

The Cumulative Incidence and Risk Factors of Recurrent Venous Thromboembolism in the Elderly

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Background: Incidence and outcomes of recurrent venous thromboembolism (VTE) in the elderly are still not fully elucidated. The purpose of this study was to determine the incidence and identify the risk factors of VTE recurrence in this population.

Methods: A prospective cohort study of a one-year follow-up of 277 patients aged ≥ 65 years with primary VTE was performed at King Abdulaziz Medical City, a tertiary care teaching hospital in Riyadh, Saudi Arabia. Demographic data, risk factors, and the consequences of VTE (recurrence, bleeding, and mortality) were recorded.

Results: Of the 277 VTE patients, 39 (14%) were diagnosed with recurrent VTE over a median follow-up period of 12 months. The cumulative incidence of recurrent VTE was 12.75 per hundred patient-year (95% CI, 8.24–17.36). In multivariate Cox regression, malignancy (hazard ratio [HR], 2.87, 95% CI, 1.32–6.24, $p=0.008$) and surgery (HR 2.78, 95% CI, 1.36–5.67, $p=0.005$) were identified as independent risk factors for recurrent VTE. Metformin had a significant independent protection effect (HR, 0.16, 95% CI, 0.08–0.33, $p<0.001$). During follow-up, two patients in the recurrent VTE group and five patients in the group with no recurrent VTE, all of whom were minor bleeding cases, reported no major bleeding. Seven (18%) patients in the recurrent VTE group and nine (4%) patients in the group with no recurrent VTE died ($p<0.001$).

Conclusion: The findings of this study show that elderly patients with initial VTE have a recurrent rate (14%), with a cumulative incidence rate of 12.75 per hundred patient-year. Malignancy and surgery were the most important clinical risk factors to impact significantly the development of recurrent VTE in our elderly population. Metformin may have a protective effect against recurrent VTE in the elderly population, and a larger study is needed to validate our findings.

Keywords: elderly, incidence, recurrence, risk factors, venous thromboembolism

Introduction

Venous thromboembolism (VTE) constitutes a spectrum of events ranging from asymptomatic distal deep venous thrombosis (DVT) and subsegmental pulmonary embolism (PE), to limb threatening DVT and fatal PE.¹ The annual incidence of VTE ranges from 1.5 to 3.0 cases per 1,000 individuals, and is considered the third most common cause of cardiovascular disease and death after myocardial infarction and stroke.^{1,2} The risk of VTE and its recurrence is higher in the population aged 65 years or more, and the risk in patients above 70 years old are four to six times higher than in younger patients; additionally, this risk doubles with each decade of ageing.^{2,3} Importantly, elderly patients also exhibit a higher mortality rate due to more frequent fatal VTE and coexistent comorbidities.^{4–6} Based on VTE

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stratification, the risk of recurrent provoked VTE by temporary risk factors such as surgery or pregnancy is lower than when VTE was unprovoked.^{7–9} The risk of recurrence among VTE patients is influenced also by sex, as males have a significantly higher risk of developing a second episode of VTE than females.^{10–12} Although recurrent VTE is an important cause of morbidity and mortality among the elderly, little has been written about the risk factors predisposing to recurrent VTE in the elderly. The aims of our study were to assess the possible risk factors associated with recurrent VTE in a prospective cohort of elderly patients, and to determine the cumulative incidence of recurrence rate and the frequency of bleeding and mortality.

Patients and Methods

In this single-centre, prospective cohort analysis, elderly patients aged 65 years and above with first episode of objectively confirmed VTE, deep vein thrombosis, or pulmonary embolism were identified between 1 February 2016 and 31 December 2019, in the inpatient and outpatient settings at King Abdulaziz Medical City, Health Affairs, Ministry of National Guard, Riyadh, Saudi Arabia. Objectively confirmed VTE is defined as: a symptomatic VTE confirmed by ultrasound imaging for DVT and spiral computed tomography (CT) imaging for PE. Surgical intervention, thrombolytic therapy used, terminal illnesses, or severe dementia were an exclusion criterion. The following demographic characteristics including age, sex, weight, and height were recorded. Site of index VTE, category of index VTE, initial anticoagulant agents, duration of anticoagulation, medication currently used (proton pump inhibitors, antiplatelet, metformin, and statins therapy), comorbidities (hypertension, diabetes mellitus, COPD, dyslipidaemia, inflammatory bowel disease, chronic heart failure, and chronic kidney diseases), imaging reports (CT scan or Doppler ultrasound), and laboratory findings (Haemoglobin and international normalised ratios) were abstracted using standardised data collection spread sheets. All events were objectively reviewed during the inpatient stay or outpatient visit face-to-face, and periodic reviews were made of patients' electronic medical records.

