracerebral hemorrhage (ICH), presence of an external ventricular drain, use of anti-fibrinolytics and the need for additional and sometimes emergent procedures. Knowledge of VTE risk factors can help clinicians identify patients that may benefit most from chemoprophylaxis. The purpose of this study was to determine the incidence and risk factors for in-hospital VTE (deep vein thrombosis [DVT] or pulmonary embolus [PE]) in a large cohort of patients with aSAH.

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## 2. Materials and methods

### 2.1. Patient selection

The Nationwide Inpatient Sample (NIS) database (Healthcare Cost and Utilization Project [HCUP], Agency for Healthcare Research and Quality, Rockville, MD, USA) represents a 20% stratified sample of USA community (non-federal) hospitals. NIS data is coded based on diagnosis and procedure codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NIS database was queried from 2002 to 2010 due to the introduction of co-morbidity data in 2002 and dedicated endovascular coiling codes in 2001. Inclusion criteria were hospital admissions with age ⩾18, principal diagnosis of subarachnoid hemorrhage (ICD-9-CM 430) or intracerebral hemorrhage (431) and principal procedure of either clipping (39.51) or coiling (39.72, 39.75, 39.76) of an aneurysm. Exclusion criteria were secondary diagnosis of anomalies of cerebrovascular system (747.81, i.e. arteriovenous malformation/fistula) or a secondary procedure of arteriovenous fistula repair (39.53) or stereotactic radiosurgery (92.30).

### 2.2. Data collection and outcome

Patient characteristics such as age, race, sex, and aneurysm treatment were obtained. Co-morbidities were obtained using the Elixhauser method [18]. This method utilizes secondary diagnoses, codes less likely reflecting in-hospital complications, and exclusion of diagnosis related group-related diagnoses to capture co-morbidities that are likely present on admission (POA) [18]. This method has been used extensively in the NIS literature [19–22]. The Elixhauser co-morbidities metastatic cancer, lymphoma, and solid tumor without metastasis were grouped into a general category of "malignancy". Co-morbidities with 10 or fewer occurrences were excluded per the HCUP NIS data use agreement. Psychiatric co-morbidities were also excluded. Lastly, pulmonary circulation disorders were excluded due to likely confounding with PE diagnosis codes. Hospital characteristics such as hospital region, bed size, and teaching status were also obtained.

The following in-hospital complications were collected using secondary diagnosis codes: pulmonary/cardiac (495.7, 507.0, 507.8, 512.1, 518.4, 518.51–518.53, 518.7, 518.81–518.82, 518.84, 997.31–997.32, 997.39, 997.93, 410.0–410.92, 997.1), infectious (038.0–038.9, 995.91–995.92, 320.0–320.9, 481, 482.1–482.9, 486, 510.0–510.9, 513, 519.2, 519.01, 590.1, 590.80, 595.0, 595.9, 599.0, 996.64, 998.51, 998.59, 999.31–999.32), ventriculostomy procedure (02.2), and vasospasm (435.8, 435.9, 39.50).

The primary outcome was occurrence of VTE (DVT or PE). This included acute DVT of the lower extremities (453.40, 453.41, 453.42), upper extremities (453.82–453.88), inferior vena cava (453.2), or unspecified location (453.89, 453.9), and PE (415.11, 415.12, 415.13, 415.19). We did not include thrombophlebitis, or chronic or superficial thrombosis. Of note, there are no ICD-9-CM codes to differentiate DVT that occur above *versus* below the knee, which have different risk of PE [23].

Secondary outcomes were in-hospital mortality, discharge disposition, length of stay and total hospital charges. Discharge disposition was categorized as routine (home or home health care) and non-routine (transfer to short-term hospital, skilled nursing, intermediate care, or another facility, or death) or unknown (discharged alive with destination unknown or against medical advice). Total hospital charges were inflation-adjusted to 2010 $USD using the United States Bureau of Labor Statistics Consumer Price Index Inflation Calculator [24].

### 2.3. Statistical analysis

Preoperative factors were compared between patients who experienced a VTE and those who did not using Pearson's chi-squared test for categorical variables and analysis of variance for continuous variables. Logistic regression was used to assess the association between each preoperative factor and VTE. Factors found to be significant in univariate analyses were included into the multivariate model. The association between VTE and other adverse outcomes was investigated via logistic regression. Sensitivity analyses were done using age as a continuous variable and dichotomizing length of stay and hospital charges. A $p$ value of <0.05 was significant. Odds ratios are expressed with 95% confidence intervals. SAS (version 9.2, SAS Institute, Cary, NC, USA) was used.

## 3. Results

Inclusion and exclusion criteria resulted in 16,191 hospital admissions. Admissions with missing co-morbidity data were excluded resulting in 15,968 records eligible for analysis (Fig. 1). Overall rates of VTE (DVT or PE), DVT alone, and PE alone were 4.4%, 3.5%, and 1.2%, respectively (Table 1). VTE rate increased from 2000 to 2010 due to a corresponding increase in DVT rates (Fig. 2). In 2009–2010 (n = 3960), incidence of VTE, DVT alone, and PE alone were 7.2%, 6.3%, and 1.3%, respectively. There was a minimal increase of VTE in those with a principal diagnosis of ICH (4.8%) *versus* SAH (4.3%).

On univariate analysis (Supplemental Table 1), patients greater than 65 years old and those aged 40–65 years were 2.0 and 1.6 times more likely to develop VTE, respectively, than those less than 40 years old. Teaching hospitals accounted for 86% of aSAH admissions, but were twice as likely to have a VTE during admission. Lastly, more aneurysms were clipped (56%) than coiled (44%) overall; however, there was no difference in VTE rate between the two groups.

In univariate analysis, the co-morbidities that had the greatest association with VTE were neurologic disorders, coagulopathy, weight loss, and paralysis (Supplemental Table 2). Other statistically significant but less powerful risk factors were congestive heart failure (CHF), fluid and electrolyte disorders, obesity, and anemia.

In multivariate analysis, the strongest risk factors for VTE were neurologic disorders and coagulopathy. Other statistically significant risk factors included weight loss, teaching hospital, age >65 years, age 40–65 years, fluid and electrolyte disorders, paralysis, and CHF (Table 2). In multivariate analysis, black race and male sex were significant independent risk factors.

VTE was strongly associated with pulmonary/cardiac and infectious complications, ventriculostomy procedure and vasospasm (Table 3). VTE was also associated with increased non-routine discharge, but also associated with decreased overall in-hospital mortality rate. Mean hospital length of stay and total inflation-adjusted hospital charges (2010 $USD) were nearly double in patients with VTE (Table 4).

## 4. Discussion

To our knowledge this is the largest study to evaluate the incidence of VTE after aSAH. In the modern era, VTE incidence specific to aSAH has been evaluated in two small studies [25,26]. One study used a screening lower extremity Doppler ultrasound (LED) protocol in 178 patients and found leg DVT in 3.4%; the incidence of PE was 1.1% [25]. In an unscreened cohort of 57 patients, there were no DVT or PE. The second study used a LED screening protocol in 125 patients and found leg DVT in 24%, with PE in 3% [26]. In an