

BACKGROUND

Venous thromboembolism (VTE) constitutes an undesirable outcome in the care of trauma patients. In the United States, the annual healthcare costs associated with VTE is estimated at \$1.5 billion⁽¹⁾ and close to 100,000 people die from VTE yearly.⁽²⁾ Among trauma patients who develop pulmonary embolism (PE), mortality is as high as 19%.⁽³⁾ These data highlight the significant health burden that VTE exerts on the healthcare system. It is therefore important to identify patients that are higher risk for developing these complications and institute measures to prevent the occurrence of VTE among them.

Compared to the general trauma population, patients with traumatic brain injury (TBI) are at increased risk for VTE.^(3, 4) Studies that have prospectively screened for VTE among hospitalized TBI patients have found rates ranging from 20 – 32%.⁽⁵⁻⁷⁾ Collectively, these studies have shown that older age, longer hospital stays, higher injury severity, and concomitant moderate-to-severe injuries in other body regions were independently associated with the higher VTE rates among this population. However, most of these studies include patients that have concomitant high-risk injuries, which may obscure the true patterns of VTE among TBI patients. With the growing evidence that the risk of VTE among trauma patients may persist for months following the traumatic events,⁽⁸⁾ there is increasing interest in long-term preventive strategies for VTE. However, it is not clear how long active prevention for VTE should last among TBI patients. Furthermore, there are no studies to show the long-term incidence of VTE among TBI patients.

Therefore, the objective of this study was to examine the long-term incidence of VTE among patients with isolated TBI. We hypothesized that patients with isolated TBI will remain at increased risk for VTE for up to one year following hospital discharge.

METHODS

Data Source and Study Sample

We analyzed patient discharge data from the California State Inpatient Database, Healthcare Cost and Utilization Project, 2007 – 2011, which contains records from up to 98% of the hospitals in the state.(9) A unique feature of the database includes the ability to link records of care received at multiple hospitals, thereby evaluating long-term outcomes of various conditions.(10) Patients were assigned unique identifiers, which were verified in 88.2% of patients 18 – 64 years old and 97.5% of patients 65 years and older.(11) Only patients with verified patient identifiers were included in our analyses.

Using International Classification of Diseases – Clinical Modification, 9th Revision (ICD-9-CM) diagnosis codes, we identified TBI admissions for patients 18 years and above between 2007 and 2010. To ensure at least one year of follow up for every case of TBI, we did not include index cases of TBI that occurred during the last year of the available data (2011) in our analyses. TBI admissions were defined as admissions with ICD-9-CM diagnosis codes of 800.xx, 801.xx, 803.xx, 804.xx, 850.xx – 854.xx. To restrict analyses to patients deemed to have isolated moderate to severe head injuries, we included patients who had Head Anatomical Injury Scale (AIS) scores ≥ 3 and had AIS scores < 3 in all other body regions. AIS scores for each body

region were derived using a validated method with the ICDPIC module in Stata.(12, 13) Patients with AIS scores of 6 (non-survivable) were excluded from the analysis.

Demographic details of the patients were extracted from the database. Because several studies have shown that patients older than 65 years have significantly different responses to injury (14-16) and most studies on VTE use age cut-offs between 40 and 55 years,(3, 7) we categorized our cohort as 18 – 44 years, 45 – 64 years, and ≥ 65 years old. We also included details on sex, race/ethnicity (White, Hispanic, Black, Others), and insurance type (public, private, self-pay, other). “Others” insurance types included Worker’s Compensation, County Indigent Programs, Other Government aids and Other Indigent funds.(10) We calculated the Charlson Co-morbidity Index (CCI) using the CHARLSON command in Stata.(17) The CCI is a validated score that uses 19 possible diagnoses to predict mortality and perioperative complications in longitudinal data.(18-20) CCI was classified as < 2 and ≥ 2 (higher being worse) based on previously published classifications.(21, 22)

To account for injuries in other body regions, we calculated Injury Severity Scores (ISS) from ICD-9-CM diagnosis codes using the ICDPIC module in Stata.(12, 23, 24) ISS ranges from 0 – 75 (higher being more severe) and it is generally accepted that scores > 15 indicate more severe injuries.(25, 26) We categorized scores into commonly used categories: 9 – 15, 16 – 24, ≥ 25 .(27, 28) We categorized the hospital length of stay (LOS) as 0 – 3, 4 – 7, and >7 days based on the distribution of the sample (50th percentile corresponds to 3 days, 75th percentile corresponds to 7 days) to ensure a reasonable spread of the patients. We classified patients as having an operation if they had any of the ICD-9-CM procedure codes described by Haut et al. as representing major

surgery.(29) Patients' discharge dispositions were categorized as Home, Home Health Care, Other Hospitals, Skilled Nursing Facility (SNF)/Intermediate Care Facility (ICF)/Other Facilities, and Against Medical Advice (AMA).

