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Risk Factors for Venous Thromboembolism after Acute Trauma: A Population-Based Case-Cohort Study

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Abstract

Background—Predictors of venous thromboembolism (**VTE**) after trauma are uncertain.

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Conflicts of Interest
All authors report no conflict of interest.

Objective—To identify independent predictors of VTE after acute trauma.

Methods—Using Rochester Epidemiology Project (**REP**) resources, we identified all Olmsted County, MN residents with objectively-diagnosed incident VTE within 92 days after hospitalization for acute trauma over the 18-year period, 1988–2005. We also identified all Olmsted County residents hospitalized for acute trauma over this time period and chose one to two residents frequency-matched to VTE cases on sex, event year group and ICD-9-CM trauma code predictive of surgery. In a case-cohort study, demographic, baseline and time-dependent characteristics were tested as predictors of VTE after trauma using Cox proportional hazards modeling.

Results—Among 200 incident VTE cases, the median (interquartile range) time from trauma to VTE was 18 (6, 41) days. Of these, 62% cases developed VTE after hospital discharge. In a multiple variable model including 370 cohort members, patient age at injury, male sex, increasing injury severity as reflected by the Trauma Mortality Prediction Model (TMPM) Mortality Score, immobility prior to trauma, soft tissue leg injury, and prior superficial vein thrombosis were independent predictors of VTE (C-statistic=0.78).

Conclusions—We have identified clinical characteristics which can identify patients at increased risk for VTE after acute trauma, independent of surgery. Almost two thirds of all incident VTE events occurred after initial hospital discharge (18 day median time from trauma to VTE) which questions current practice of not extending VTE prophylaxis beyond hospital discharge.

Keywords

venous thromboembolism; deep vein thrombosis; pulmonary embolism; trauma; fracture; epidemiology

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Introduction

Hospitalization for acute trauma is an independent risk factor for incident VTE (hazard ratio [HR] =4.6)[1] and accounts for about 12% of all incident VTE occurring in the community.[2] Failure to provide appropriate VTE prophylaxis to hospitalized, at-risk patients is considered a medical error by the Institute of Medicine.[3] However, acute trauma patients also are at increased risk for a bleeding complication related to VTE chemoprophylaxis such that one would prefer to target such prophylaxis to those high VTE-risk trauma patients who would benefit most. Several studies have identified risk factors for VTE during hospitalization for trauma.[4–7] However, the duration of hospitalization after trauma has decreased such that many trauma-related VTE events now occur after hospital discharge. Independent predictors of VTE, both during and after hospitalization for acute trauma, are uncertain.[8] To address this important gap in knowledge, we performed a population-based case-cohort study and tested demographic, pre-injury and in-hospital characteristics as potential predictors of incident symptomatic VTE among patients with hospitalization for acute trauma.

Methods

Study Design and Setting

This population-based case-cohort study was conducted in Olmsted County, Minnesota (2010 census population = 144,248). Olmsted County provides a unique opportunity for investigating risk factors for VTE after hospitalization for trauma. Mayo Clinic, together with Olmsted Medical Center (**OMC**) provide essentially all of the trauma medical care delivered to County residents.[9–11] The Rochester Epidemiology Project (**REP**) medical records-linkage system affords access to comprehensive details regarding all medical care provided to all residents for their entire period of residence in the County. In a comparison to the U.S. Census enumeration for Olmsted County, the REP Census enumeration had excellent validity for every Census year since 1930.[9] Trauma was defined as major fracture or severe soft tissue injury requiring hospitalization that occurred ≤ 92 days prior to the incident VTE event as previously reported.[1] The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Study Population