A prospective follow-up was continued for 12 months to assess the main outcome variables over the study period. Recurrent VTE (DVT or PE) was considered when confirmed by the same imaging methods and documented in the electronic medical record, and the treating clinician

had resumed anticoagulant therapy for at least a period of three months. Death and bleeding occurrence are assessed and reported; major bleeding in non-surgical patients is defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or requiring a transfusion of at least two units of packed red blood cells, and/or reduction in haemoglobin level of more than 20 gm/L.¹³

Statistical Analysis

Baseline characteristics were compared using student-*t*-test for continuous variables and chi-square test for categorical variables as appropriate. The Kaplan-Meier method was used to construct VTE recurrence probabilities. All recruited patients were available for analysis, and were censored at time of recurrent event, death, loss to follow-up, or end of one-year follow-up. Univariate and multivariate Cox proportional hazard regression models were fitted to determine factors associated with hazard of VTE recurrence. These factors included: immobilisation, malignancy, obesity, surgery, and use of metformin. All tests were two-sided and a *p*-value <0.05 was considered significant.

Result

Of the 324 initial recruited patients with initial VTE, 47 patients were excluded because they had one or more exclusion criterion. The final sample size consisted of 277 patients. Overall, the mean (\pm SD) age was 70 (\pm 4) years and 52% were males. Based on the site of index VTE, 168 (61%) patients had PE (with or without DVT), 90 (32%) had proximal DVT, and 19 (7%) had isolated distal DVT. The majority of patients in both groups were treated with warfarin (77% vs 75%). The demographic and clinical characteristics of the study population are shown in Table 1.

Figure 1 shows the Kaplan-Meier recurrence probabilities curve plot. Overall, VTE recurrence rate was 14% (39/238) with cumulative incidence rate of 12.75 per hundred patient-year (95% CI, 8.24–17.36). The cumulative incidence was further analysed according to the site of index VTE and the categorisation of index VTE. The cumulative incidences of recurrent VTE per hundred patient-year was 7.51 (95% CI, 2.35–12.68) for patients who developed PE with or without DVT, 4.37 (95% CI, 0.29–8.20) for patients with proximal DVT, and 0.98 (95%

Table 1 Baseline Characteristics of the Patients

Variables	Recurrent VTE (n = 39)	No Recurrent VTE (n = 238)	P value
Age, year Mean (\pm SD)	69 (\pm 7.7)	70 (\pm 8.2)	0.730
Male sex, no. (%)	20 (51)	124 (52)	0.567
BMI, kg/m ² Mean (\pm SD)	29 (\pm 7.3)	27 (\pm 8.2)	0.535
Co-morbidity, no. (%)			
DM	30 (78)	198 (83)	0.575
HTN	31 (79)	196 (82)	0.309
COPD	10 (26)	66 (24)	0.825
Dyslipidemia	22 (56)	140 (59)	0.200
Inflammatory bowel disease	5 (13)	28 (12)	0.747
Chronic heart failure	8 (20)	52 (22)	0.944
Chronic Kidney diseases	4 (10)	25 (11)	0.966
Site of index VTE, no. (%)			
Isolated distal DVT	3 (8)	16 (7)	0.836
Proximal DVT	13 (33)	77 (32)	0.931
PE with/without DVT	23 (59)	145 (61)	0.908
Categorization of index VTE, no. (%)			
Provoked			
Malignancy-related VTE	11 (28)	18 (8)	<0.001
Immobilization (>3 days)	25 (64)	111 (47)	0.043
Obesity, BMI \geq 30kg/m ²	12 (31)	41 (17)	0.046
Surgery	23 (59)	63 (26)	<0.001
Unprovoked	6 (15)	19 (8)	0.135
Outcomes			
Bleeding*	2 (5%)	5 (2%)	0.281
Death	7 (18%)	9 (4%)	<0.001

Note: *All were minor bleeding.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

