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ORIGINAL RESEARCH

Incidence and Predictors of Recurrence and Mortality Following First Venous Thromboembolism Among the Saudi Population: Single-Center Cohort Study

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Background: Little is written about recurrence and mortality rates after a first episode of venous thromboembolism (VTE) among Saudi population.

Aim: Determine incidence rates and assess predictors of recurrence and mortality following the first VTE event.

Patients and Methods: A total of 1124 patients aged ≥18 years with symptomatic VTE confirmed by imaging tests were evaluated. The incidence of VTE recurrence and mortality were assessed. The association between patient characteristics, and VTE recurrence and mortality was explored by estimating the hazard ratio (HR) and 95% confidence interval (CI). The difference between cancer-related, provoked and unprovoked VTE in terms of recurrence and mortality was explored using Kaplan–Meier curves.

Results: The annual incidence rate of the first VTE was 1.7 per 1000 patients. Of 1124 patients with first VTE, 214 (19%) developed recurrent VTE, and 192 (17%) died with overall incidence rates of 15.8 per 100 person-years (95% CI, 13.8–18.0) and 10.0 per 100 person-years (95% CI, 8.7–11.5). Intensive care unit (ICU) admission (HR, 2.15; 95% CI, 1.67–3.10), presence of active cancer (HR, 2.97; 95% CI, 1.87–3.95), immobilization (HR, 2.52; 95% CI, 1.79–3.67), infection (HR, 2.32; 95% CI, 1.94–3.45), and pulmonary embolism ± deep venous thrombosis (HR, 2.22; 95% CI, 1.56–3.16) were found to be independent predictors of recurrent VTE. Recurrence carries a high hazard of mortality (HR, 5.21; 95% CI, 3.61–7.51). The estimated median time to VTE recurrence was lower in cancer-related VTE (18.7 months) compared with provoked (29.0 months) and unprovoked VTE (28.4 months). The estimated survival median time was lower in cancer-related VTE (21.8 months) compared with provoked (30.5 months) and unprovoked VTE (29.8 months).

Conclusion: Immobilization and presence of active cancer, infection, and PE ± DVT were significant predictors of recurrent VTE. Patients who developed recurrent VTE had a 5.2-fold higher hazard of mortality compared with patients with no VTE recurrence.

Keywords: incidence, mortality, predictors, recurrent, venous thromboembolism, active cancer

Introduction

Venous thromboembolism (VTE) is a condition comprising deep venous thrombosis (DVT) and pulmonary embolism (PE). PE occurs due to a blood clot wedged into one of the arteries of the lungs.[1] DVT occurs due to a blood clot development in the deep veins, most commonly originating in the lower limb, and can also originate in the pelvis and upper limb.[2–5] The annual incidence rate of the first VTE ranges from 1 to 3 per 1000.[6] Prior studies reported rates of recurrence and mortality after first VTE ranging from 5% to 40%[7–10] and from 3% to 30%,[11–15] respectively. These variations may have been influenced by different elements, such as study design, conduction setting (community or hospital), and/or the type and duration of anticoagulants used. The VTE events tend to recur in the presence of several predictors in individuals with a first VTE, including older age, male sex, obesity, site of index VTE, categorization of

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index VTE, history of VTE, family history of prior VTE, chronic heart disease, thrombophilia, inflammatory bowel disease, active cancer, and chronic heart disease.[3,7,12–19] The incidence rates, predictors of recurrence, and mortality after the first VTE among the Saudi population are unknown. To fill this knowledge gap, we conducted a cohort study to determine the incidence rates and to explore the predictors associated with recurrence and mortality events after the first VTE.

Methods

Study Design and Settings

A retrospective, single-center cohort study was conducted from January 2016 to December 2019 at King Abdulaziz Medical City (KAMC), a tertiary care hospital, Riyadh, Saudi Arabia. All adult patients with a confirmed first VTE (ie, those with DVT, PE, or both) were followed up for 36 months. The study was approved by the institutional review board at King Abdullah International Medical Research Center.