Using REP resources, we identified all Olmsted County, MN residents with incident deep vein thrombosis (**DVT**) and/or pulmonary embolism (**PE**) as previously described.[12,13] Determination of VTE was based on explicit criteria after review of complete provider-linked medical records by trained experienced nurse abstractors under the direction of a board-certified vascular medicine specialist (JAH). Records were reviewed from date first seen by a REP provider until the either death or last REP encounter. For the purposes of this study, VTE cases were limited to residents with objectively-diagnosed incident DVT and/or PE over the 18-year period, 1988–2005, that occurred within 92 days (365 days divided by 4, or ~ 3 months) after hospitalization for acute trauma. A deep vein thrombosis (**DVT**; leg, inferior vena cava, hepatic, portal, splenic, mesenteric or renal vein thrombosis) was considered objectively-diagnosed when acute symptoms and signs were present and confirmed by venography, compression venous duplex ultrasonography, impedance plethysmography, computed tomography, magnetic resonance imaging (MRI), pathology examination of thrombus removed at surgery, or autopsy. A pulmonary embolism (**PE**) was considered objectively-diagnosed when acute symptoms and signs were present and confirmed by pulmonary angiography, ventilation and perfusion lung scan interpreted as high probability for PE, computed tomographic pulmonary angiography, MRI, pathology examination of thrombus removed at surgery, or autopsy. Routine screening for asymptomatic DVT or PE was not performed. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates. REP resources also were used to identify all Olmsted County residents with hospitalization for acute trauma over the study period, 1988–2005, using an ICD-9-CM trauma code algorithm that was derived and validated using previously-identified Olmsted County residents with incident DVT and/or PE within 92 days after hospitalization for acute trauma.[1] Since we previously identified surgery as an independent VTE risk factor[1], we wished to identify VTE risk factors among acute trauma patients who had surgery. Therefore, we further refined our ICD-9-CM trauma code algorithm in order to stratify residents with trauma into those likely to and those unlikely to require surgery. Each of the injury codes was reviewed by a board-certified trauma surgeon (MSP) and if an ICD-9-CM injury code was associated with an operative intervention at least 20% of the time, the trauma code was considered likely to require surgery. Using this refined algorithm, the list of Olmsted County residents with trauma from 1988–2005 was stratified by likelihood of having surgery. These lists were further stratified by sex and three time periods (i.e., 1988–1993, 1994–1999, 2000–2005), and then residents within each of the 12 lists were randomized. Using these 12 randomized lists, the cohort was selected such that the number of cohort members in each of the 12 strata was at least equal to the number of VTE cases in that stratum. Potential cohort members with a VTE event at any time prior to the trauma event date were excluded. Residents with an ICD-9-CM trauma code that predicted an increased likelihood of requiring surgery and selected to be in the cohort were included regardless of whether they actually underwent surgery.

Measurements

Using explicit criteria, trained and experienced nurse abstractors reviewed all medical records (inpatient, outpatient, emergency department, nursing home, autopsy, death certificate, etc.) in the community for all cases and cohort members who provided consent to review of their medical records for research purposes; over 95% of residents consented.[10,14] All records were reviewed from date first seen by a REP healthcare provider until the earliest of death or other loss to follow-up, or 92 days after the trauma event date, as previously performed.[15] Data related to surgery were also collected, including number of operations prior to or after admission for trauma, type of operations (general, gynecological, neurologic, orthopedic, cardiac), intraoperative transfusions (type and number of units), and duration and type of anesthesia (**Appendix**). Because injury severity scores (ISS) were not uniformly available, we used a validated trauma mortality prediction model based on anatomic injury scale provided by Dr. Turner Osler.[16] The model weighs each injury code to provide the probability of hospital mortality. For trauma patients who had minor injuries with no injury codes, the lowest mortality score (0.06%) from among the remaining patients with a score was imputed. We have termed this variable as the “Trauma Mortality Prediction Model (**TMPM**).”

Statistical Analyses

For cases and cohort members, data collection of variables was categorized into the following groups: 1) baseline characteristics present at the trauma event date; 2) baseline characteristics present within 92 days prior to trauma event date; 3) baseline characteristics present at any time prior to the trauma event date; and 4) time-dependent characteristics after the trauma date, censored at VTE event date for cases, and at last follow-up for 92 days after the trauma event date for cohort members. We performed a case-cohort study with weighted cohort sampling by incorporating inverse sampling probability weights in the analysis. Patient demographic and baseline characteristics were assessed as potential predictors of VTE using Cox proportional hazards modeling. Characteristics with a prevalence of less than 5% were excluded from consideration in the multiple variable analyses. Subsequently, backwards selection was performed to identify a final model, using an alpha-level of 0.10 for remaining in the model. Mechanical and chemoprophylaxis were included as time-dependent variables regardless of statistical significance due to their clinical relevance. The concordance (**C**-) statistic was calculated to estimate how well our multiple variable Cox proportional hazard model correctly predicts symptomatic VTE related to recent hospitalization for acute trauma. Data are presented as median and interquartile range (**IQR**) and hazard ratio (**HR**) with 95% confidence intervals (95% CI).

