Incidence, Risk Factors, Risk Assessment Model and Compliance of Patients on Anticoagulants for Asymptomatic Venous Thromboembolism in Nononcological Urological Inpatients

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Purpose: To study the incidence, risk factors for developing asymptomatic venous thromboembolism and the compliance of patients on anticoagulants for asymptomatic venous thromboembolism (VTE) in nononcological urological medium-high risk inpatients, and build a risk assessment model (RAM) for early screening for asymptomatic VTE.

Materials and Methods: We conducted a retrospective analysis of 573 inpatients admitted to a nononcological urological ward of a tertiary hospital in China from January 1, 2017, to June 30, 2019. Data were collected using the electronic medical record system, and patients underwent a follow-up by phone 6 months after discharge.

Results: Among the 573 medium-high risk inpatients, 73 (15.4%) were diagnosed with VTE, including 20 (4.2%) symptomatic and 53 (11.2%) asymptomatic. Prior history of VTE, a history of anticoagulants or antiplatelet agents before admission, and D-dimer ≥ 1 were the potential risk factors identified for asymptomatic VTE. Patients with poor awareness of VTE and its dangers, and patients who lived more than 1 hour away from the hospital had a high probability of poor compliance with anticoagulation therapy after discharge. Using D-dimer (1.785 μg/ml), we built a RAM for the early diagnosis of asymptomatic VTE.

Conclusion: We found that patients with urinary nontumor VTE had low compliance with anticoagulation therapy after discharge. The key factors for determining asymptomatic VTE in nononcological urological inpatients included prior history of VTE, a history of taking anticoagulants or anti-platelet agents before admission, and D-dimer ≥ 1. Furthermore, we found that the threshold of D-dimer should be elevated to 1.785 μg/ml to predict asymptomatic VTE.

Keywords: asymptomatic; nononcological; compliance; risk assessment model; urology; venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE), which denotes both pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common cause of morbidity and mortality after urological surgeries. VTE was a particularly common problem in the past, with an estimated 22% incidence rate due to no prophylaxis for patients who underwent pelvic surgeries[1]. Although the occurrence of VTE has decreased in recent years, including for both uro-oncologic and nononcological surgeries[2,3], VTE is still a serious perioperative adverse event. Furthermore, it places a heavy burden on the healthcare systems and brings about higher mortality with potentially fatal PE.

VTE can be either symptomatic or asymptomatic, with the former often being much easier for clinicians to identify. Asymptomatic VTE can also cause fatal PE and it is associated with an increased risk in all-cause mortality[4]. The European Association of Urology (EAU) and the Canadian Urological Association (CUA) recommend providing perioperative thromboprophylaxis for both symptomatic and asymptomatic VTE[5,6]. However, the evidence grades in these guidelines are relatively weak, for example, in EAU guidelines, the recommended levels of prophylaxis for many urological nontumor surgeries are weak, including transurethral resection of the prostate (TURP), prostatectomy, laparoscopic without pelvic lymph node dissection (PLND), nephrectomy, and reconstructive pelvic surgery et al[6]. And whether thromboprophylaxis for asymptomatic VTE can balance thrombosis prevention and bleeding remains uncertain[7]. Although the Caprini risk assessment tool is recommended to evaluate the occurrence of postoperative VTE[8], a high proportion of patients after urological surgeries are still classified into the high-risk group. This suggests that the validity of this evaluation model is open to question. One way we felt this issue could be overcome was by building a risk assessment model (RAM) for VTE.