We linked patient records in the database to hospital information in the American Hospital Association database. We identified characteristics of the hospitals included in our study and extracted data on the trauma center status, teaching status and bed sizes of the hospitals.

Assessment of Outcomes

The primary outcome was a diagnosis of VTE, which comprises of deep venous thrombosis (DVT) and PE. DVT was defined by ICD-9-CM diagnosis codes corresponding to 451.1x, 451.81, 451.83, 453.2x, 453.4x and PE was defined by ICD-9-CM diagnosis codes corresponding to 415.1x. VTE was assessed at different time points: during the index admission, 30 days, 60 days, 90 days, 180 days, and 1 year following injury. Hospital mortality was also calculated as the proportion of hospital deaths among TBI patients during the index admissions.

Statistical Analyses

The demographic, injury and hospital characteristics of the patients were evaluated using descriptive statistics. We calculated the cumulative incidence of VTE as the number of VTE cases at a certain time point divided by the number of cases of TBI at the beginning of the study. The cumulative incidence of VTE was assessed at the earlier described time points. Estimates were calculated for the overall cohort and for patient groups stratified by Head AIS scores.

Factors associated with VTE during the index admission and at one year following injury were identified using univariate logistic regression models built separately for each variable. Factors that were marginally significantly associated with VTE on the univariate analysis ($P < 0.1$) were included in further multivariate analyses. Multivariate logistic regression models were fitted to identify independent associations with VTE during the index admissions and at one year following injury. To ensure we were assessing post-discharge VTE, analyses of VTE at one year were restricted to patients who were discharged from the index admissions (not including transfers) and did not include VTEs that occurred during the index admission. All models were built with robust standard errors clustered on the individual hospitals to account for the non-independence of patients treated at the same facilities.

To evaluate the impact of other patient factors that may influence long-term VTE risk, we performed sensitivity analyses by imposing stricter restrictions on our cohort. For these analyses, we excluded patients that had any operations, as previously described, at any point after discharge. Patients that had any ICD-9-CM diagnosis codes corresponding to traumatic injuries (800.xx – 904.xx, 910.xx – 929.xx, 950.xx – 959.xx) at least 30 days after the index event were also excluded. We used a cut-off of 30 days to ensure that we were more likely identifying new trauma diagnoses and not previously made diagnoses that had not resolved. We also excluded patients that were diagnosed with primary hypercoagulable states (ICD-9-CM diagnosis code: 289.81). All analyses were done using Stata Statistical Software: Release 13 (College Station, TX: StataCorp LP) and the significance level was set as $P < 0.05$.

RESULTS

There were 38,984 cases of isolated TBI included in our analyses and the incidence of VTE during the index admission was 1.31%. Of these patients, 389 (1.00%) had DVT and 176 (0.45%) had PE. Majority of patients were 65 years and older (55%), male (60%) and White (65%) (**Table 1**). The median hospital length of stay was 3 days. However, 22% of patients were on admission for more than 7 days. Up to 98% of patients had Head AIS scores of 3 or 4. About 30% of the cohort had operations during the index admission. Of these, 66% had neurological operations while majority of the others had cardiovascular procedures and procedures in the digestive system. Only 49% of patients were discharged directly home. A large proportion of our cohort was treated at hospitals with at least 300 beds (65%).

The cumulative incidence of VTE continued to rise after the initial hospitalization. At one month following injury, the cumulative incidence of VTE rose to 1.87% and by one year, it was 2.83% (**Table 2**). Stratification by AIS scores showed that the rise in VTE cumulative incidence was most steep for patients with Head AIS scores of 4. AIS scores of 5 were associated with the least drastic increase in cumulative incidence over time and began to plateau at 60 days. Hospital mortality during the index admission was 8.51% in the overall cohort but was as high as 74.88% when patients with Head AIS scores of 5 were examined in isolation.

The major risk factors associated with VTE during the index admission were having operations [adjusted Odds Ratio: 5.59; 95% Confidence Interval: 4.28 – 7.29] and longer hospital LOS

(**Table 3**). Compared to patients that stayed for ≤ 3 days in the hospital, LOS of 4 – 7 days [1.74; 1.23 – 2.47] and LOS of > 7 days [5.25; 3.84 – 7.19] were associated with higher odds of VTE.