Results

Over the 18-year period, 1988–2005, we identified 200 Olmsted County residents with incident VTE within 92 days after hospitalization for acute trauma (cases), and 370 residents with hospitalization for acute trauma who did not develop VTE (cohort). Compared to cohort members, VTE cases were significantly older and heavier (as reflected by the BMI), and had a significantly greater use of VTE mechanical or chemoprophylaxis and IVC filter placement after trauma (Table 1). No patients received an IVC filter prior to trauma admission. Most cases (73%) and 58% of the cohort were admitted on the day of trauma event; 13% of cases and 16% of cohort members were admitted the day after the trauma event date. In addition to the initial hospitalization for trauma, 29% of cases and 17% of cohort members had multiple hospitalizations within 92 days after the trauma event date.

The distribution of VTE event types were DVT alone (n=93), PE alone (n=80) and PE with DVT (n=27). The DVT occurred in a variety of anatomical sites but most commonly in the leg (Table 2); some patients had DVT at multiple locations. The median time from trauma to onset of symptoms/signs of VTE was 18 (IQR 6, 41) days; 124 (62%) cases developed VTE after hospital discharge. Forty-three (21.5%) cases and 18 (4.9%) cohort members died within 92 days of their trauma ($p < 0.0001$).

VTE prophylaxis regimen characteristics for cases and cohort members

The VTE prophylaxis regimen characteristics for VTE cases and cohort members are shown in Table 3. For chemoprophylaxis, subcutaneous heparin was given to 130 patients, IV heparin to 27 patients, low molecular weight heparin to 95 patients and warfarin to 64 patients; 59% of these patients received more than one type of chemoprophylaxis. For mechanical prophylaxis, external pneumatic compression was used in 192 patients and foot pumps were used in 9 patients. The percentages of patients receiving solely mechanical prophylaxis and solely chemoprophylaxis were significantly and marginally higher, respectively, in cases compared to cohort members, while the percentages receiving both mechanical and chemoprophylaxis did not differ significantly between cases and cohort members. The median duration of mechanical prophylaxis was significantly higher in cases compared to cohort members but not for chemoprophylaxis. However, the median percentage of time at risk spent on prophylaxis was significantly higher in cases compared to cohort members (Table 3). Cases and cohort members were equally likely to experience delay (more than two days after admission) in receiving chemoprophylaxis regardless of the VTE prophylaxis regimen. Overall, the median durations of hospitalization and of prophylaxis did not change significantly over the study period, 1988–2005 (Table 4).

For the 128 cases who received VTE prophylaxis, the median time between cessation of prophylaxis and development of VTE was 1 (IQR 0, 16) day. Of these, 23 cases simultaneously discontinued both types of prophylaxis, 55 cases received only mechanical prophylaxis last, and the last regimen for the remaining 50 cases was chemoprophylaxis only.

Thirty-one percent of cases and 34% of cohort members continued to receive some form of prophylaxis for at least one day after discharge from the index hospitalization; 19% of cases and 35% of cohort members who received only chemoprophylaxis continued chemoprophylaxis post-discharge ($p < 0.0001$). The additional prophylaxis use post-discharge could have been during subsequent hospitalization(s); 60% of cases and 52% of cohort members who continued chemoprophylaxis had at least one additional hospitalization. Twenty six percent of cases and 15% of cohort members who received solely mechanical prophylaxis continued post- dismissal ($p < 0.0001$); all had at least one additional hospitalization. Forty seven percent of cases who received both chemo- and mechanical prophylaxis continued receiving prophylaxis post-dismissal; 71% of these patients had at least one additional hospitalization. Similarly, 43% of cohort members who received both chemo and mechanical prophylaxis continued prophylaxis post- dismissal, and 66% had at least one additional hospitalization.