Identification of Participants

All adult patients aged ≥18 years with a first episode of VTE were identified using the BestCare system, an electronic medical record database, during the study period. Hospital admissions, outpatient clinic visits, and radiology databases were searched at KAMC to identify all patients diagnosed with symptomatic VTE confirmed objectively (by computed tomography scan for PE and Doppler ultrasound for DVT).

Trained personnel validated all VTE cases based on the presence of all the following inclusion criteria: (a) patients aged ≥18 years; (b) primary physician had made a diagnosis of VTE in the electronic database system; (c) presence of symptomatic VTE; (d) VTE confirmed objectively; (e) therapeutic dose of parenteral (heparin or low-molecular-weight heparin) or oral (warfarin, apixaban, rivaroxaban, or dabigatran) anticoagulants had been received by the patient for a minimum of 3 months. Patients who did not fulfill the inclusion criteria were excluded. The exclusion criteria includes: (a) pediatric patients <18 years old; (b) Patients with no valid confirmation methods of VTE neither clinically nor diagnosed objectively; (c) patients who received anticoagulants as VTE prophylaxis and not as therapeutic dose. The following baseline characteristics for all VTE cases were recorded: age, sex, body mass index (BMI), obesity (defined as BMI ≥ 30 kg/m^2), site of index VTE, categorization of index VTE, medical and surgical history, laboratory findings, current medications, and initial parenteral and/or oral anticoagulants used. VTE was classified based on the occurrence site as PE ± DVT, proximal DVT± distal DVT, and isolated DVT. Furthermore, VTE was categorized into cancer-related, provoked, or unprovoked. VTE in patients with active cancer, regardless of a provoking factor's presence, was considered cancer-related VTE. VTE events can be classified as provoked or unprovoked, based on the guidelines published by the Scientific and Standardization Committees on Control of Anticoagulation and on Predictive Variables of the International Society of Thrombosis and Haemostasis (ISTH).[20]

Risk factors for provoked VTE are either transient major risk factors (ie, major surgery >30 minutes, hospitalization or immobility ≥3 days, Cesarean section), transient minor risk factors (minor surgery <30 minutes, hospitalization <3 days, pregnancy, estrogen therapy, reduced mobility ≥3 days), or persistent risk factors. Unprovoked VTE was considered in the presence of Factor V Leiden, prothrombin G20210A mutation, and the absence of cancer or provoking factors. The study outcomes include the occurrence of recurrent VTE after the first event was defined as new or recurrent VTE using the same identification and inclusion criteria. In patients with suspected recurrent VTE, the American Society of Hematology (ASH) guideline panel recommends starting with a d-dimer assay with a low and intermediate pretest probability, if the d-dimer results are negative (less than 0.50), no further testing or treatment is required.[21] For positive d-dimer results (0.50 or greater), it should be followed by CT angiography or VQ scan in PE and Doppler ultrasonography in DVT.[21] In patients with a high pretest probability CT angiography/VQ scan and Doppler ultrasonography are recommended as the initial choice of study.[21] Death was recorded during the study period. We also assessed the presence of bleeding and classified bleeding into major or minor using the guidelines of major bleeding published by the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis.[22] Major bleeding was considered when bleeding was fatal, or bleeding was

symptomatic in a critical area or organ, and/or hemoglobin level decreased by ≥20 g/L or more, or when a patient received two or more units of packed red blood cells.[22]

Data Analysis

We compared baseline characteristics among patients with and without recurrence of VTE using the Chi-square test and the nonparametric Wilcoxon rank sum test as appropriate. We estimated the median time of recurrent VTE by categorization type (provoked, unprovoked, and cancer-related) of the index VTE event using Kaplan–Meier curves and compared groups using the Log rank test. We also estimated the median time of death by categorization type (provoked, unprovoked, and cancer-related) of the index VTE event using Kaplan–Meier curves and compared groups using the Log rank test. We explored the association between predictors and the time to a VTE recurrence and death using Cox regression models. The method yields hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). All recruited patients were censored at time of recurrent events, death, or end of follow-up period. All analyses were completed using Statistical Package for Social Science (SPSS) software (USA, version 26).