In recent years, urologists have paid increasing attention to the occurrence and prevention of perioperative

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Table1. Comparison between inpatients with asymptomatic and symptomatic VTE

Characteristics	Asymptomatic VTE	Symptomatic VTE	*P*-value
Age (years)	65.53 ± 10.08	59.00 ± 12.61	.024*
≤ 65	28 (52.8%)	12 (60.0%)	
≥ 66	25 (47.2%)	8 (40.0%)	
Gender			.977
Male	32 (60.4%)	12 (60.0%)	
Female	21 (39.6%)	8 (40.0%)	
BMI(kg/m^2)	22.64 ± 2.79	23.25 ± 3.18	.462
≤ 18.5	3 (5.7%)	1 (5.0%)	
18.5-23.9	33 (62.3%)	8 (40.0%)	
≥ 23.9	17 (32.1%)	11 (55.0%)	
D-Dimer (μg/mL, max)	2.34 (1.23-3.53)#	6.68 ± 9.81	.829
Caprini score(max)	5.87 ± 2.21	6.15 ± 4.74	.800
ASA score	3.00 (2.00-3.00)#	2.77 ± 0.93	.886
Operation time(min)	87.88 ± 49.49	81.38 ± 59.52	.721
Intraoperative blood loss (ml)	20.00 (5.00-100.00)#	44.46 ± 81.96	.266

Abbreviations: VTE, venous thromboembolism; BMI, body mass index; ASA, American society of Aneshesiologists physical status classification system
#Median and interquartile range
*Statistically significant (α = 0.05)

VTE. However, noncancer urological patients have still not received much attention from urologists. The incidence of VTE after urological nononcological surgeries is considered to be relatively low, but the results of our prior study and other research have contradicted this idea[9,10]. The main urinary system nononcological diseases are urinary stones, benign prostate hyperplasia, ureteral stricture, varicocele, renal cyst, urethral stricture, stress urinary incontinence, and others. Although physical and drug therapies to prevent thrombosis are conducted across the globe, VTE-related mortality after urological nononcological surgery remains a concern. Moreover, few studies have focused on asymptomatic VTE in urological nononcological hospitalized patients, and thus this issue remains unresolved for nononcological urologists.

At present, most research on VTE compliance focuses on the prevention of postoperative thrombosis in non-urologic patients. For example, a prior compliance study compared the benefits of using either preventive anticoagulants with those from using mechanical methods to prevent VTE after gynecological tumor surgery and total hip and knee replacement surgery[11-13]. However, there are few relevant studies on the compliance of VTE anticoagulation therapy after discharge, especially in patients with non-tumor VTE in the urology department. When evaluating the effect of anticoagulant therapy, we feel it is important to understand the patient's compliance with anticoagulant therapy.

For this reason, the main aim of our preliminary study was to retrospectively investigate the incidence rates, risk factors, and compliance of nononcological inpatients in urology. Using these data, we then established a RAM for the screening of asymptomatic VTE by using the appropriate threshold of D-dimer.

MATERIALS AND METHODS

Study Population

This was a retrospective, single-center, cohort study approved by the Ethics Committee of Xiangya Hospital (no. 2019030078). Consecutive inpatients who were admitted to the nononcological urological unit and who underwent diagnostic imaging (including computed tomography, pulmonary angiography and ultrasound) be-

Table 2. Baseline characteristics associated with asymptomatic VTE.

Characteristics	No. of Sample Size	Asymptomatic VTE N (%)	Asymptomatic VTE Incidence (%)	Univariate Analysis	Unadjustd OR (95%CI)
Total	553 (100.0%)	53 (100%)	9.6%		
Emergency Surgery					
No	520 (94.07%)	49 (92.4%)	9.4%	*P* = .545 #	1.0
Yes	33 (5.97%)	4 (7.6%)	12.1%	1.3 (0.4-3.9)	
Gender					
Male	350 (65.67%)	32 (60.38%)	9.1%	*P* = .643	1.0
Female	203 (34.33%)	21 (39.62%)	10.3%	1.1 (0.6-2.0)	
Age (years)					
≤ 65	375 (67.81%)	28 (52.83%)	7.5%	*P* = .014	1.0
≥ 66	178 (32.19%)	25 (47.17%)	14.0%	2.0 (1.1-3.6) *	
BMI (kg/m^2)					
18.5-23.9	304 (54.97%)	37 (69.81%)	10.5%	*P* = .182#	1.0
≥24	38 (6.87%)	4 (7.55%)	12.2%	0.8 (0.3-2.5)	
24-27.9	133 (24.05%)	9 (16.98%)	6.8%	0.5 (0.2-1.1)	
≥28	64 (11.57%)	3 (5.66%)	4.7%	0.4 (0.1-1.2)	
35-39.9	14 (2.53%)	0	0%		

Abbreviations: VTE, venous thromboembolism; OR, odds ratios; BMI, body mass index.
*Statistically significant (α = 0.05)
Fisher's exact test

Table 3. Characteristics of medical history associated with asymptomatic VTE.