Univariable and Multivariable Analyses

The results of univariate tests of demographic, baseline and time-dependent characteristics as potential predictors of VTE related to hospitalization for acute trauma are shown in Table 5. Increasing patient age and BMI at injury, current or prior tobacco smoking, any documented non-hospital related immobility prior to trauma, superficial vein thrombosis, soft tissue injury to the leg and number of surgeries were associated with an increased hazard of symptomatic VTE. In the multivariable model, patient age at injury, male sex, current or prior tobacco smoking, increasing injury severity as reflected by the Trauma Mortality Prediction Model (**TMPM**), immobility prior to trauma, soft tissue injury to leg and prior superficial vein thrombosis were associated with a significantly increased hazard of VTE (Table 6; model C-statistic = 0.78); mechanical prophylaxis and chemoprophylaxis after trauma were not predictors of (reduced risk of) VTE.

Including cases and cohort members, a total of 217 men and 353 women were included in this study. Men were significantly younger than women (median [IQR] age: 47 [30, 72] vs. 76 [53, 85] years, respectively), had a significantly higher prevalence of current or past tobacco smoking (53% vs. 43%, respectively; p=0.013), and were significantly less likely to receive chemoprophylaxis (36% v. 48%, respectively; p=004). The median TMPM scores were similar in both sexes but men had a significantly higher maximum score (86% vs. 42%, respectively; $p < 0.001$) as compared to women. We investigated a possible interaction between sex and TMPM; in the multivariate model, the interaction term was not statistically significant (p=0.23). Additionally, there was no interaction between age and TMPM (p=0.85).

Of the 14 men (12 cases, 2 cohort) who had TMPM > 15%, the following primary injury patterns were noted: 8/14 intracranial injuries, 1/14 cervical spine injury, 2/14 pelvic fractures, 2/14 thoracic injuries and 1 with femur fracture. The median duration (days) of mechanical prophylaxis and chemoprophylaxis for these men were 1 (0, 15) and 1 (0, 12), respectively; the median duration of days on any prophylaxis was 9 (0, 24). For women, there were only 5 patients (4 cohort, 1 case) who had TMPM > 15%; all had intracranial injuries. For these women, the median duration of mechanical prophylaxis and chemoprophylaxis were 9 (0, 34) and 1 (0, 14), respectively. The median duration of days on any prophylaxis was 9 (0, 39).

Discussion

This is the first population-based, case–cohort study to test important demographic, baseline and time-dependent characteristics as potential independent predictors of symptomatic VTE related to hospitalization for acute trauma. Our study is the first to identify pre-injury and in-hospital risk factors as predictors of VTE for up to 92 days after trauma admission. Most risk factors identified in our multivariable model can be obtained during the first 24 hours of admission. In particular, prior history of superficial vein thrombosis, non-hospital related immobility and male sex were important risk factors for symptomatic VTE after traumatic injury with the greatest HRs of 2.7, 2.4, and 2.1 respectively. The literature is replete with well-designed work elucidating risk factors for VTE in trauma patients.[4–7] However, there is no population-based study evaluating the risk factors of VTE in trauma patients both during and hospital discharge. Often the follow-up is limited and evaluation of VTE does not extend past hospital discharge. Additionally, we focused our study on the symptomatic and objectively-diagnosed incident DVT and/or PE cases only. [12, 13]

