Venous Thromboembolism in Patients Discharged From the Emergency Department With Ankle Fractures: A Population-Based Cohort Study

Keerat Grewal, MD, MSc*; Clare L. Atzema, MD, MSc; Rinku Sutradhar, PhD; Karl Everett, MSc; Daniel Horner, MBBS, MD; Cameron Thompson, MSc; John Theodoropoulos, MD, MSc; Bjug Borgundvaag, PhD, MD; Shelley L. McLeod, MSc, PhD; Kerstin de Wit, MD, MSc

*Corresponding Author. E-mail: keerat.grewal@sinaihealth.ca.

Study objective: Temporary lower limb immobilization may be a risk for venous thromboembolism. The purpose of this study was to examine the 90-day incidence of venous thromboembolism among patients discharged from an emergency department (ED) with ankle fractures requiring temporary immobilization. Secondary objectives were to examine individual factors associated with venous thromboembolism in this population and to compare the risk of venous thromboembolism in patients with ankle fractures against a priori-selected control groups.

Methods: This was a retrospective cohort study using province-wide health datasets from Ontario, Canada. We included patients aged 16 years and older discharged from an ED between 2013 and 2018 with closed ankle fractures requiring temporary immobilization. We estimated 90-day incidence of venous thromboembolism after ankle fracture. A Cox proportional hazards model was used to evaluate risk factors associated with venous thromboembolism, censoring at 90 days or death. Patients with ankle fractures were then propensity score matched to 2 control groups: patients discharged with injuries not requiring lower limb immobilization (ie, finger wounds and wrist fractures) to compare relative hazard of venous thromboembolism.

Results: There were 86,081 eligible patients with ankle fractures. Incidence of venous thromboembolism within 90 days was 1.3%. Factors associated with venous thromboembolism were older age (hazard ratio [HR]: 1.18; 95% confidence interval [CI]: 1.00 to 1.39), venous thromboembolism or superficial venous thrombosis history (HR: 5.18; 95% CI: 4.33 to 6.20), recent hospital admission (HR: 1.33; 95% CI: 1.05 to 1.68), recent nonankle fracture surgery (HR: 1.58; 95% CI: 1.30 to 1.93), and subsequent surgery for ankle fracture (HR: 1.80; 95% CI: 1.48 to 2.20). In the matched cohort, patients with ankle fractures had an increased hazard of venous thromboembolism compared to matched controls with finger wounds (HR: 6.31; 95% CI: 5.30 to 7.52) and wrist fractures (HR: 5.68; 95% CI: 4.71 to 6.85).

Conclusion: The 90-day incidence of venous thromboembolism among patients discharged from the ED with ankle fractures requiring immobilization was 1.3%. These patients had a 5.7- to 6.3-fold increased hazard compared to matched controls. Certain patients immobilized for ankle fractures are at higher risk of venous thromboembolism, and this should be recognized by emergency physicians. [Ann Emerg Med. 2022;79:35-47.]

Please see page 36 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Venous thromboembolism, which includes deep venous thrombosis and pulmonary embolism, is a common and important source of morbidity and mortality worldwide. The incidence of venous thromboembolism has been reported to be in the range of 1 to 2 per 1,000 person-years.[1-3] Deep venous thrombosis progresses to pulmonary embolism in one third to one half of untreated cases.[4,5] Deep venous thrombosis is also complicated by postthrombotic syndrome, characterized by chronic swelling, pain, and edema in the affected limb, in 20% to 60% of patients.[6] Both deep venous thrombosis and pulmonary embolism reduce patient quality of life.[7] Patients with pulmonary embolism are at risk of developing long-term complications, such as right ventricular dysfunction and chronic pulmonary hypertension, and a pulmonary embolism diagnosis is recognized to cause long-term psychological distress among patients.[8-11]

Editor's Capsule Summary

What is already known on this topic

Temporary lower limb immobilization with a cast or brace for the treatment of orthopedic injuries is associated with venous thromboembolism.

What question this study addressed

What is the incidence of and risk factors for venous thromboembolism in emergency department patients with lower limb immobilization for ankle fracture?

What this study adds to our knowledge

Among 86,081 patients with an ankle fracture, the incidence of venous thromboembolism at 90 days was 1.3%. Older age, history of venous thromboembolism, recent hospitalization or surgery, and surgery for the ankle fracture were associated with venous thromboembolism.

How this is relevant to clinical practice

Thromboprophylaxis should be considered in high-risk patients with temporary lower limb immobilization.

Temporary lower limb immobilization is associated with venous thromboembolism.[12,13] A 2017 Cochrane review on venous thromboembolism in lower limb immobilization reported an incidence of venous thromboembolism ranging from 4% to 40%.[13] However, one study has reported an incidence of venous thromboembolism as low as 0.5% in patients with foot and ankle trauma.[14] Meaningful pooling of data has been hampered by significant heterogeneity between studies, including inclusion of several types of injuries (ie, lower leg, ankle, foot, Achilles tendon); patients who received thromboprophylaxis and those who did not; and varying outcome definitions, including symptomatic and asymptomatic venous thromboembolism.[15,16]

Physicians commonly apply temporary lower limb immobilization (plaster/fiberglass or air casts) when treating patients with ankle fractures. Pharmacological thromboprophylaxis may reduce the risk of subsequent venous thromboembolism in these patients.[16] However, given the lack of consensus on absolute venous thromboembolism risk and the limited high-level evidence on risk stratification, widespread international variation in practice exists. Although several international guidelines on thromboembolism prophylaxis in lower limb immobilization have provided recommendations on the issue, they are inconsistent, often vague, and based on low- to moderate-quality evidence.[17-22]

Goals of This Investigation

The objective of this study was to determine the 90-day incidence of venous thromboembolism (ie, pulmonary embolism or deep venous thrombosis) for patients discharged from the emergency department (ED) with closed ankle fractures who required temporary lower limb immobilization. Secondary objectives were 1) to identify individual risk factors associated with the risk of venous thromboembolism in this population and 2) to compare the hazard of venous thromboembolism in this cohort to those in matched cohorts discharged from the ED with injuries that did not require lower limb immobilization (ie, uncomplicated finger wounds and wrist fractures).