CI, 0.12–2.91) for patients with isolated distal DVT. The cumulative incidences of recurrent VTE were 9.52 (95% CI, 7.30–11.74) and 3.86 (95% CI, 2.61–4.97) per hundred patient-year in provoked and unprovoked VTE, respectively. Of the 39 elderly patients with recurrent VTE, 23 (59%) were PE with or without DVT, 13 (33%) were proximal DVT with or without distal DVT and three (8%) patients experienced isolated distal DVT. Age was categorized into five groups of five-years range (65–69, 70–74, 75–79, 80–84, and \geq 85 years). The assumption of proportional hazard was not violated (test of equality of survival distributions for the different levels of age category) as this test shows that the hazards for recurrence did

not differ by age. Thus, age was not a competing risk factor (advancing age was not associated with increased rates of recurrent VTE). Malignancy-related VTE ($p<0.001$), immobilisation ($p=0.043$), obesity ($p=0.046$), and surgery ($p<0.001$) were significantly higher in the recurrent VTE compared to the group with no recurrent VTE, [Table 1](#).

The initial anticoagulant, duration of therapy, and current medications used are presented in [Table 2](#). The vast majority of recurrent VTE (36 of 39; 92%) were diagnosed after anticoagulation treatment had been completed. Of the patients diagnosed with recurrent VTE during anticoagulation therapy (three of 39) one was on warfarin and two on NOAC therapy. The two patients who developed recurrent VTE during NOACs therapy were shifted to warfarin. International normalised ratios (INR) monitoring was followed for all available results to evaluate the magnitude of anticoagulation agent. Of the 208 patients who received vitamin K antagonist (warfarin), 183 patients (88%) with regular INR monitoring were available and followed-up ([Table 3](#)). The mean percentage of time range in therapeutic (2–3), supratherapeutic (>3), and subtherapeutic (<2) INRs were similar in patients with and without recurrent VTE (77 \pm 13 vs 75 \pm 16, $p=0.903$; 23 \pm 15 vs 19 \pm 13, $p=0.525$; 8 \pm 7 vs 6 \pm 5, $p=0.605$, respectively). Patients who developed recurrent VTE during warfarin therapy had subtherapeutic INR. The duration of anticoagulation therapy of patients with and without recurrent VTE were similar ($p=0.801$). The majority of patients with no recurrent VTE were using metformin significantly more than those patients with recurrent VTE (76% vs 31%, $p<0.001$). Similarly, antiplatelet use was more frequent in patients with no recurrent VTE than those with recurrent VTE, but was not statistically significant (57% vs 41%, $p=0.061$), [Table 2](#).

In multivariate cox regression, malignancy (hazard ratio [HR], 2.87, 95% CI, 1.32–6.24, $p=0.008$) and surgery (HR, 2.78, 95% CI, 1.36–5.67, $p=0.005$) were identified as independent risk factors for recurrent VTE. Metformin had a significant protection effect against recurrent VTE (HR, 0.16, 95% CI, 0.08–0.33, $p<0.001$), [Table 4](#).

Overall, seven patients experienced bleeding while receiving anticoagulation (2.5%); two patients in the recurrent VTE group and five patients in the group with no recurrent VTE ([Table 1](#)). All had minor bleeding with no major bleeding reported. Difference in incidence rates was not statistically significant (5% vs 2.1%, $p=0.281$). During follow-up, seven (18%) patients in the recurrent VTE

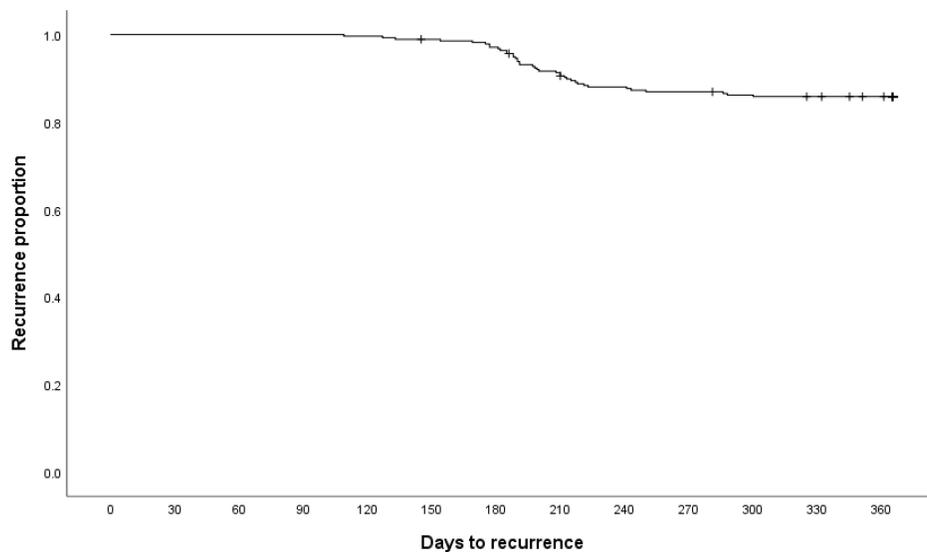


Figure 1 Kaplan–Meier recurrence probabilities curve.

group, and nine (4%) in the group with no recurrent VTE died ($p < 0.001$, Table 1).