Recently, Godat et al., showed that the period of VTE risk after acute injury is highest during first 3 months after injury.[17] They utilized the California Office of Statewide Health Planning and Development Discharge (OSHPD) database, which is an administrative database. Even though it lacks the extensive chart review as was done in our study, their findings are consistent with our study in regards to patients being at the highest risk of developing VTE during first 3 months after injury. Surprisingly, we found that VTE prophylaxis (treated as a time-dependent variable) was not an independent (protective) risk factor among acute trauma patients in univariable and multiple variable analyses. This may have been due to the low percentage of time patients who received prophylaxis during the at-risk period (first 92 days from the day of hospitalization for trauma). It is noteworthy that 62% of cases developed VTE after hospital dismissal, which is similar to 56% of VTE events diagnosed after discharge in patients who have undergone elective and urgent surgical procedures.[18] In our study, only 31% of cases received some form of prophylaxis for at least one day after discharge. Given these findings, future studies are needed to test the efficacy and safety of prolonged, out-of-hospital VTE prophylaxis among patients hospitalized for acute trauma. While the most appropriate duration of post discharge prophylaxis remains unclear, the median time (IQR) from trauma to diagnosis of VTE was 18 (6, 41) days in our study. For patients undergoing elective total hip or knee replacement, extended-duration chemoprophylaxis varying from 28 to 42 days reduced the risk of VTE.[19, 20] Currently, we are not aware of any studies showing that chemoprophylaxis (or any other prophylaxis) reduces the rate of symptomatic VTE in acute trauma patients. The 9th ACCP guidelines only suggest "use of low dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), or mechanical prophylaxis over no prophylaxis" in major trauma patients, and give this recommendation the lowest grade of evidence.[21]

Most cases (73%) and 58% of the cohort were admitted on the day of trauma event; 13% of cases and 16% of cohort members were admitted the day after the trauma event date. Our definition of acute trauma did not require that the trauma be life-threatening as we wished to test trauma severity, as reflected by the TMPM score, as a potential predictor of VTE among trauma patients. While minor trauma is a VTE risk factor compared to no trauma[22], we found that increasing trauma severity was an independent predictor of VTE among patients with acute trauma.

While surgery within 92 days after hospitalization for acute trauma was not a predictor of VTE, we emphasize that this result likely reflects our process for selecting the cohort. We have previously shown that surgery is a major risk factor for VTE after adjusting for acute trauma.[1] Thus, our aim was to identify risk factors for VTE after trauma that are independent of surgery.

In the process of choosing our random cohort, we refined our ICD-9 trauma code algorithm in order to stratify Olmsted County residents with trauma into those likely and those unlikely to require surgery. Hence, selection of cohort patients with trauma were stratified by likelihood of having surgery based on their injury codes. Consequently, 59.5% of cases and 60.8% of cohort had 1 or more surgical procedures after trauma ($p = 0.76$).

Regarding other potential risk factors of VTE, there were very few patients who were pregnant (0.7%), had liver disease (1.6%) or pre-existing neurologic disease (3.9%) such that these variables were not retained in the final multiple variable model. Women often have additional risk factors for VTE such as oral contraceptive use, hormone therapy, pregnancy or the postpartum period.[1] However, we found that men, relative to women, were at higher risk of developing symptomatic VTE after trauma admission (HR 2.1, 95% CI: 1.4 −3.1) despite a similar median TMPM. Additionally, while fracture is a known VTE risk factor compared to individuals with no trauma, among patients with acute trauma, fracture was not an independent risk factor for VTE.

There are several limitations in this study. Injury severity scores were not consistently available. Hence, the TMPM score was used, which is calculated from ICD-9 injury codes. However, 96 patients had no injury codes. These 96 patients had minor injuries, compression fractures or burns and were assigned the lowest TMPM score from among the remaining patients with a score available.[11] Finally, laboratory test results were not electronically available for the entire cohort and could not be included in the analyses.

Conclusions

Increasing patient age, male sex, increasing injury severity, immobility prior to trauma, soft tissue injury to the leg and prior superficial vein thrombosis can identify patients at increased risk for VTE within 92 days after hospitalization for acute trauma, independent of surgery. These characteristics may be useful for stratifying trauma patients into high- and low-VTE risk, and targeting VTE prophylaxis to those patients who would benefit most. VTE prophylaxis rates were higher in VTE cases than cohort members, suggesting that prophylaxis was either inadequate or failed. Of particular note, 62% of cases developed VTE after hospital discharge, suggesting a potential role for extended out-of-hospital prophylaxis. Confirmation of these hypotheses will require additional studies.