METHODS

Study Design and Setting

We conducted a retrospective cohort study of population-based administrative health data from Ontario, Canada. Patient information was obtained from province-wide databases held at ICES (formerly known as the Institute for Clinical Evaluative Sciences). This study received ethics approval from the Research Ethics Board at Sinai Health. Our study followed the Strengthening of the Reporting of Observational Studies in Epidemiology guidelines.

Data Sources

Data regarding ED visits were obtained from the Canadian Institute of Health Information-National Ambulatory Care Reporting System (CIHI-NACRS). NACRS is an administrative database that contains anonymized, abstracted data on all ED patient visits in Ontario. CIHI's Discharge Abstract Database was used to obtain acute care hospitalizations and inpatient surgical procedures. The Same Day Surgery database was used to capture outpatient surgery. The Ontario Health Insurance Plan (OHIP) database contains all physician billings for medically necessary care. The Registered Persons Database contains mortality information for all Ontario residents, including out-of-hospital deaths. The Ontario Drug Benefit database contains medical prescriptions for patients over the age of 65 or patients with provincial drug coverage. These datasets were linked using unique encoded identifiers and analyzed at ICES. Ontario has universal health care coverage for medically necessary care; therefore, these databases contain the majority of health care utilization in the province. Further description of databases and codes used can be found in Appendix E1 (available at http://www.annemergmed.com).

Study Participants

We identified patients aged 16 years and older with a valid OHIP number who were discharged from the ED between January 2013 and December 2018 with closed ankle fractures requiring temporary lower limb immobilization. Only the first ED visit for an ankle fracture for each patient during the study period was included. The main discharge diagnosis in NACRS, which uses International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes, was used to identify patients with closed ankle fractures that would require lower limb immobilization. Descriptions of these codes can be found in Appendix E1. We validated these ICD-10 codes in NACRS using a chart review at one site to determine the positive predictive value of these codes to identify temporary immobilization in the ED.

We excluded visits where patients left the ED without being seen or against medical advice. We excluded patients who were known to be on anticoagulation with warfarin, a direct oral anticoagulant, or low-molecular-weight heparin (based on Ontario Drug Benefit records at the time of the emergency visit for the ankle fracture) because their risk of developing subsequent venous thromboembolism was presumed to be very low. As a surrogate for anticoagulation in patients for whom we did not have medication information, we also excluded patients with diagnoses of atrial fibrillation in the previous 5 years, as many of these patients would be expected to be on anticoagulation for stroke prophylaxis.

Outcomes

The primary outcome was the 90-day incidence of venous thromboembolism (pulmonary embolism and/or deep venous thrombosis) following discharge from the ED with an ankle fracture requiring immobilization. The index date was the date of discharge from the ED. Patients were then followed for 90 days or until death, whichever occurred first. Deep venous thrombosis sites included upper and lower extremity deep venous thromboses, including the vena cava. We identified venous thromboembolism diagnoses in the inpatient or outpatient settings using the NACRS, Discharge Abstract Database, and OHIP databases. The diagnostic codes used to identify venous thromboembolism in each of the databases can be found in Appendix E1. Secondary outcomes were 1) to examine individual risk factors associated with the hazard of venous thromboembolism over 90 days in this population and 2) to compare the hazard of venous thromboembolism in patients with ankle fracture to those of 2 groups of matched control patients discharged from the ED with uncomplicated finger wounds or closed wrist fractures. These control groups were selected a priori based on the following criteria: commonly seen in the emergency setting, often discharged home from the ED, and having sustained an acute trauma not necessarily associated with venous thromboembolism.

Covariates

Covariates included in the statistical models were chosen a priori based on a review of the literature as potential risk factors or confounders of venous thromboembolism. Covariates were measured near index and included the following: demographic factors (age, sex), comorbidities (cancer diagnosed within the previous 5 years, coronary artery disease, chronic obstructive pulmonary disease, diabetes, hypertension, cerebrovascular disease), history of venous thromboembolism or superficial venous thromboembolism, pregnancy at the time of fracture, previous hospitalization within 90 days, previous nonankle-related surgery within 90 days, and surgery for the fracture. Covariable definitions can be found in Appendix E1.

Statistical Analysis

Baseline patient characteristics were compared between patients with and without venous thromboembolism using frequencies for categorical variables and medians with interquartile ranges for continuous variables.