Characteristics	No. of Sample Size	Asymptomatic VTE N (%)	Asymptomatic VTE Incidence (%)	Univariate Analysis	Unadjustd OR (95% CI)
Hypertension					
No	368 (66.55%)	18 (33.96%)	9.5%	*P* = .934	1.0
Yes	185 (33.45%)	18 (33.96%)	9.7%	1.0 (0.6-1.9)	
Diabetes					
No	493 (89.15%)	4 (7.55%)	9.9%	*P* = .416	1.0
Yes	60 (10.85%)	4 (7.55%)	6.7%	0.6 (0.2-1.9)	
Prior VTE					
No	524 (95.30%)	13 (24.53%)	7.6%	*P* < .001#	1.0
Yes	29 (4.70%)	13 (24.53%)	44.8%	9.8(4.4-21.9) *	
Family history of VTE					
No	522 (94.39%)	3 (5.66%)	9.6%	*P* = 1.000#	1.0
Yes	31 (5.61%)	3 (5.66%)	9.7%	1.0 (0.3-3.4)	
History of varicose veins in the lower extremities					
No	534 (96.56%)	4 (7.55%)	9.2%	*P* = .099#	1.0
Yes	19 (3.44%)	4 (7.55%)	21.1%	2.6 (0.8-8.3)	
History of surgery within a month					
No	520 (94.03%)	6 (11.32%)	9.0%	*P* = .117 #	1.000
Yes	33 (5.97%)	6 (11.32%)	18.2%	2.2 (0.9-5.7)	
Anticoagulants or anti-platelet agents prescription before admission					
No	534 (96.56%)	6 (11.32%)	8.8%	*P* = .006#	1.0
Yes	19 (3.44%)	6 (11.32%)	31.6%	4.8(1.7-13.2) *	
COPD					
No	544 (98.37%)	1 (1.89%)	9.6%	*P* = .599 #	1.0
Yes	9 (1.63%)	1 (1.89%)	11.1%	1.2 (0.1-9.6)	
Coronary atherosclerotic heart disease					
No	517 (93.49%)	1 (1.89%)	10.1%	*P* = .238#	1.0
Yes	36 (6.51%)	1 (1.89%)	2.8%	0.3 (0.0-1.9)	
Other cardiovascular diseases					
No	529 (95.66%)	3 (5.66%)	9.5%	*P* = .494 #	1.0
Yes	24 (4.34%)	3 (5.66%)	12.5%	1.4 (0.4-4.8)	
Cancer history					
No	533 (896.38%)	2 (3.77%)	9.6%	*P* = 1.000 #	1.0
Yes	20 (3.62%)	2 (3.77%)	10.0%	1.1 (0.2-4.7)	
Cerebral stroke history					
No	525 (94.94%)	4 (7.55%)	9.3%	*P* = .331#	1.0
Yes	28 (5.06%)	1.6 (0.5-4.9)			

Abbreviations: VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; OR, odds ratios.
*Statistically significant ($\alpha = 0.05$)
Fisher's exact test

tween January 1, 2017, and June 30, 2019, at Xiangya Hospital were enrolled in our study.

Inclusion and exclusion criteria

Patients were regarded as medium-high risk inpatients and advised to finish diagnostic imaging if they had one or more of the following situations: over 75 years old, had prior VTE, a body mass index over 35 kg/m^2, a first degree relative (parent, full sibling, or child) with VTE, or a D-Dimer value over 0.5 μg/mL. For patients assessed as medium-high risk inpatients, we will perform D-Dimer examinations after admission and after surgery. Patients were excluded if they were younger than 18 years old, had postoperative pathological examination results that showed malignancy, or had incomplete clinical medical records. In total, 573 eligible inpatients were selected for the study (**Figure 1**).