Results

Patient Sample and Characteristics

During the study period, out of 1265 identified patients with first VTE, 141 patients did not fulfill the inclusion criteria and were excluded (Figure 1). The final assessed numbers of the first VTE incident were 1124 patients. The mean age was 63.7 ± 20.3 years, the proportion of women was 52.7%, and the proportion of obesity (≥30 kg/m^2) was 29.5%. Among patients with recurrent VTE, 72.9% of patients had PE ± DVT, and 23.4% had proximal DVT ± distal DVT. The categorization of recurrent VTE events was 34.1% for cancer-related VTE, 56.6% for provoked, and 9.3% for unprovoked. Furthermore, obesity, ICU admission, previous hospitalization, systemic infection, and surgery± trauma were significantly higher in the recurrent group (Table 1).

Incidence

The cumulative incidence of first VTE during this study period was 1.7 per 1000 patients. Of the 1124 patients with a first VTE event, 214 patients had recurrent VTE during the follow-up period (median of 29 months; interquartile range (IQR), 21–36). The overall incidence rate of recurrent VTE was 15.8 (95% CI, 13.8–18.0) per 100 person-years (PY).

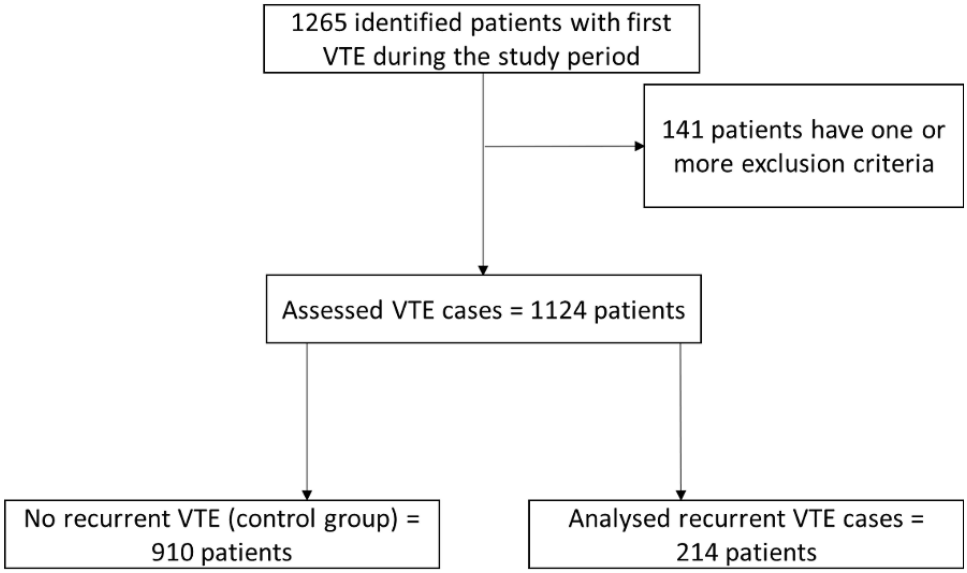

Figure 1 Flow chart of the study population. A total of 1265 patients were identified with first VTE, 141 patients did not fulfill the inclusion criteria and were excluded. The final assessed numbers of the first VTE incident were 1124 patients. Of which 910 patients with no recurrent VTE (control group) and 214 patients with recurrent VTE.