The cumulative incidence function was used to estimate the 90-day risk of venous thromboembolism, censoring for death. To evaluate the individual risk factors described above and their associations with the hazard of venous thromboembolism, we developed 2 Cox proportional hazards models, censoring at 90 days or death. We used a robust sandwich variance estimation approach to account for clustering of patients by institution. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Model 1 was a baseline model with time-fixed covariates, where only variables available at the time of the ED visit were included, including previous hospitalization or nonankle-related surgery within the 90 days prior to the ED visit. Model 2 included time-varying covariates for capturing hospitalizations and nonankle-related surgery: patients could have been hospitalized or had nonankle-related surgery in the 90 days prior to the index ED visit or between the index emergency visit and the end of follow-up. In the latter model, we also included a variable for surgery for the ankle fracture, which was treated as a time-varying covariate. Several sensitivity analyses were conducted on both models. First, we used a strict definition of venous thromboembolism, where patients must have had a billing code for venous thromboembolism imaging within 3 days of a diagnostic venous thromboembolism code to be considered to have venous thromboembolism. Next, patients with a history of venous thromboembolism were excluded to ensure all venous thromboembolism diagnostic codes were new diagnoses of venous thromboembolism. Finally, patients with surgery for the fractures were excluded to ensure there were no systemic differences, such as receiving thromboprophylaxis, between patients who underwent surgical management for their fractures and those who did not.

Patients with ankle fractures were then propensity score matched to 2 cohorts of control patients discharged from the ED with uncomplicated finger wounds and closed wrist fractures. This allowed us to compare the relative hazard of venous thromboembolism between patients with ankle fractures and patients with other injuries that did not require lower limb immobilization. For each cohort, the propensity score was estimated using logistic regression in which exposure status was regressed on multiple variables. The variables included in the model included demographics, previous hospitalizations or surgeries, hospital characteristics, and ED visit characteristics. Exact variables and definitions can be found in Appendix E1. Patients in each cohort were matched on the logit of the propensity score using a 1:1 without replacement approach and caliper width of 0.2 of the standard deviation of the logit of the propensity score.[23] Balance in baseline covariates for each cohort were evaluated using standardized differences.[23] Standardized differences less than 0.10 were used to determine if the groups were well matched. Cox proportional hazards models were used to determine the hazard of venous thromboembolism in each cohort, where a robust sandwich variance estimation approach was used to account for possible correlation due to the matched design.[24] We conducted post hoc power calculations for each matched cohort to identify venous thromboembolism. We conducted 3 sensitivity analyses for each propensity score matched cohort. First, we compared outcomes using the strict definition of venous thromboembolism. Next, because surgery is thought to be associated with venous thromboembolism, a time-varying covariate for surgery between the index ED visit and the end of follow-up was added to adjust for surgery between the index ED visit and end of follow-up. We then excluded patients with surgery for the fractures and rematched groups. All analyses were conducted using SAS 9.4.

RESULTS

We identified 93,899 ED visits by patients discharged from the ED with closed ankle fractures requiring temporary lower limb immobilization. After applying exclusion criteria, 86,801 patients were included in the study (Figure 1). In our chart review, the positive predictive value of the ICD-10 codes for closed ankle fracture to identify temporary immobilization in the ED was 94.0% (95% CI: 91.9% to 95.7%) (599/637 of patients were immobilized).

Approximately 55% of patients included in the study were female, and 17% were over the age of 65. Other baseline characteristics are described in Table 1. The 90-day incidence of venous thromboembolism after the index ED visit for an ankle fracture was 1.3% (Figure 2). The 90-day incidence of venous thromboembolism was 1.1% (952 patients) when we used a strict definition of venous thromboembolism requiring a billing code for venous

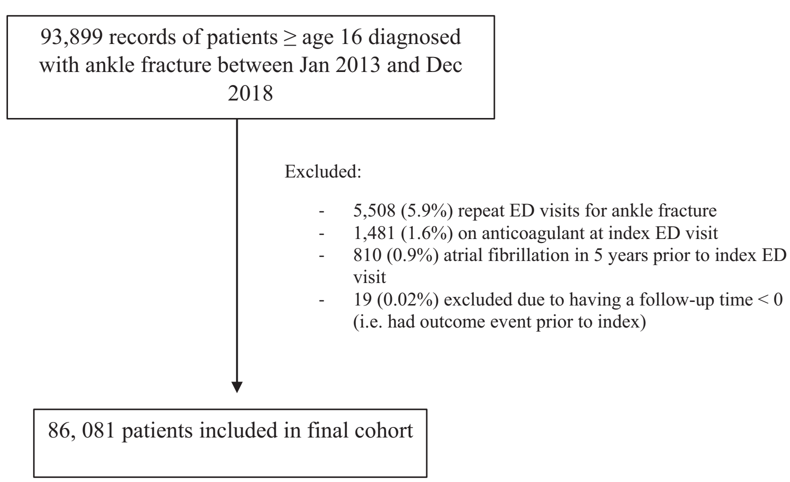

Figure 1. Study flowchart.

Table 1. Baseline characteristics of patients discharged from the ED with ankle fractures requiring immobilization.