Procedures

Asymptomatic VTE was defined when a hospitalized VTE patient displayed no VTE related symptoms (such as swelling and painful in the lower limbs, pain in lower limbs, decreased SpO_2, dyspnea, chest pain, or an electrocardiogram (ECG) performance with unstable circulation)[14]. Patients who were assessed with medium-high thrombosis risk inpatients underwent Doppler ultrasound examination of lower extremity blood vessels after admission and after surgery, and 25 postoperative patients underwent pulmonary artery CTA for the occurrence of suspicious symptoms of pulmonary embolism like difficulty breathing, chest pain, etc.

All the data were retrospectively collected from the Electronic Medical Record System (EMRS) and anesthetic records in Xiangya Hospital through each inpatient's unique ID number. In addition, the Caprini RAM was also collected and it was invented by Caprini et al. Caprini RAM is based on the risk of the risk factors to stratify the patients for VTE risk. For patients with a very low risk of VTE (Caprini score of 0), additional prevention is not recommended. For patients with low risk of VTE (Caprini score of 1-2), mechanical or drug prevention is recommended. Patients with intermediate risk of VTE (Caprini score of 3-4) to high risk (Caprini score of $\geq$ 5) are recommended for anticoagulant alone or combined with mechanical prevention[15]. The occurrence of VTE was detected by the imaging procedure reports, diagnosed by board-certified radiologists as well as the course records written by attending doctors. Preoperative bleeding was defined as hematuria, blood in the stool, and bleeding in other parts of the body.

Regardless of the size (massive or small) and location (proximal or distal) of the thrombus, once the VTE occurred in the deep veins of the lower extremities or the pulmonary artery and its branches, we considered that a VTE event had occured. The occurrence of sepsis was defined according to the Sepsis - 3 criteria and the calculation formula for creatinine clearance (Cock-

Table 4. Other related characteristics associated with asymptomatic VTE.

Characteristics	No. of Sample Size	Asymptomatic VTE N (%)	Incidence (%)	Univariate Analysis	Unadjustd OR (95% CI)
Preoperative bleeding					
No	521 (94.21%)	48 (90.57%)	9.2%	*P* = .218#	1.0
Yes	52 (5.79%)	5 (9.43%)	15.6%	1.8 (0.7-5.0)	
Preoperative sepsis					
No	526 (95.12%)	48 (90.57%)	9.1%	*P* = .167 #	1.0
Yes	27 (4.88%)	5 (9.43%)	18.5%	2.3 (0.8-6.2)	
Creatinine clearance levels (mL/min[a]		0.6(0.5-0.8)			
<15	45 (8.14%)	8 (15.09%)	17.8%	*p* = .001#	1.0
15-29	37 (6.69%)	5 (9.43%)	13.5%	0.7 (0.2-2.4)	
30-59	179 (32.37%)	24 (45.28%)	13.4%	0.7 (0.3-1.7)	
60-90	227 (41.05%)	16 (30.19%)	7.0%	0.4 (0.1-0.9) *	
D-Dimer (μg/mL,max)					2.1 (1.3-3.3) *
< 0.5	135 (24.41%)	6 (11.32%)	4.4%	p=.001#	1.0
0.5-1	104 (18.81%)	4 (7.55%)	3.8%	0.9 (0.2-3.1)	
≥1	314 (56.78%)	43 (81.13%)	13.7%	3.4 (1.4-8.2) *	
Caprini score, max					1.6 (0.9-2.7)
≤2	19 (3.44%)	2 (3.77%)	10.5%	*p* = .125 #	1.0
3-4	191 (34.54%)	12 (22.64%)	6.3%	0.6 (0.1-2.8)	
≥5	343 (62.02%)	39 (73.58%)	11.4%	1.1 (0.2-4.9)	
Re-admission surgery					
No	548 (99.10%)	52 (98.11%)	9.5%	*p* =.397#	1.0
Yes	5 (0.90%)	1 (1.89%)	20.0%	2.4 (0.3-21.7)	
Complications					
No	536 (96.93%)	50 (94.34%)	9.3%	*p* = .217#	1.0
Yes	17 (3.07%)	3 (5.66%)	17.6%	2.1 (0.6-7.5)	

Abbreviations: VTE, venous thromboembolism; OR, odds ratios.
a.Creatinine clearance levels were calculated with the use of the Cockcroft–Gault equation
*Statistically significant (α = 0.05)
Fisher's exact test

croft-Gault equation) was conducted based on creatinine levels[15,16].