Discussion

In this Saudi Arabian prospective follow-up cohort study of the elderly with VTE we found that recurrent VTE was 14%. The cumulative recurrence VTE incidence was 12.75 per hundred patient-year. The incidence rates of first VTE increases with age,^{2,14,15} and was reported that

the incidence of VTE increased by 2.5-fold among age group ≥ 80 years old compared to the age group of 60–69 years old.² However, the risk of recurrent VTE with advanced age is still not fully elucidated, with some studies reporting higher incidence rates,¹⁶ and others reporting lower incidence rate among patients of advanced age.¹⁷ The incidence of recurrence rate among our elderly population was higher than in a study of mixed retrospective-prospective cohort of elderly patients (10%),¹⁸ but slightly lower than in prospective and retrospective studies (15% and 17%), respectively.^{19,20} However, advanced age (≥ 80 years) in our patients is not associated with increased risk of developing recurrent VTE. Several studies have reported lower risk of recurrent VTE in patients who are aged 80 years or more compared to those aged less than 80 years.^{2,18,19} In a retrospective study of Californian

Table 2 Initial Anticoagulants, Duration and Current Medications

Variables	Recurrent VTE (n = 39)	No Recurrent VTE (n = 238)	P value
Initial anticoagulant agents			0.823
Enoxaparin	5 (13)	34 (14)	
Unfractionated heparin	1 (2)	6 (3)	
Fondaparinux	0	3 (1)	
Warfarin	30 (77)	178 (75)	
NOAC	3 (8)	17 (7)	
Duration of anticoagulant therapy			0.801
3 months	5 (13)	23 (10)	
6 months	11 (28)	70 (29)	
>6 months	23 (59)	145 (61)	
Current medications			0.061
Antiplatelet	16 (41)	136 (57)	0.858
Statin	21 (54)	135 (57)	0.459
PPI	18 (46)	89 (37)	<0.001
Metformin	12 (31)	181 (76)	

Abbreviations: NOAC, non-vitamin K oral anticoagulant; PPI, proton pump inhibitor; VTE, venous thromboembolism.

Table 3 Monitoring the Quality of Vitamin K Antagonist Used by Patients

INR Index	Mean Percentage of Time in Different INR Range (\pm SD)		P value
	Recurrent VTE (n=28)	No Recurrent VTE (n=171)	
Therapeutic (2.0–3.0)	77 (\pm 13)	75 (\pm 16)	0.903
Subtherapeutic (<2.0)	15 (\pm 8)	19 (\pm 6)	0.525
Supratherapeutic (>3.0)	8 (\pm 3)	6 (\pm 2)	0.605

Abbreviations: INR, international normalized ratio; SD, standard deviation; VTE, venous thromboembolism.

Table 4 Univariate and Multivariate Cox Regression for Risk Factors Associated with Recurrent VTE

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Malignancy	3.88 (1.93–7.80)	<0.001	2.87 (1.32–6.24)	0.008
Surgery	3.49 (1.84–6.60)	<0.001	2.78 (1.36–5.67)	0.005
Obesity	2.05 (1.04–4.10)	0.039	0.92 (0.44–1.95)	0.831
Immobilization	2.24 (1.16–4.31)	0.016	1.36 (0.66–2.84)	0.408
Use of metformin	0.16 (0.08–0.32)	<0.001	0.16 (0.08–0.33)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

residents diagnosed with VTE, authors found a 15% reduction in the incidence rates of recurrent VTE per increasing decade of life.¹⁷ Similarly, Spencer et al, in their population-based study concluded that advanced age was not associated with increased risk of recurrent VTE.¹⁸