Characteristic, n (%)	Total (N=86,081)	VTE (n=1,117)	No VTE (n=84,964)
Demographics			
Age >65 years	14,788 (17.2%)	243 (21.8%)	14,545 (17.1%)
Age, median (IQR)	49 (32–61)	54 (44–64)	49 (32–61)
Sex, female	47,516 (55.2%)	655 (58.6%)	46,861 (55.2%)
Sex, male	38,565 (44.8%)	462 (41.4%)	38,103 (44.8%)
Rural	8,025 (9.3%)	116 (10.4%)	7,909 (9.3%)
Income quintile			
1 (lowest quintile)	17,053 (19.8%)	192 (17.2%)	16,861 (19.8%)
2	16,893 (19.6%)	223 (20.0%)	16,670 (19.6%)
3	17,279 (20.1%)	226 (20.2%)	17,053 (20.1%)
4	16,928 (19.7%)	244 (21.8%)	16,684 (19.6%)
5 (highest quintile)	17,672 (20.5%)	* (20.7%)	* (20.5%)
Missing	256 (0.3%)	* (0.1%)	* (0.3%)
Comorbidities			
ADG score, mean (SD)	5.41 (3.65)	6.20 (3.99)	5.40 (3.65)
RUB			
0	4,935 (5.7%)	38 (3.4%)	4,897 (5.8%)
1	4,246 (4.9%)	55 (4.9%)	4,191 (4.9%)
2	13,921 (16.2%)	148 (13.2%)	13,773 (16.2%)
3	43,280 (50.3%)	535 (47.9%)	42,745 (50.3%)
4	13,504 (15.7%)	203 (18.2%)	13,301 (15.7%)
5	6,195 (7.2%)	138 (12.4%)	6,057 (7.1%)
Frailty	2,393 (2.8%)	37 (3.3%)	2,356 (2.8%)
Cerebrovascular disease	1,150 (1.3%)	19 (1.7%)	1,131 (1.3%)
Chronic obstructive pulmonary disease	1,124 (1.3%)	13 (1.2%)	1,111 (1.3%)
Congestive heart failure	736 (0.9%)	22 (2.0%)	714 (0.8%)
Coronary artery disease	1,630 (1.9%)	29 (2.6%)	1,601 (1.9%)
Diabetes mellitus	2,889 (3.4%)	32 (2.9%)	2,857 (3.4%)
Hypertension	5,196 (6.0%)	87 (7.8%)	5,109 (6.0%)
Renal failure	1,428 (1.7%)	30 (2.7%)	1,398 (1.6%)
Liver failure	422 (0.5%)	* (0.4%)	* (0.5%)
VTE risk factors			
Hospital admission last 90 days	1,732 (2.0%)	28 (2.5%)	1,704 (2.0%)
Hospital admission last 90 days or before end of follow-up	8,053 (9.4%)	207 (18.5%)	7,846 (9.2%)
Surgery in last 90 days	2,909 (3.4%)	58 (5.2%)	2,851 (3.4%)
Surgery in last 90 days or before end of follow-up	6,779 (7.9%)	138 (12.4%)	6,641 (7.8%)
Cancer in last 5 years	1,881 (2.2%)	36 (3.2%)	1,845 (2.2%)
Chemotherapy in last 1 year	1,073 (1.2%)	23 (2.1%)	1,050 (1.2%)
Radiotherapy in last 1 year	282 (0.3%)	8 (0.7%)	274 (0.3%)
Superficial venous thrombosis	119 (0.1%)	11 (1.0%)	108 (0.1%)
VTE in last 10 years	2,849 (3.3%)	165 (14.8%)	2,684 (3.2%)
Pregnancy at time of the fracture	269 (0.3%)	* (0.3%)	* (0.3%)
Surgery for the fracture	16,150 (18.8%)	288 (25.8%)	15,862 (18.7%)
ED characteristics			
Hospital type			
Community	52,696 (61.2%)	668 (59.8%)	52,028 (61.2%)
Pediatric	223 (0.3%)	* (0.1%)	* (0.3%)

Table 1. Continued.

Characteristic, n (%)	Total (N=86,081)	VTE (n=1,117)	No VTE (n=84,964)
Small	5,707 (6.6%)	* (7.8%)	* (6.6%)
Teaching	14,723 (17.1%)	214 (19.2%)	14,509 (17.1%)
Missing	12,732 (14.8%)	147 (13.2%)	12,585 (14.8%)
Outcomes			
VTE within 90 days	1,117 (1.3%)	1,117	
DVT within 90 days	881 (1.0%)	881 (78.9%)	N/A
PE within 90 days	354 (0.4%)	354 (31.7%)	N/A
VTE diagnosis code in conjunction with imaging code within 90 days	859 (1.0%)	859 (76.9%)	N/A
All-cause mortality within 90 days	248 (0.3%)	19 (1.7%)	229 (0.3%)

ADG, John Hopkins Adjusted Diagnostic Groups; *DVT*, deep venous thrombosis; *IQR*, interquartile range; *PE*, pulmonary embolism; *RUB*, resource utilization band; *VTE*, venous thromboembolism.

*Cells suppressed due to small sample sizes. Other cells may have been suppressed to prevent back calculation.

thromboembolism imaging within 3 days of a venous thromboembolism diagnostic code. Of the included patients, 248 (0.3%) died within 90 days.

In the baseline model (model 1) examining factors present at the time of injury, the following were significantly associated with an increased hazard of venous thromboembolism: surgery in the previous 90 days (HR: 1.39; 95% CI: 1.06 to 1.81) and history of venous thromboembolism/superficial venous thromboembolism (HR: 5.12; 95% CI: 4.28 to 6.13). In model 2, in which hospitalizations and surgery after the diagnosis of ankle fracture were added as time-varying covariates, age over 65 (HR: 1.18; 95% CI: 1.00 to 1.39), hospitalization (HR: 1.33; 95% CI: 1.05 to 1.68), nonankle-related surgery (HR: 1.58; 95% CI: 1.30 to 1.93), history of venous thromboembolism/superficial venous thromboembolism (HR: 5.18; 95% CI: 4.33 to 6.20), and surgery for ankle fracture (HR 1.80, 95% CI: 1.48 to 2.20) were all significantly associated with increased hazards of venous thromboembolism. Table 2 shows results for both models.