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Appendix

1. Characteristics noted at time of admission:

- **i.** Age/ Gender/ mechanism of injury/ weight/ height
- **ii.** Systolic blood pressure
- **iii.** Diastolic blood pressure
- **iv.** Hospitalization for trauma
- **v.** Fracture (location) – arm/leg/pelvis/ spine
- **vi.** Soft tissue injury location (arm/leg)
- **vii.** Leg paresis or paralysis
- **viii.** Head Injury/ spinal cord injury/large vein injury
- **ix.** Post-partum (delivered on trauma date)
- **x.** Admission labs
- **xi.** Any infection (arrives with a history of infection)

2. Baseline Characteristics present within 92 days prior to trauma date:

- **xii.** Hormonal contraception or therapy
- **xiii.** Active cancer
- **xiv.** Chemotherapy
- **xv.** Lipid lowering therapy
- **xvi.** Pregnant and/or postpartum

- **xvii.** Immobilization (not hospital related)
- **xviii.** Hospitalization prior to trauma
  1. Days of hospitalization
  2. Admit to intensive care unit
  3. Ventilator therapy
- **xix.** Nursing home/chronic care facility confinement prior to trauma
- **xx.** Transfemoral venous catheter/ arterial catheter/ central venous catheter
- **xxi.** Tobacco history
- **xxii.** IVC filter (insertion and removal dates)
- **xxiii.** Anticoagulation therapy (IV heparin within 72 hrs; warfarin or LMWH within 3 days or unknown)
- **xxiv.** Non-surgical procedures i.e. PTCA, Bronchoscopy
- **xxv.** Technical surgery information (90 days prior to trauma):
  1. Type of Surgery (cardiac surg, Gen Surg, Gyn, Neuro or orthopedic or any combination)
  2. Operative blood loss
  3. Specify procedure
  4. Duration of Surgery
  5. Duration and Type of anesthesia
  6. Venous injury
  7. Intra-operative transfused blood products (date/ time/number of units/type) including auto-donate

3. Baseline Characteristics present at any time prior to trauma date:

- **xxvi.** Superficial vein thrombosis
- **xxvii.** Chronic lung disease
- **xxviii.** Chronic liver disease
- **xxix.** Chronic renal disease
- **xxx.** Neurologic disease with leg paresis
- **xxxi.** Hyperlipidemia
- **xxxii.** Congestive heart failure
- **xxxiii.** Systemic lupus erythematosus

- **xxxiv.** Mixed connective tissue disease
- **xxxv.** Scleroderma
- **xxxvi.** Dermatomyositis
- **xxxvii.** Rheumatoid arthritis

4. Time Dependent characteristics present at any time after trauma event date, censored at VTE event date for cases, and at 92 days after the trauma event date for the cohort members.

- **i.** Active cancer
- **ii.** Hospitalization (admission and discharge dates)
- **iii.** Nursing home confinement (admission and discharge dates)
- **iv.** Transfemoral venous catheter/ arterial catheter/ central venous catheter (dates of placement and removal)
- **v.** Ventilator therapy (dates of start and stop)
- **vi.** ICU admission (dates of duration)
- **vii.** Lipid lowering therapy
- **viii.** Chemotherapy
- **ix.** Statin use
- **x.** Any infections
- **xi.** Immobility (hospital) dates
- **xii.** Immobility – hospital comments:
- **xiii.** complete bedrest/ out of bed with assist/ bathroom privileges/ up ad lib
- **xiv.** IVC filter dates of placement and removal
- **xv.** Seen by physical therapy for immobility
- **xvi.** Extremity pneumatic compression use
- **xvii.** Foot pump use
- **xviii.** Subcutaneous unfractionated heparin (start and stop dates)
- **xix.** IV unfractionated heparin (start and stop dates)
- **xx.** Low molecular weight heparin (start and stop dates)
- **xxi.** Warfarin as prophylaxis (start and stop dates)
- **xxii.** Non-surgical procedures i.e. PTCA, Bronchoscopy

xxiii. Type of Surgery (cardiac surg, Gen Surg, Gyn, Neuro or orthopedic or any combination)

xxiv. Operative blood loss

xxv. Specify procedure

xxvi. Duration of Surgery

xxvii. Duration and Type of anesthesia

xxviii. Venous injury

xxix. Intra-operative transfused blood products (date/time/number of units/type) including auto-donate