Table 1 Patient Demographic Characteristics

Variables	Recurrent VTE N=214	No Recurrent VTE N=910	P-value
Age, years, mean (±SD)	63.3 (±19.8)	63.9 (±20.4)	0.689
Sex, no (%) Male Female	 92 (43.0) 122 (57.0)	 440 (48.8) 470 (51.6)	0.158
BMI, mean(±SD)	28.9 (±8.7)	28.5 (±8.5)	0.531
Site of index VTE, no. (%)			0.001
Isolated distal DVT	8 (3.7)	60 (6.6)	
Proximal DVT ± distal DVT	50 (23.4)	309 (34.8)	
PE ± DVT	156 (72.9)	533 (58.6)	
Categorization of index VTE, no. (%)			<0.001
Cancer-related VTE	73 (34.1)	140 (15.4)	
Provoked	121 (56.5)	672 (73.8)	
Unprovoked	20 (9.3)	98 (10.8)	
Risk factors, no. (%)			
ICU admission	98 (45.8)	31 (3.4)	<0.001
Central venous catheter	55 (25.7)	191 (21.0)	0.134
Obesity	77 (36.0)	255 (28.0)	0.022
Immobilization	81 (37.9)	210 (23.1)	<0.001
Previous hospitalization	109 (50.9)	327 (35.9)	<0.001
Infection	62 (29.0)	86 (9.5)	<0.001
Family history	6 (3.1)	19 (2.3)	0.551
Surgery ± trauma	88 (41.1)	277 (30.4)	0.003
Co-morbidities, no (%)			
Hypertension	117 (54.7)	517 (56.8)	0.570
Diabetes mellitus	89 (41.6)	423 (46.5)	0.196
Hyperlipidemia	30 (14.0)	105 (11.5)	0.315
Heart failure	42 (19.6)	144 (15.8)	0.178
Chronic kidney disease	33 (15.4)	109 (12.0)	0.173
Thyroid disease	20 (9.3)	114 (12.5)	0.195
Initial treatment, no. (%)			0.540
Enoxaparin	105 (49.1)	413 (45.4)	
Unfractionated heparin	67 (31.3)	297 (32.6)	
NOACs	60 (28.0)	286 (31.4)	
Warfarin	83 (38.8)	310 (34.1)	

(*Continued*)

Table 1 (Continued).

Variables	Recurrent VTE N=214	No Recurrent VTE N=910	P-value
Labs, mean(±SD)			
Hemoglobin (g/L)	112.9 (±25.6)	113.7 (±24.6)	0.707
Serum creatinine (mmol/L)	110.5 (±114.1)	108.5 (±125.7)	0.828
Serum albumin (g/L)	32.5 (±6.6)	31.8 (±6.7)	0.246
Bleeding, no (%)	53 (24.8)	196 (21.5)	0.306
Death, no (%)	71 (33.2)	121 (13.3)	<0.001

Furthermore, the incidence rates of recurrent VTE per 100 PY were 26.5 (95% CI, 21.0–33.3) in cancer-related VTE, 12.8 (95% CI, 10.7–15.3) in provoked VTE, and 14.5 (95% CI, 9.4–22.4) in unprovoked VTE. The highest incidence rate of recurrent VTE was observed during the first 3 months of follow-up (19.0 per 100 PY, 95% CI 16.8–21.4). Using Kaplan–Meier, the estimated recurrence median time (months) was significantly lower in cancer-related VTE (18.7 months) compared to provoked (29.0 months) and unprovoked VTE (28.4 months, $p < 0.001$ by the Log rank test; Figure 2).

Of the 1124 patients with a first VTE event, 192 died during the study period. There were 71 (33.2%) deaths in the 214 recurrent group patients and 121 (13.3%) deaths among the 910 patients with nonrecurrent VTE ($p<0.001$). The overall mortality rate was 10.0 per 100 PY (95% CI, 8.7–11.5). The mortality rate in cancer-related VTE patients was 16.4 per 100 PY (95% CI, 12.6–21.3), 7.8 per 100 PY (95% CI, 6.5–9.3) in provoked VTE, and 8.8 per 100 PY (95% CI, 5.6–13.9) in unprovoked VTE. The estimated survival median time was significantly lower in cancer-related VTE (21.8 months) compared to provoked (30.5 months) and unprovoked VTE (29.8 months, $p < 0.001$ by the Log rank test; Figure 3).