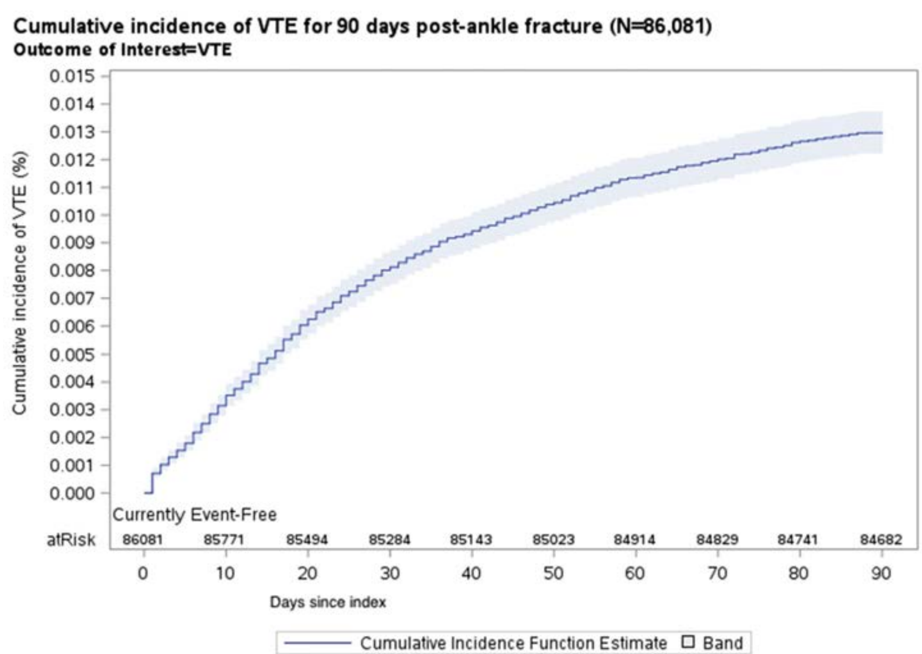

Figure 2. Cumulative incidence of venous thromboembolism over 90 days.

Table 2. Unadjusted and adjusted hazard ratios for venous thromboembolism after discharge from the ED with ankle fractures requiring temporary lower limb immobilization (N=86,081).

Characteristic	Unadjusted Model HR (95% CI)*	Model 1 Baseline Model HR (95% CI)*	Model 2 Baseline Model + Time-Varying Covariates for Hospital Admission, Surgery, and Surgery for the Fracture HR (95% CI)*
Demographics			
Age >65 years	1.35 (1.17–1.56)	1.14 (0.98–1.34)	1.18 (1.00–1.39)
Sex, female (REF=male)	1.15 (1.02–1.30)	1.07 (0.95–1.21)	1.09 (0.97–1.23)
Comorbidities			
Cerebrovascular disease	1.29 (0.77–2.16)	0.91 (0.54–1.53)	0.89 (0.53–1.48)
COPD	0.89 (0.54–1.48)	0.68 (0.41–1.15)	0.67 (0.40–1.12)
Coronary artery disease	1.39 (1.02–1.90)	1.11 (0.80–1.54)	1.08 (0.78–1.50)
Hypertension	1.32 (1.07–1.63)	1.23 (0.99–1.52)	1.21 (0.98–1.50)
Diabetes mellitus	0.85 (0.59–1.22)	0.76 (0.53–1.09)	0.75 (0.53–1.08)
Risk factors			
Hospital admission last 90 days	1.27 (0.89–1.81)	0.91 (0.62–1.33)	–
Hospital admission last 90 days or between index and end of follow-up†	2.06 (1.74–2.44)	–	1.33 (1.05–1.68)
Nonankle surgery in last 90 days	1.57 (1.22–2.02)	1.39 (1.06–1.81)	–
Nonankle surgery in last 90 days or between index and end of follow-up†	1.86 (1.56–2.22)	–	1.58 (1.30–1.93)
Cancer in last 5 years	1.50 (1.08–2.08)	1.16 (0.83–1.60)	1.13 (0.81–1.57)
VTE or SVT in last 10 years	5.35 (4.52–6.33)	5.12 (4.28–6.13)	5.18 (4.33–6.20)
Pregnancy at time of fracture	0.86 (0.28–2.61)	0.91 (0.30–2.77)	0.90 (0.29–2.76)
Surgery for fracture†	1.17 (0.92–1.49)	–	1.80 (1.48–2.20)

COPD, Chronic obstructive pulmonary disease; *REF*, reference category; *SVT*, superficial venous thrombosis.
*Sandwich variance estimators used to account for clustering by institution.
†Time-varying covariate.

The results of the sensitivity analyses on both models examining factors associated with venous thromboembolism are presented in Appendix E1 (Results, Table E6).

Patients with ankle fractures were then propensity score matched to patients with finger wounds and wrist fractures. There were 70,449 pairs (81.8% ankle fracture patients matched) in the ankle fracture versus finger wound cohort and 52,800 pairs (64.2% wrist fracture patients matched) in the ankle fracture versus wrist fracture cohort. Patients in each matched cohort were well balanced, with all standardized differences less than 0.10 (Tables 3 and 4). Patients with ankle fractures had an approximate 6-fold increased hazard of venous thromboembolism compared to patients with finger wounds (HR: 6.31; 95% CI: 5.30 to 7.52). Similarly, the hazard of venous thromboembolism for patients with ankle fractures was approximately 5-fold higher than for patients with wrist fractures (HR: 5.68; 95% CI: 4.71 to 6.85). Table 5 describes outcomes in the propensity-matched cohorts. Post hoc power calculations showed adequate power (>99%). The sensitivity analysis using a strict definition of venous thromboembolism resulted in a larger HR for venous thromboembolism in both cohorts. The sensitivity analyses that added a time-varying covariate for surgery between the ED visit and end of follow-up, and excluding patients who required surgery for their fractures, did not change the magnitude or direction of the results substantially. The propensity-matched cohort outcomes and the results of the sensitivity analyses are shown in Table 5.