xxx. Transfused blood products given during times other than in the operating room (date/time/number of units/type)

xxxi. Autotransfusion (in the operating room)

xxxii. Transfused blood products given during times other than in the operating room (date/time/number of units/type)

xxxiii. Disposition

xxxiv. Immobility (nonhospital)

xxxv. Leg cast or immobilizer

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Highlights

- To identify predictors of VTE in trauma patients during and after their initial hospital discharge
- Two thirds of patients who developed VTE did so after initial hospital discharge
- Median time from trauma to acute VTE was 18 days
- Prophylaxis beyond initial hospitalization needs to be evaluated

Table 1

Demographic and Baseline Characteristics of Venous Thromboembolism (VTE) Cases and Cohort Members

Characteristic	VTE Cases (N=200)	Cohort Members (N=370)	P-value
Age at Trauma, median (IQR); *years*	74 (54, 85)	58 (33, 81)	<0.001[1]
Male sex; *n (%)*	79 (40)	138 (37)	0.605[2]
BMI, median (IQR); *kg/m²*	26 (23, 30)	25 (22, 29)	0.004[1]
Trauma Mortality Prediction Model (TMPM), median (IQR); %	1.2 (0.06, 2.0)	0.8 (0.3, 1.7)	0.188[1]
Mechanical prophylaxis; *n (%)*	86 (43)	113 (31)	0.003[2]
Arm Fracture	24 (13%)	76 (20.5%)	0.010[2]
Leg Fracture	96 (48%)	165 (45%)	0.436[2]
Chemoprophylaxis; *n (%)*	103 (52)	145 (39)	0.005[2]
IVC filter after trauma; *n (%)*	9 (4.5)	2 (0.5)	0.002[3]

[1] Wilcoxon rank sum test

[2] Chi-square test

[3] Fisher's exact test

Table 2

Locations of DVTs of Cases (53 patients had DVT in Multiple Locations)

Thrombosis Location	**Number**	**Percent**
Lower extremity, distal	34	19.7
Lower extremity, proximal	124	71.7
Upper extremity	3	1.7
Jugular/subclavian vein	5	2.9
Inferior vena cava	3	1.7
Portal vein	2	1.2
Renal vein	1	0.6
Other	1	0.6

Missing Information = 7 locations

Table 3

Venous Thromboembolism (VTE) Prophylaxis Regimen Characteristics for Cases and Cohort Members

VTE Prophylaxis Regimen Characteristic	VTE Cases (total n=200)	Cohort Members (total n=370)	P-value
Chemoprophylaxis only, *n (%)*	52 (26)	71 (19)	0.059†
Median (IQR) duration, *days*	7(3, 17)	8(3, 14)	0.59‡
Median (IQR) percentage of time at risk, %	49 (19, 86)	10 (4, 23)	0.0001‡
Start of prophylaxis, *n (%)*			0.72†
On day of admission	18(35)	28 (39)	
1–2 days after admission	28 (54)	33 (46)	
≥3 days after admission	6(12)	10(14)	
Mechanical prophylaxis only, *n (%)*	35(18)	39(11)	0.018†
Median (IQR) duration, *days*	8(4, 15)	5 (3, 9)	0.042‡
Median (IQR) percentage of time at risk, %	94(50, 100)	7(3, 10)	<0.0001‡
Start of prophylaxis, *n (%)*			0.93†
On day of admission	28 (80)	31 (79)	
1–2 days after admission	5(14)	5(13)	
≥3 days after admission	2(6)	3(8)	
Chemoprophylaxis and mechanical prophylaxis, *n (%)*	51 (26)	74 (20)	0.130†
Median (IQR) duration, *days*	11 (8, 19)	12 (8, 24)	0.61‡
Median (IQR) percentage of time at risk, %	65(27, 100)	14 (9, 30)	<0.0001‡
start of prophylaxis, *n (%)*			0.58†
On day of admission	41 (80)	55 (74)	
1–2 days after admission	8(16)	17(23)	
≥3 days after admission	2 94)	2(3)	