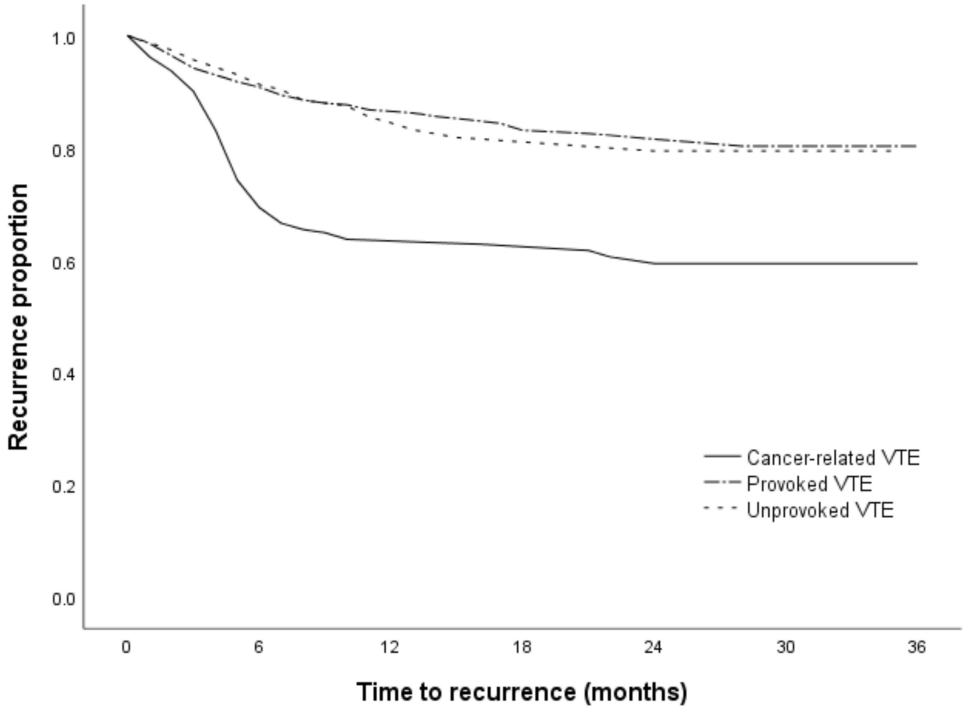

Figure 2 Kaplan–Meier venous thromboembolism (VTE) recurrence probabilities curve by categorization of the index events. The estimate recurrence median time was significantly lower in cancer-related VTE (18.7 months) than provoked (29.0 months) and unprovoked VTE (28.4 months, p<0.001 by the Log rank test).