LIMITATIONS

This study has several limitations. We examined health care use by ED patients in Ontario, which limits generalization of our findings to other settings. We were

Table 3. Balance in baseline covariates in patients with ankle fractures compared to propensity score matched patients with finger wounds.

Characteristic, n (%)	Ankle Fracture (n=70,449)	Finger Wound (n=70,449)	Standardized Difference
Demographics			
Age >65 years	10,614 (15.1%)	10,504 (14.9%)	0
Sex, female	37,568 (53.3%)	36,501 (51.8%)	0.03
Rural	6,793 (9.6%)	6,243 (8.9%)	0.03
Income quintile			
1 (lowest quintile)	13,998 (19.9%)	13,741 (19.5%)	0.01
2	13,879 (19.7%)	13,469 (19.1%)	0.01
3	14,151 (20.1%)	14,211 (20.2%)	0
4	13,974 (19.8%)	14,207 (20.2%)	0.01
5 (highest quintile)	14,447 (20.5%)	14,821 (21.0%)	0.01
Comorbidities			
ADG score, mean (SD)	5.28 (3.58)	5.20 (3.56)	0.02
RUB			
0	4,210 (6.0%)	4,474 (6.4%)	0.02
1	3,626 (5.1%)	3,754 (5.3%)	0.01
2	11,752 (16.7%)	12,085 (17.2%)	0.01
3	35,631 (50.6%)	35,667 (50.6%)	0
4	10,778 (15.3%)	10,164 (14.4%)	0.02
5	4,452 (6.3%)	4,305 (6.1%)	0.01
Frailty	1,472 (2.1%)	1,455 (2.1%)	0
Cerebrovascular disease	790 (1.1%)	751 (1.1%)	0.01
Congestive heart failure	486 (0.7%)	491 (0.7%)	0
Coronary artery disease	1,289 (1.8%)	1,207 (1.7%)	0.01
COPD	831 (1.2%)	776 (1.1%)	0.01
Diabetes mellitus	2,230 (3.2%)	2,065 (2.9%)	0.01
Hypertension	4,118 (5.8%)	3,873 (5.5%)	0.02
Liver failure	292 (0.4%)	284 (0.4%)	0
Renal failure	973 (1.4%)	933 (1.3%)	0
Risk factors			
Hospital admission last 90 days	1,171 (1.7%)	1,154 (1.6%)	0
Surgery in last 90 days	2,255 (3.2%)	2,047 (2.9%)	0.02
Cancer in last 5 years	1,402 (2.0%)	1,312 (1.9%)	0.01
Chemotherapy in last 1 year	747 (1.1%)	725 (1.0%)	0
Radiotherapy in last 1 year	198 (0.3%)	196 (0.3%)	0
SVT in last 5 years	100 (0.1%)	73 (0.1%)	0.01
VTE in last 10 years	2,207 (3.1%)	2,037 (2.9%)	0.01
Pregnancy at time of fracture	230 (0.3%)	175 (0.2%)	0.01
ED characteristics			
Hospital type			
Community	50,625 (71.9%)	51,316 (72.8%)	0.02
Pediatric	184 (0.3%)	181 (0.3%)	0
Small	5,595 (7.9%)	5,220 (7.4%)	0.02
Teaching	14,045 (19.9%)	13,732 (19.5%)	0.01
Triage level			
1 (highest acuity)	60 (0.1%)	63 (0.1%)	0
2	3,710 (5.3%)	3,955 (5.6%)	0.02

Table 3. Continued.

Characteristic, n (%)	Ankle Fracture (n=70,449)	Finger Wound (n=70,449)	Standardized Difference
3	30,013 (42.6%)	30,192 (42.9%)	0.01
4	35,271 (50.1%)	34,919 (49.6%)	0.01
5 (lowest acuity)	1,330 (1.9%)	1,265 (1.8%)	0.01
Unknown	65 (0.1%)	55 (0.1%)	0

unable to examine differences between casts/splints and walking boots. We were unable to ascertain weight-bearing status, which may also affect venous thromboembolism outcomes. We included several types of ankle fractures and cannot say all patients were definitely immobilized in the ED. However, our chart review of ankle fracture codes showed 94% of patients received immobilization in the ED. Inadvertently including patients who did not require immobilization would likely result in a conservative bias in our estimate of incidence of venous thromboembolism and a loss of precision related to the HRs for risk factors associated with venous thromboembolism. Our study used administrative data from Ontario, and there may be potential misclassification bias if there were coding errors for the variables used in this study. However, our sensitivity analysis requiring a code for venous thromboembolism imaging in addition to a diagnosis code did not greatly impact the proportion of patients diagnosed with venous thromboembolism during 90-day follow-up. Furthermore, many studies have previously used these databases and found good agreement between chart reviews and the databases for mandatory variables and the main ED diagnoses for various diseases.[25-28] We may have missed cases of venous thromboembolism if patients presented to other provinces for their care. In Ontario, there is not universal medication coverage; therefore, we were unable to identify all patients aged less than of 65 years on anticoagulation. However, to address this, we excluded those with diagnoses of atrial fibrillation. Inadvertently including a small proportion of anticoagulated patients would have meant a smaller reported incidence of venous thromboembolism and bias toward the null. As such, our reported incidence of venous thromboembolism, HR estimates, and the strength of reported associations between individual risk factors and venous thromboembolism are likely to be conservative estimates. We were unable to examine several traditional variables that have often been associated with venous thromboembolism, such as hormone treatment, coagulation disorders (ie, Factor V Leiden, protein C and S deficiency), family history, and body mass index because we could not ascertain this data. Future large-scale prospective studies will be required to adequately assess all pertinent risks. We examined a specific population of patients with closed ankle fractures; therefore, our results are not generalizable to other injuries requiring lower limb immobilization, such as Achilles tendon ruptures and ligament injuries. Finally, we used propensity score matching to compare patients with ankle fractures to control patients to ensure the effects of potential confounders were well balanced between groups. However, by using this method and matching patients with ankle fractures to control cohorts with finger wounds and wrist fractures, there were 18% and 39% of patients with ankle fractures, respectively, that were excluded in this analysis.