At 6 months after discharge, we checked on each patients' thrombosis progression through a phone follow-up. If we were unable to follow-up with a patient after 3 consecutive days of attempts, they were excluded from our study.

Statistical Analysis

All statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA). Categorical variables were described using frequency and percentage while means and standard deviations were applied to the continuous variables. A chi-square testing and independent t test were used to assess the risk factors for asymptomatic VTE to compare asymptomatic and symptomatic VTE. The minimum expected cell frequency was accessed, and when the data did not meet Pearson's χ 2 test conditions ($E \geq 5$ and $n \geq 40$), Fisher exact test is used. The normality and homogeneity of variance were assessed, and median and interquartile range of variables with skewed distribution were reported. When the P-values were under 0.1 in the univariate analyses, the related factors were chosen to be evaluated by multivariable logistic regression analysis. A receiver operating characteristic (ROC) curve was plotted by referring to the sensitivity vs. 1 – specificity of D-dimer level. The areas under the curve (AUCs), cutoff value sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and Youden index were used to assess the prediction model in this study. A *P*-value of < .05 was considered to be statistically significant.

RESULTS

Of the 592 patients selected in the initial sample, 19 (3.2%) patients were excluded based on the exclusion criteria, leaving a total of 573 patients for our study. Among these patients, 73 (15.4%) were diagnosed with VTE, including 20 (4.2%) symptomatic VTE patients and 53(11.2%) asymptomatic patients. The diagnoses of the patients include urinary stones (305, 53.2%), benign prostate hyperplasia (58, 10.1%), benign adrenal

Table 5. Clinical factors associated with asymptomatic VTE based on multivariable logistic regression analysis

Variable	Characteristics	Adjusted OR aOR	95% CI	*p*-value
Age	58.69 ± 12.81	1.0	.9-1.0	.112
Prior VTE		10.0*	3.9-25.9	< .001
Anticoagulants or anti-platelet agents prescription before admission		4.2*	1.3-13.9	.019
Creatinine clearance levels (mL/min)a		63.91 ± 29.061.0*	1.0-1.1	.023
D-Dimer, (μg/mL,max)	2.65 ± 4.74	0.2*	.1-.4	< .001
History of varicose veins in the lower extremities		1.5	.4-5.7	.552

Abbreviations: VTE, venous thromboembolism; OR, odds ratios.
*Statistically significant (α = 0.05)
baseline level($p < 0.1$)

Table 6. Cross tabulation of D-Dimer to predict the occurrence of asymptomatic VTE

D-Dimer Prediction of Asymptomatic VTE(95% CI)		Observed Asymptomatic VTE (95% CI) No	Yes	Total
No	n	96	1	97
	% of predicted asymptomatic VTE	99.0% (99.5%-99.7%)	1.0% (0.3%-4.5%)	100.0%
	% of observed asymptomatic VTE	63.6% (57.8%-76.9%)	6.7% (3.0%-30.4%)	
	% of total patients	57.8% (52.6%-70.0%)	0.6% (0.3%-2.7%)	
Yes	n	55	14	69
	% of predicted asymptomatic VTE	79.7% (77.1%-85.0%)	20.3% (15.0%-22.9%)	100.0%
	% of observed asymptomatic VTE	36.4% (25.7%-40.6%)	93.3% (50.8%-99.7%)	
	% of total patients	33.1% (23.3%-36.9%)	8.4% (4.6%-9.6%)	
Total	n	151 15	166	
	% of observed asymptomatic VTE	100.0% 100.0%	100.0%	
	% of total patients	91.0% 9.0%	100.0%	

Abbreviations: VTE, venous thromboembolism.

tumor (39, 6.8%), ureteral stricture (24, 4.2%), varicocele (12, 2.1%), renal cyst (19, 3.3%), urethral stricture (10, 1.7%), stress urinary incontinence (15, 2.6%), others (91, 15.9%). When comparing the baseline characteristics between asymptomatic and symptomatic VTE, only age showed a significant difference, which suggested that asymptomatic VTE was more common in older inpatients (**Table1**).