†Chi-square test

‡Wilcoxon rank sum test

Table 4

Duration of Hospitalization and Prophylaxis in Days of Those Patients who Received Prophylaxis (Cases and Cohort Patients)*

Time Period#	Duration of Hospitalization	Duration of Any Prophylaxis	Duration of Chemoprophylaxis
1988 – 1993	7 (2, 14)	8.5 (4, 15)	7 (3, 14)
1994 – 1999	6 (3, 12)	9 (5, 16)	7.5 (2.5, 13.5)
2000 – 2005	6 (3, 12)	9 (5, 16)	7 (4, 13)

*Median (IQR)

#These are the same time periods used to pick random cohort patients

Table 5

Variables Considered as Candidates in Multiple Variable Modeling

Variable	**HR (95% CI)**	**P-value**	**Global P-value**
Age at trauma, per 10 years	1.2 (1.1, 1.3)	<0.001	
Male sex	1.4 (0.99, 1.9)	0.057	
Body mass index			0.006
Normal	1.0 (ref)		
Overweight	1.7 (1.2, 2.5)	0.003	
Obese	1.7 (1.1, 2.6)	0.025	
Current or past tobacco smoker	1.6 (1.1, 2.2)	0.006	
Trauma Mortality Prediction Model (TMPM), per 10 % increase	1.6 (1.4, 1.8)	<0.001	
Any blood product transfusion	0.9 (0.6, 1.3)	0.509	
Any non-hospital related immobility prior to trauma	1.7 (1.2, 2.6)	0.005	
Days from trauma to hospital admission			0.055
0 (day of admission)	1.0 (ref)		
1–2	0.6 (0.4, 0.98)	0.043	
>2	1.2 (0.7, 1.8)	0.486	
Hospitalized within 3 months prior to trauma	1.1 (0.7, 1.7)	0.682	
Additional hospitalization after trauma admission	1.5 (1.0, 2.1)	0.035	
Congestive heart failure	1.7 (1.1, 2.5)	0.013	
Hyperlipidemia	1.4 (0.98, 2.0)	0.067	
Chronic lung disease	1.3 (0.8, 1.9)	0.279	
Hormone therapy	1.3 (0.6, 2.7)	0.555	
Prior superficial vein thrombosis	3.1 (1.8, 5.2)	<0.001	
Blunt Injury	0.6 (0.4, 1.00)	0.05	
Pelvic fracture	1.6 (0.9, 3.0)	0.116	
Spinal fracture	1.5 (0.9,2.5)	0.134	
Leg fracture	0.7 (0.5, 0.97)	0.032	
Arm fracture	0.6 (0.4, 1.1)	0.129	
Soft tissue injury, leg	1.9 (1.2, 2.9)	0.003	

Variable	HR (95% CI)	P-value	Global P-value
Soft tissue injury, arm	1.2 (0.7, 2.0)	0.458	
Active cancer	2.5 (1.4, 4.3)	0.002	
Number of surgeries after trauma			0.002
0	1.0 (ref)		
1	0.7 (0.5, 1.1)	0.114	
>1	2.3 (1.3, 4.2)	0.006	
Mechanical prophylaxis	1.6 (0.9, 2.8)	0.082	
Chemoprophylaxis	0.9 (0.5, 1.5)	0.600	

Table 6

Final Multiple Variable Cox Proportional Hazard Model

Characteristic	HR (95% CI)	P-value
Age at trauma, per 10 years	1.4 (1.3, 1.5)	<0.001
Male sex	2.1 (1.4, 3.1)	<0.001
Current or former tobacco smoker	1.4 (0.99, 2.1)	0.054
Trauma Mortality Prediction Model (TMPM), per 10 % increase	1.9 (1.6, 2.2)	<0.001
Prior superficial vein thrombosis	2.7 (1.5, 4.8)	<0.001
Any non-hospital related immobility prior to trauma	2.4 (1.5, 3.7)	<0.001
Soft tissue injury, leg	1.9 (1.2, 3.1)	0.009
Mechanical prophylaxis	1.4 (0.8, 2.4)	0.270
Chemoprophylaxis	0.8 (0.5, 1.3)	0.333