DISCUSSION

In this study of over 86,000 patients discharged from the ED with closed ankle fractures requiring temporary lower limb immobilization, the 90-day incidence of venous thromboembolism was 1.3%, and these patients had a 5- to 6-fold increased hazard of venous thromboembolism compared to matched controls with finger wounds or wrist fractures. Venous thromboembolism was associated with a prior history of venous thromboembolism, surgery before and after the injury, hospital admission, and older age.

Previous work has not focused on patients in the ED setting; however, a systematic review by Horner et al[15] examined individual risk factors for venous thromboembolism after lower limb immobilization, including 15 studies and 80,678 patients. In this systematic review, age was the risk factor most consistently associated with development of venous thromboembolism, with odds ratios ranging from 1.05 to 3.48. Severity of injury and body mass index were the next most consistent individual risk factors associated with venous thromboembolism. When incorporating postfracture surgery and subsequent hospital admission, we also found that older age was associated with an increased risk of venous thromboembolism. In addition, our results concur with other research reporting associations with history of venous thromboembolism, history of surgery, and surgery for ankle fracture.[1,2] While we did not find that cancer was significantly associated with an increased risk of venous thromboembolism, the number of patients with cancer in

Table 4. Balance in baseline covariates in patients with ankle fractures compared to matched patients with wrist fractures.

Characteristic, n (%)	Ankle Fracture (n=52,800)	Wrist Fracture (n=52,800)	Standardized Difference
Demographics			
Age >65 years	12,157 (23.0%)	11,841 (22.4%)	0.01
Female	33,610 (63.7%)	33,808 (64.0%)	0.01
Rural	4,787 (9.1%)	4,751 (9.0%)	0
Income quintile			
1 (lowest quintile)	10,490 (19.9%)	10,271 (19.5%)	0.01
2	10,517 (19.9%)	10,486 (19.9%)	0
3	10,488 (19.9%)	10,498 (19.9%)	0
4	10,410 (19.7%)	10,493 (19.9%)	0
5 (highest quintile)	10,895 (20.6%)	11,052 (20.9%)	0.01
Comorbidities			
ADG score, mean (SD)	5.63 (3.68)	5.57 (3.65)	0.02
RUB			
0	2,683 (5.1%)	2,791 (5.3%)	0.01
1	2,364 (4.5%)	2,342 (4.4%)	0
2	7,844 (14.9%)	8,047 (15.2%)	0.01
3	26,958 (51.1%)	27,060 (51.3%)	0
4	8,744 (16.6%)	8,447 (16.0%)	0.02
5	4,207 (8.0%)	4,113 (7.8%)	0.01
Frailty	1,849 (3.5%)	1,724 (3.3%)	0.01
Cerebrovascular disease	810 (1.5%)	782 (1.5%)	0
Congestive heart failure	526 (1.0%)	503 (1.0%)	0
Coronary artery disease	1,064 (2.0%)	1,016 (1.9%)	0.01
COPD	794 (1.5%)	778 (1.5%)	0
Diabetes mellitus	1,753 (3.3%)	1,703 (3.2%)	0.01
Hypertension	3,413 (6.5%)	3,333 (6.3%)	0.01
Liver failure	322 (0.6%)	326 (0.6%)	0
Renal failure	989 (1.9%)	963 (1.8%)	0
Risk factors			
Hospital admission last 90 days	987 (1.9%)	974 (1.8%)	0
Surgery in last 90 days	1,819 (3.4%)	1,805 (3.4%)	0
Cancer in last 5 years	1,373 (2.6%)	1,345 (2.5%)	0
Chemotherapy in last 1 year	743 (1.4%)	752 (1.4%)	0
Radiotherapy in last 1 year	210 (0.4%)	186 (0.4%)	0.01
SVT in last 5 years	79 (0.1%)	60 (0.1%)	0.01
VTE in last 10 years	1,926 (3.6%)	1,917 (3.6%)	0
Pregnancy at time of fracture	90 (0.2%)	78 (0.1%)	0.01
Surgery for fracture	7,761 (14.7%)	7,761 (14.7%)	0
ED characteristics			
Hospital type			
Community	38,063 (72.1%)	38,164 (72.3%)	0
Pediatrics	196 (0.4%)	195 (0.4%)	0
Small	3,785 (7.2%)	3,680 (7.0%)	0.01
Teaching	10,756 (20.4%)	10,761 (20.4%)	0
Triage level			
1 (highest acuity)	75 (0.1%)	83 (0.2%)	0
2	3,848 (7.3%)	4,128 (7.8%)	0.02

Table 4. Continued.