Table 2 shows the patient characteristics associated with asymptomatic VTE. There is a statistically significant difference in age (adjusted odds ratio (OR) = 2.2, 95%CI: 1.1-3.6), with age ≥ 66 having a higher risk of asymptomatic VTE compared to those aged ≤ 65. **Table 3** shows the characteristics of medical history associated with asymptomatic with patients who had prior VTE (aOR = 9.8, 95%CI: 4.4-21.9) and who had received anticoagulant or antiplatelet agent use before admission (aOR = 4.8, 95%CI: 1.7-13.2) being more vulnerable to asymptomatic VTE.

Other characteristics which may contribute to asymptomatic VTE were also analyzed. **Table 4** shows creatinine clearance (aOR = 0.6, 95%CI: 0.5-0.9) to be a protective factor for asymptomatic VTE while D-Dimer (aOR = 2.1, 95%CI: 1.3-3.3) appears as a potential risk factor, with patients with D-Dimer ≥ 1 being significantly associated with a susceptibility toward asymptomatic VTE.

Multivariable logistic regression analysis was carried out to combine all the potential risk factors for asymptomatic VTE mentioned above (**Table 5**). The linearity for quantitative predictors was assessed, and the multicollinearity problem was avoided (.794, 95%CI: .741-.848). The AUC for the logistic regression model was calculated (**Figure 2**). Hosmer-Lemeshow goodness of fit test was used to evaluate the calibration ability of the prediction model. The results show that Hosmer-Lemeshow χ 2 =10.725, P = .218 > .05, suggesting that the difference between the predicted value of the model and the actual observed value is not statistically significant, and the prediction model has good calibration ability. Patients who experienced prior VTE (aOR = 11.3, 95%CI: 4.4-29.0), received anticoagulant

Table 7. Univariate analysis of compliance with anticoagulation therapy after discharge, good compliant group vs poor compliant group

Variable	OverallPopulation(n = 56)	Good Compliance (n =27)	Poor Compliance(n = 24)	*P* -value	OR Value
Level of education					
Grade school and illiteracy	17 (33.3%)	8	9	*P* = .91	1.0
Junior high school and technical secondary school	15 (29.4%)	8	7		1.9 (0.3-10.5)
High school	11 (21.6%)	6	5		1.5 (0.3-8.4)
Undergraduate and junior college	8 (15.7%)	5	3		1.4 (0.2-8.9)
Admission time					
2017/01/01-2017/12/31	8 (15.7%)	4	4	*P* =.235	1.0
2018/01/01-2018/12/31	22 (43.1%)	9	13		2.0 (0.4-10.5)
2019/01/01-2019/06/30	21 (41.2)	14	7		2.9 (0.8-10.0)
Understanding of VTE and its dangers					
Understand	37 (72.5%)	25	12	*P* = .001	1.0
Don't understand	14 (27.5%)	2	12		12.5 (2.4-64.9)*
Patient satisfaction with hospital treatment					
Satisfied	43 (84.3%)	24	19	*P* = .571	1.0
Not satisfied	8 (15.7%)	3	5		2.1 (0.5-10.0)
Self-rated general health					
Lower than average	4 (7.8%)	1	3	*P* = .256	1.0
Average	42 (82.4%)	22	20		0.3 (0.0-3.2)
Higher than average	5 (9.8%)	4	1		0.1 (0.0-2.0)
Time spending on the journey to the hospital					
< 1h	16 (31.4%)	12	4	*P* = .033	1.0
≥ 1h	35 (68.6%)	15	20		4.0 (1.1-14.9)*
Transportation to the hospital					
Car	31 (60.8%)	17	14	*P* = .622	1.0
Train	12 (23.5%)	5	7		1.4 (0.3-6.8)
Bus	8 (15.7%)	5	3		2.3 (0.4-14.6)