The VTE recurrence independent risk factors after a first event of VTE in our elderly population study were provoked by malignancy and surgery (HR, 2.87 and 2.78, respectively). Patients with malignancy-associated thrombosis have a higher risk of VTE recurrence of up to 20%, despite receiving anticoagulation.^{21,22} Jara-Palomares et al reported a rate of 8.8% (95% CI: 4.3–15.5%) developed VTE recurrence within six months in patient with malignancy.²³ A recent study by Nemeth et al of patients undergoing surgery, identified 3,741 patients with one or more prior episodes of treated VTE who were followed for as long as 10 years in a Dutch registry; during follow-up, 580 (15.5%) underwent surgery and 601 (16.1%) developed a recurrent thrombotic event. The 1-month cumulative incidence of recurrent VTE for all surgery types was 2.1% (95% CI, 1.2%–3.6%), which increased to 3.3% (95% CI, 2.1%–5.1%) at three months and 4.6% (95% CI, 3.1%–6.6%) at six months, compared with an incidence of 0.8% (95% CI, 0.6%–1.1%) at three months in patients unexposed to surgery. At six months, risk of recurrent VTE ranged from 2.3% to 9.3%, depending on surgery type. The authors concluded that surgery was associated with an increased risk of recurrent VTE in patients with a history of VTE; risk remained high for up to six months after the procedure.²⁴ The risk of VTE associated with immobilisation is well recognized in surgical and medical patients.²⁵ However, immobilisation in this study was not an independent risk factor for recurrent VTE in elderly patients. Immobility was not different in either recurrent or no recurrent VTE groups, most probably due to similarity either in their presenting illness or comorbid conditions. The results of this study show that

recurrent VTE is more likely to occur in patients with malignancy and provoked by surgery. Hence, it is important that clinicians are aware of different risk factors that can enhance decision-making discussions with patients about the risks and benefits of the different durations of anticoagulation.

Elderly patients who did not developed VTE recurrence were much more predominantly anticoagulated with antiplatelets (aspirin and clopidogrel) compared with their counterparts with recurrent VTE (73% vs 41%). Antiplatelets have some protective effect but did not reach statistical significance ($p=0.065$). Similarly, more elderly patients who did not developed VTE recurrence were taking metformin compared to those who developed VTE recurrence (65% vs 31%). Lu et al, in their study, suggested that metformin use had significant protective effects against the development of VTE in patients with diabetes, independent of age, sex, and comorbidities.²⁶ Metformin was shown to be effective in preventing both VTE and arterial thrombosis without a significant risk of bleeding.²⁷ It acts by inhibiting platelet activation via reducing extracellular mitochondrial DNA (mtDNA) release. Other than decreasing platelet activation, metformin exerts its protective effects by reducing some markers of endothelial activation, von Willebrand factor, vWF, and the adhesion molecule sVCAM-1,^{27,28} and it decreases inflammation and levels of plasminogen activator inhibitor 1 (PAI-1).^{29–31} All these factors put together can account for the anti-thrombotic action of metformin.

The one-year mortality rate of patients who experienced a VTE recurrence (18%) is a 6.2-fold higher risk of death compared to patients without VTE recurrence (4%). These findings are consistent with Lauber et al,²⁰ who found a similar mortality rate (20%) in their study of elderly patients. Moreover, the mortality rate of 18% observed in our elderly population study is lower than the rate of 26% in the multicentre Swiss cohort study.³²

This study has several potential limitations. First, the cohort used to perform the analysis was limited to elderly (≥ 65 years old), which may preclude age as a risk factor for recurrent VTE, and we were unable to compare our elderly population data with younger patients. Second, patients with dementia or terminal illness were excluded, which may have an effect on overall mortality. Third, initial treatment in the vast majority (75%) was prescribed warfarin; therefore our findings may not be generalisable to population prescribed NOACs. Fourth, sample size and the number of events in the present study were relatively small, and may limit generalisability of the findings.

Conclusion

The findings of this study show that elderly patients with initial VTE have a recurrent rate (14%) with a cumulative incidence rate of 12.75 per hundred patient-year. Malignancy and surgery were the most important clinical risk factors to impact significantly the development of recurrent VTE in our elderly population. Metformin may have a protective effect against recurrent VTE in the elderly population, and a larger study is needed to validate our findings.

Ethical Approval

The study was approved by the Institutional Review Board (IRB) committee at King Abdullah International Medical Research Centre (KAIMRC), Health Affairs, Ministry of National Guard (IRB at KAIMRC is the only committee approves research studies at Health Affairs, Ministry of National Guard). KAIMRC and King Abdulaziz Medical Centre report to the Health Affairs, Ministry of National Guard. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Disclosure

The author declares that he has no conflict of interest.

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