Characteristic, n (%)	Ankle Fracture (n=52,800)	Wrist Fracture (n=52,800)	Standardized Difference
3	25,642 (48.6%)	25,773 (48.8%)	0
4	22,339 (42.3%)	21,972 (41.6%)	0.01
5 (lowest acuity)	854 (1.6%)	801 (1.5%)	0.01
Unknown	42 (0.1%)	43 (0.1%)	0

our cohort was low, and we may have been underpowered to detect differences in the risk of venous thromboembolism between patients with and without cancer.

While the incidence of venous thromboembolism in our study was relatively low, patients with ankle fractures requiring lower limb immobilization had a significantly higher risk of venous thromboembolism than the matched control groups. This highlights the need for clinicians to be aware of the increased risk of venous thromboembolism in this patient population and communicate this risk to patients. Several studies have examined the use of thromboprophylaxis to reduce the risk of venous thromboembolism in patients requiring lower limb immobilization. The POT-CAST randomized control trial of 1,435 patients with lower leg casting compared prophylactic low-molecular-weight heparin during immobilization to no anticoagulation. This study found no significant different in the relative risk of venous thromboembolism or bleeding side effects between groups.[29] However, a meta-analysis of 6,857 patients from 13 randomized trials found that low-molecular-weight heparin and fondaparinux reduced the risk of venous thromboembolism.[16] The results of the POT-CAST trial, combined with the results of our study (which showed a relatively low incidence of venous thromboembolism but high hazard of venous thromboembolism in patients with ankle fractures compared to control patients), suggest that perhaps not all patients with lower limb immobilization require thromboprophylaxis. Identification of high-risk patients for whom the risk of venous thromboembolism outweighs the risk of bleeding may be an effective strategy to offer thromboprophylaxis.[30] Further research is required in order to identify which patients at high risk require thromboprophylaxis.

Although thromboprophylaxis is not currently universally offered to patients with lower limb immobilization, thromboprophylaxis decision rules to identify patients who would benefit from prophylaxis do exist. However, there are no widely used, well-validated scores. A recent systematic review of risk assessment tools for use in patients requiring lower limb immobilization identified 7 risk assessment tools.[31] The TRiP(cast) score includes 14 variables to predict venous thromboembolism following any lower limb injury requiring

Table 5. Hazard of venous thromboembolism in ankle fracture patients compared to propensity score matched patients with finger wounds and wrist fractures.

Outcomes	Ankle Fracture n (%)	Finger Wound n (%)	HR (95% CI)	Ankle Fracture n (%)	Wrist Fracture n (%)	HR (95% CI)
VTE	917 (1.3%)	146 (0.2%)	6.31 (5.30–7.52)	735 (1.4%)	130 (0.2%)	5.68 (4.71–6.85)
Sensitivity Analyses						
Strict definition of VTE	705 (1.0%)	59 (0.1%)	11.93 (9.15–15.56)	558 (1.1%)	66 (0.1%)	8.57 (6.63–11.08)
Time-varying model accounting for surgery during follow-up period						
VTE	–	–	6.71 (5.58–8.06)	–	–	6.11 (5.02–7.44)
Surgery			8.58 (4.26–17.26)			4.62 (2.51–8.52)
Exclude patients with ankle surgery (and wrist surgery) during follow-up period						
VTE	–	–	5.30 (4.40–6.39)	–	–	4.91 (4.03–5.99)

HR, hazard ratio; *VTE*, venous thromboembolism.

immobilization.[32] Similarly to our findings, age, history of venous thromboembolism, history of superficial venous thromboembolism, and recent surgery are all predictors in the TRiP(cast) score. The L-TRiP score includes age, hospital admission, surgery, history of superficial venous thromboembolism, and various comorbidities in its risk score.[33] GEMNet guidelines suggest thromboprophylaxis for patients with recent hospitalization or major surgery, history of venous thromboembolism, or older age.[18] The Plymouth Rule includes age, history of venous thromboembolism, and recent abdominal surgery.[34] Prospective research is required to establish whether decision rule-guided thromboprophylaxis is safe and effective in reducing venous thromboembolism after lower limb immobilization and identify which high-risk patients, specifically, would benefit from thromboprophylaxis.

In conclusion, the 90-day incidence of venous thromboembolism among patients discharged from the ED with ankle fractures requiring immobilization was 1.3%, a 5- to 6-fold increased hazard compared to matched controls with finger wounds or wrist fractures. Our results suggest that certain patients immobilized for ankle fractures are at higher risk of venous thromboembolism and should be considered for thromboprophylaxis.

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Author affiliations: From the Schwartz/Reisman Emergency Medicine Institute, Sinai Health, Toronto, Ontario, Canada (Grewal, Thompson, Borgundvaag, McLeod); the Division of Emergency Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Grewal, Atzema); ICES, Toronto, Ontario, Canada (Grewal, Atzema, Sutradhar, Everett); the Department of Emergency Services, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Atzema); the Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Sutradhar); the Salford Royal NHS Foundation Trust, Salford, UK (Horner); the Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK (Horner); the Division of Orthopedic Surgery, Sinai Health, Toronto, Ontario, Canada (Theodoropoulos); the Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada (Borgundvaag); the Department of Emergency Medicine, Queens University, Kingston, Ontario, Canada (McLeod); and the Department of Medicine, McMaster University, Hamilton, Ontario, Canada (de Wit).

Author contributions: KG, CLA, BB, SLM, JT, and KdW conceptualized the study. KG, CLA, RS, and KdW developed the data creation plan and analysis plan. KE conducted the analysis. CT conducted the validation study. All authors contributed to data interpretation. KG, KdW, and DH created the first draft of the manuscript, and all authors provided critical feedback and edits for the final manuscript. KG takes responsibility for the integrity of the work as a whole.

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