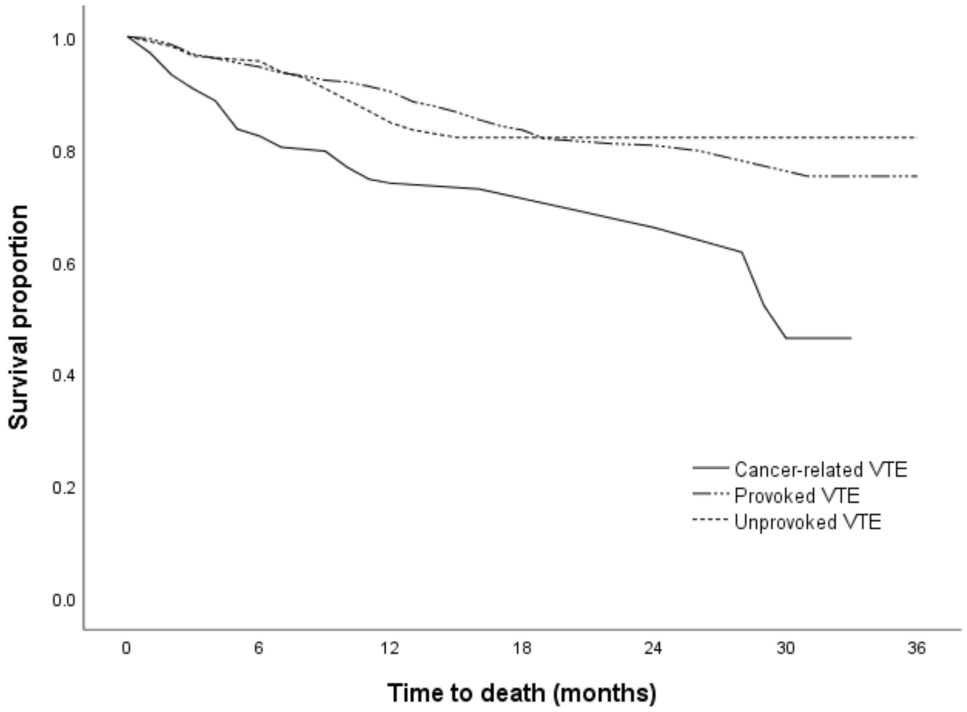

Figure 3 Kaplan–Meier venous thromboembolism (VTE) mortality probabilities curve by categorization of the index events. The estimate survival median time was significantly lower in cancer-related VTE (21.8 months) than in provoked VTE (30.5 months) and unprovoked VTE (29.8 months, p<0.001 by the Log rank test).

Predictors Associated with Recurrent VTE

Univariate cox regression analysis demonstrated significant differences in eight variables of patients with recurrent VTE: admission to ICU (p<0.001), active cancer (p<0.001), immobilization (p<0.001), infection (p<0.001), PE± DVT (p<0.001), previous hospitalization (p<0.001), obesity (p=0.021), and surgery ± trauma (p = 0.002). The eight variables were further used for multivariate cox regression analysis to identify significant predictors associated with recurrent VTE (Table 2). Five out of eight variables were found to be independently associated with recurrent VTE: admission to ICU (hazard ratio (HR), 2.15; 95% confidence interval (CI), 1.67–3.10; (p<0.001)), active cancer (HR, 2.97; 95% CI, 1.87–3.95; p<0.001), immobilization (HR, 2.52; 95% CI, 1.79–3.67; p < 0.001), infection (HR, 2.32; 95% CI, 1.94–3.45;

Table 2 Univariate and Multivariate Cox Regression for Risk Factors Associated with Recurrent VTE[a]

Variables	Univariate		Multivariate	
	HR[b] (95% CI[c])	P value	HR (95% CI)	P value
Admission to ICU[d]	3.62 (2.56–5.32)	<0.001	2.15 (1.67–3.10)	<0.001
Active cancer	2.92 (2.20–3.88)	<0.001	2.97 (1.87–3.95)	<0.001
Immobilization	2.83 (2.06–3.88)	<0.001	2.52 (1.79–3.67)	<0.001
Infection	3.16 (2.35–4.25)	<0.001	2.32 (1.94–3.45)	<0.001
PE[e] ± DVT[f]	1.81 (1.34–2.44)	<0.001	2.22 (1.56–3.16)	<0.001
Previous hospitalization	1.94 (1.48–2.54)	<0.001	1.05 (0.84–1.31)	0.694
Obesity	1.39 (1.05–1.83)	0.021	1.18 (0.88–1.58)	0.260
Surgery ± trauma	1.55 (1.18–2.04)	0.002	1.26 (0.93–1.71)	0.139

Notes: [a]Venous thromboembolism; [b]Hazard ratio; [c]Confidence interval; [d]Intensive care unit; [e]Pulmonary embolism; [f]Deep vein thrombosis.

Table 3 Univariate and Multivariate Cox Regression for Predictors Associated with Mortality

Variables	Univariate		Multivariate	
	HR[a] (95% CI[b])	P value	HR (95% CI)	P value
Admission to ICU[c]	1.87 (1.26–2.79)	0.002	1.53 (0.97–2.43)	0.075
Active cancer	2.30 (1.68–3.14)	<0.001	1.89 (1.37–2.61)	0.001
Immobilization	1.79 (1.36–2.84)	0.007	1.31 (0.83–1.94)	0.110
Infection	1.81 (1.25–2.61)	0.002	1.35 (0.92–1.99)	0.128
Obesity	1.65 (1.15–2.35)	0.006	1.86 (1.16–2.15)	0.001
Recurrent VTE[d]	4.60 (3.36–6.28)	<0.001	5.21 (3.61–7.51)	<0.001

Notes: [a]Hazard ratio; [b]Confidence interval; [c]Intensive care unit; [d]Venous thromboembolism.

p<0.001), and PE± DVT (HR, 2.22; 95% CI, 1.56–3.16; p < 0.001). Among 62 recurrent VTE patients with infections, respiratory tract infection was reported in 48 (77%) cases.