When risk factors for VTE at one year were examined (excluding VTE that occurred during the index admissions), older age was associated with increased risk of long-term VTE. Compared to age less than 45 years, being 45 – 64 years old [1.80; 1.25 – 2.61] and being older than 64 years [2.62; 1.80 – 3.81] were associated with higher VTE risk at one year (**Table 4**). Discharge to extended care facilities vs. discharge home (2.69; 2.14 – 3.37), hospital LOS > 7 days vs. ≤ 3 days (1.64; 1.27 – 2.11) and having operations during the index admissions (1.65; 1.36 – 2.01) were associated with higher one-year VTE. Other factors associated with higher one-year VTE were being Black, Charlson Comorbidity Index ≥ 2 , and discharge to home health care.

Sensitivity analyses excluding patients who had operations ($n = 8,326$) or traumatic injuries ($n = 551$) post-discharge and those with primary hypercoagulable states ($n = 42$) showed a consistent, although slower, rise in VTE over time. Between the index admissions and one year following injury, the cumulative incidence of VTE rose from 1.14% to 1.72%. In the multivariate analyses of one-year post-discharge VTE risk, some of the risk factors earlier identified such as Black race and higher Charlson Comorbidity Index lost statistical significance (**Supplementary Table 1**). However, discharge to extended care facilities, older age, longer hospital LOS and having operations during the index admissions were still associated with VTE at one year.

DISCUSSION

VTE among hospitalized TBI patients has been extensively studied over the past few decades. Reports that TBI independently increases the risk of VTE in patients with TBI have triggered efforts towards preventing this feared complication.(3, 4, 8) Until recently, only non-pharmacologic methods of VTE prophylaxis were recommended for TBI patients owing to the increased risk of intracranial hemorrhage associated with TBI. However, recent studies have provided evidence to support early initiation of chemical VTE prophylaxis in patients that have no radiological signs of intracranial bleeding within 24 hours of injury.(4, 30, 31) While most guidelines recommend initiating VTE prophylaxis during inpatient care,(4) there is little data to show how long the actual risk of VTE persists among TBI patients. Our study showed that a significant proportion of TBI patients are at continued risk for VTE up to one year following their injuries. Although the incidence of VTE in our study sample was 1.26% during the index hospitalization, the cumulative incidence rose to 2.76% by one year following the injury. It is unlikely that these new incidences of VTE were due to secular trends in VTE over time since the annual hospitalization rate for VTE in the U.S. general population is as low as 0.2%.(32) Our findings imply that the changes that may be responsible for the development of VTE in acute TBI may persist longer than previously thought. Identifying the mediators of this prolonged risk for TBI is necessary to formulate guidelines for the appropriate care of TBI patients outside the hospital setting.

In agreement with the findings of previous studies, our study showed that longer hospital stay was a strong risk factor for VTE during the index admissions.(6, 7, 33) This relationship remained significant when we evaluated VTE at one year. Major operations during the index

admissions were also strongly associated with VTE at one year. However, injury severity did not show a linear relationship with the risk of long-term VTE. The higher hospital mortality rates we observed to be associated with more severe injuries likely explain the slower rise in the cumulative incidence of VTE in severely injured patients. Although it seemed that the incidence of VTE was associated with increased injury severity among patients that were discharged from TBI admissions, this relationship did not persist when other associated factors were accounted for. Patients with greater co-morbidity burdens were found to have higher risks for VTE at one year after their injuries. Because several diseases that comprise the CCI including diabetes and congestive heart failure are independently associated with increased long-term risk of VTE,(34, 35) the higher odds of VTE in patients with higher CCI is not surprising. These findings, however, underscore the importance of having a holistic approach to the planning of post-discharge care for TBI patients. Multidisciplinary care and early involvement of rehabilitation professionals in planning long-term care are strategies that have been suggested in order to improve post-discharge outcomes among TBI patients.(36, 37) Previous studies have shown inconsistent associations between VTE and age among TBI patients.(6, 7) Our study showed that older age was an independent risk factor for TBI at one-year. National trends show consistent increases in rates of VTE hospitalizations with 10-year increments in age for individuals above 40 years.(32) This increased risk of VTE with age indicates the need for a higher degree of proactive VTE prevention measures among older TBI patients. This may include closer surveillance for VTE, regular physical therapy and frequent review of medications.