Predictors Associated with Mortality

All death cases during the follow-up period were evaluated using a univariate cox regression model. The analysis demonstrated significant differences in six predictors: admission to ICU (p=0.002), active cancer (p<0.001), immobilization (p=0.007), infection (p=0.002), obesity (p=0.006), and recurrent VTE (p<0.001). Further analysis using multivariate cox regression was performed to identify significant predictors associated with death (Table 3). Three out of the six predictors were found to be independently associated with death: active cancer (HR, 1.89; 95% CI, 1.37–2.61; p=0.001), obesity (HR, 1.86; 95% CI, 1.16–2.15; p=0.010), and recurrent VTE (HR, 5.21; 95% CI, 3.61–7.51; p<0.001).

Discussion

In this cohort study, the cumulative incidence of first VTE was 1.7 per 1000 patients. The overall incidence rate of recurrent VTE was 15.8 (95% CI, 13.8–18.0) per 100 person-years. The incidence rate of recurrent VTE was higher among cancer patients (26.5 per 100 person-years) than provoked (12.8 per 100 person-years) and unprovoked VTE patients (14.5 per 100 person-years). The highest incidence rate of recurrent VTE was observed during the first 3 months of the follow-up period (19.0 per 100 person-years). Furthermore, the median time for active cancer patients with first VTE to develop recurrent VTE was significantly shorter (21.8 months) than in provoked (30.5 months) and unprovoked VTE (29.8 months). The overall mortality rate after the first VTE was 10.0 per 100 person-years.

A Norwegian population-based study of 710 patients with a first incident of objectively confirmed VTE recruited between 1994 and 2012.[23] The overall VTE recurrence rate in that study was lower (7.8 per 100 PY) than that reported in our study (15.8 per 100 PY). The reported overall mortality rate of the study was higher (29.9 per 100 PY) than that found in our study (10.0 per 100 PY). In a recent Saudi prospective cohort study by Aleidan of elderly patients, the 12 month follow-up incidence of recurrence was slightly lower (12.8 per 100 PY) than our current cohort study (15.8 per 100 PY). The author also reported a lower mortality rate than what we found in this study.[3] Furthermore, a meta-analysis that included 29 studies from 1980 to 2019 reported recurrent VTE and a mortality rate of 23.7 (95% CI, 20.1–27.8) and 1.9 (95% CI, 0.8–4.0) per 100 PY, respectively.[24] The outcome variations of the first VTE may be influenced by the long-term follow-up, introduction of new guidelines, novel treatment modalities, and increased awareness among treating clinicians as well as patients.[21,25,26]

In line with previous reports,[23,27–30] the independent predictors of recurrence in our study were active cancer, immobilization, infection, PE ± DVT, and admission to ICU. Patients with cancer-related VTE were reported among those with the highest risk of VTE recurrence, with a range of 2- to 9-fold increased risk compared to non-cancer

patients. Chee et al reported that patients with active cancer-associated VTE had a significantly increased risk of recurrent VTE: threefold compared to patients without cancer.[28] In a cohort study of 543 patients, where a prediction score of VTE recurrence was developed, authors found a higher risk of recurrence among cancer-associated VTE patients with a score of ≥1.[30] The potential risk of immobilization for recurrent VTE was well documented in previous studies.[28–33] In 2007, Prandoni et al reported that recurrent VTE developed in 6 of the 55 patients (10.9%) with immobility, compared to 11 of the 322 (3.4%) ambulant patients, leading to a relative risk of 2.9 (95% CI: 1.2–7.5).[33] Information on the thrombogenic effect of infection in the literature is very limited. In a retrospective Australian study, authors found that non-surgical infection was associated with a high risk of recurrent VTE.[34] In another cohort study, authors from the Netherlands observed a high risk of VTE recurrence in patients with HIV infection with a hazard of 1.67-fold compared to the control group.[35] According to our data, patients with a first PE ± DVT had a 2.2-fold higher hazard of recurrence than those with a first proximal ± distal DVT. The site of the first VTE appears to be important, with PE recurring more often than DVT.[36] In previous reports, patients with a first PE were 1.4 to 2.4 folds more likely to develop a second PE rather than a DVT.[23,37]