Discharge to extended care facilities such as skilled nursing facilities (SNFs) and intermediate care facilities was one of the strongest risk factors for developing VTE at one year. Patients

discharged to these facilities would more likely be those who had more severe long-term disability following their injuries. They are also more likely to have had risk factors previously associated with VTE such as more severe injury and higher co-morbidity. After accounting for measured patient factors associated with VTE, these patients still had increased risk of VTE. Our findings have been replicated in other studies and may be a reflection of the pattern of care received at such facilities.(38) We could not tease out the effect of the different types of extended care facilities on VTE rates. However, compared to discharge to rehabilitation facilities, discharge to skilled nursing facilities has been associated with higher mortality rates among trauma patients after adjusting for patient case mix.(39) Due to the perceived benefits of rehabilitation facilities on functional outcomes of patients with neurological diseases, there have been increased efforts in the United States to ensure these patients have access to rehabilitation facilities post-discharge.(40) Between 2004 and 2012, the percentage of brain injury patients in rehabilitation facilities increased from 3.9% to 7.9%.(40) Expanding the eligibility criteria for discharge to rehabilitation facilities and promoting preferential discharge to rehabilitation facilities among patients that may require long-term specialized care may help to reduce the long-term risk of VTE among TBI patients.

Despite the fact that our study shows that the risk of VTE doubles by one year following injury, the initial incidence of VTE we found during admission was lower than what was reported in prior studies. This may be due to the fact that most studies involved active screening for VTE with duplex ultrasound or other screening methods.(5-7) Median hospital duplex ultrasound rates are known to be less than 2 per 100 trauma admissions (41) and it is less likely that the VTE diagnoses we recorded were based solely on radiological findings. In addition, because most

prior studies examined VTE rates in patients that had other injuries known to be associated with VTE risk, the rates reported were likely due to contributions from various injuries. By excluding patients with major injuries in other body regions, we were able to identify VTE risks attributable to TBI. Although the risk of VTE in patients with isolated TBI may not be as high as previously thought, a significant proportion of patients still stand at risk of VTE. Therefore, early identification of those patients coupled with interventions to prevent VTE both in-hospital and post-discharge will be important steps to reducing VTE among TBI patients.

This study is not without limitations. We were not able to ascertain the practices of the hospitals regarding screening for VTE in TBI patients. With the large variations that exist between individual hospitals' approaches to screening for VTE, we cannot clearly distinguish clinically significant VTE from VTE diagnoses that were made solely based on radiological findings. Also, because our diagnosis of VTE was based on ICD-9-CM codes recorded by registrars with potential coding limitations, we may not be accurately capturing the risk of VTE in this population. However, previous research assessing the predictive value of VTE diagnoses extracted from discharge records show values ranging from 75% to 95%.(42) In addition, we were not able to determine deaths or VTE events that occurred outside the hospital and could not accurately estimate the population at risk at every time point. Lastly, we were not able to assess if patients were on VTE prophylaxis prior to or after their injuries and if inferior vena cava filters were placed prior to or after the development of VTE. VTE prophylaxis will likely modify the incidence of VTE in this population.(43) However, our goal was to evaluate the long-term incidence of VTE in the general TBI population regardless of treatment status and this study

serves as a reference for future assessments of the success of VTE prevention among patients with TBI.

In conclusion, patients with isolated moderate to severe head injuries have a sustained risk of VTE beyond the period of hospitalization. Older patients with high co-morbidity burdens who have major operations and are discharged to extended care facilities are more likely to develop VTE post-discharge. Better understanding of the factors associated with long-term VTE risk among TBI patients would be necessary to formulate strategies directed towards ensuring TBI patients are discharged with minimal risk of VTE.

Conflicts of Interest and Source of Funding

None of the authors declare any conflicts of interest. There was no funding for this study.

Authors' Contributions

OAo, BKY, ZRC, AR, DM, JMH, EK, AHH, JDG, AS participated in developing the study concept, hypothesis and design. OAo, AR participated in literature review. OAo, ZRC, AS performed data analysis. OAo, BKY, ZRC, AR, DM, JMH, EK, AHH, JDG, AS participated in the interpretation of the results of data analysis. OAo, AR, ZRC, JMH, AS participated in manuscript writing. OAo, BKY, ZRC, AR, DM, JMH, EK, AHH, JDG, AS critically reviewed the manuscript for content. All authors reviewed and approved the final version of the manuscript.

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