In patients with recurrent VTE, obesity and active cancer were independent predictors for mortality in our study. Patients in this study who developed recurrent VTE had a 5.2-fold higher hazard of death compared to patients with no VTE recurrence during the follow-up period. Similarly, in a previous Saudi study, the author found that patients who experienced a VTE recurrence had a 6.2-fold higher risk of death compared to patients without VTE recurrence.[3] Likewise, the study by Yamashita et al[38] found that recurrent VTE was strongly associated with a subsequent mortality hazard 3.2-fold higher in patients with recurrent VTE compared to individuals without recurrent VTE. Obese patients are at increased hazard of death by 1.9-fold compared to non-obese patients. Furthermore, obesity is associated with immobility, raised intra-abdominal pressure, a chronic low-grade inflammatory state, impaired fibrinolysis, high levels of fibrinogen, von Willebrand factor, and factor VIII levels.[39,40] When these factors combine, they lead to a prothrombotic state and elevate the risk of recurrent VTE, and subsequently increase the mortality rate. Our study showed that the hazard of death in cancer patients with VTE was 1.9-fold higher than individuals who had no cancer.

This is one of the few studies conducted in the Kingdom of Saudi Arabia that measures the incidence of VTE, VTE recurrence, and predictors for recurrence in Arab countries. This study had a relatively large sample size that likely led to accurate outcomes. We precisely distinguished proximal/distal DVT and provoked or unprovoked VTE, which cannot be seen in other research papers pertaining to VTE. Our study is valuable and inclusive as it also presents cancer-associated VTE that was rarely mentioned in any other study. Despite these strengths, our study has several potential limitations. First, all data were gathered from the BestCare database only, and this makes the results incomplete. Second, certain variables, ie, smoking status, alcohol use, oral contraceptive pill use, inferior vena cava filter (IVC) implantation, D-dimer values, and Caprini scores were missing at the time of diagnosis and during follow-up. Third, our study was a retrospective study performed in a single center, which hinders the generalizability of our findings. Therefore, a prospective study would definitely be necessary to evaluate our findings. Fourth, we could not evaluate anticoagulant agents, since there was no standard regimen used. Lastly, the study did not assess if the exact cause of death was VTE-related and was also limited by the absence of autopsy data.

Conclusion

The study found that the incidence of recurrent VTE was 15.8 per 100 person-year. Predictors for recurrence were active cancer, immobilization, infection, PE ± DVT, and ICU admission. Also, predictors associated with death were active cancer, obesity, and recurrent VTE. The study also compared hazard of death between patients who had VTE recurrence with patients with no recurrence, and found that patients with recurrent VTE had a 5.2-fold higher hazard of death.

Data Sharing Statement

The data used for this research are available from the corresponding author upon reasonable request and are subject to Institutional Review Board guidelines.

Ethical Approval and Consent to Participation

This study was approved by the Institutional Review Board, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, National Guard Health Affairs, and informed consent was waived. 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.

Acknowledgment

The abstract of this paper was submitted to the GTH 2022 conference during the submission period; however, the abstract wasn't presented as none of the authors were able to travel to present the study due to COVID-19 pandemic and the participation of the study was withdrawn from the conference.

Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, and analysis and interpretation of data; all authors took part in drafting the article and in revising it critically for important intellectual content; all authors agreed to submit to the current journal; all authors gave final approval of the version to be published; all authors agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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