Abbreviations: VTE, venous thromboembolism; OR, odds ratios; PE, pulmonary embolism.
*Statistically significant (α = 0.05)

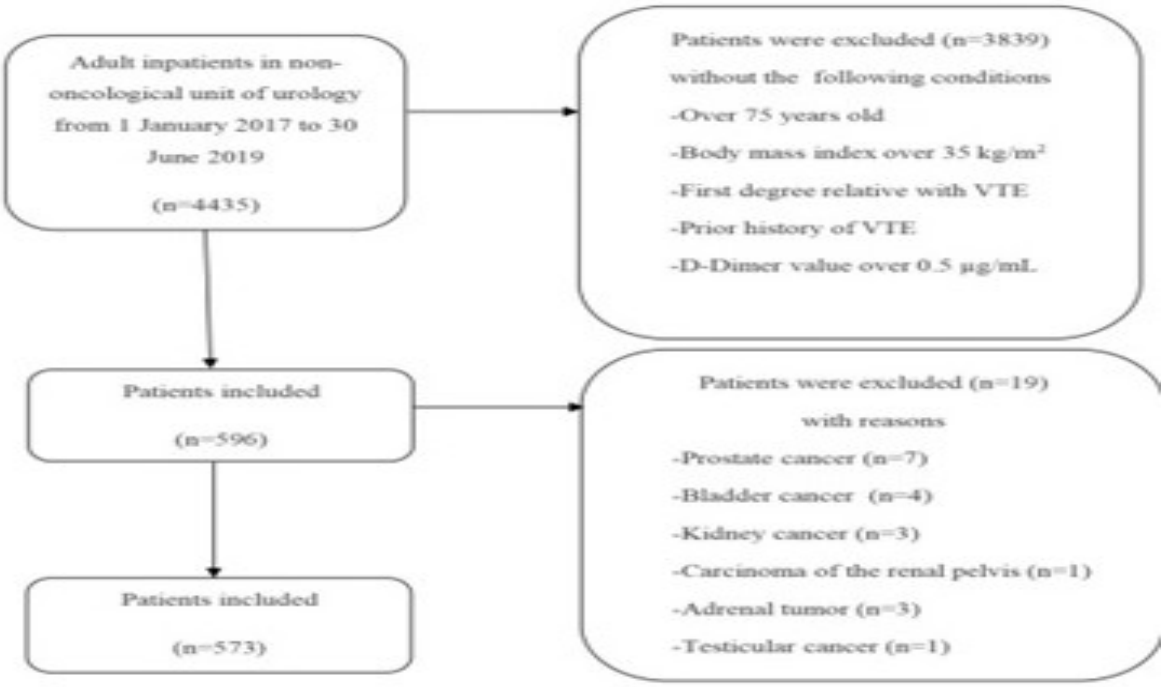

Figure 1. Flowchart of patient selection.

or antiplatelet agent use before admission (aOR = 4.5, 95%CI: 1.3-14.9) and had a D-Dimer ≥ 1 (aOR = 4.6, 95%CI: 1.55-13.5) had a positive association with a susceptibility towards asymptomatic VTE. Futhermore, a ROC curve was created to evaluate the ability of the D-Dimer value to discriminate between the symptomatic VTE and non-VTE patients (**Figure 3**). The AUCs for D-dimer diagnosis of thrombosis is .715 (95%CI: .634-.797). And the cut-off point of D-Dimer for the diagnosis of asymptomatic VTE (the threshold value of D-Dimer was determined when the sum of sensitivity and specificity was at its maximum) was 1.785. This means that patient who had a D-Dimer value ≥ 1.785 were asymptomatic VTE.

We further assessed the RAM by 4-fold cross-validation, and found its sensitivity was 93.3% (50.8%-99.7%), specificity is 63.6% (57.8%-76.9%), misdiagnosis rate is 36.4% (25.7%-40.6%); missed diagnosis

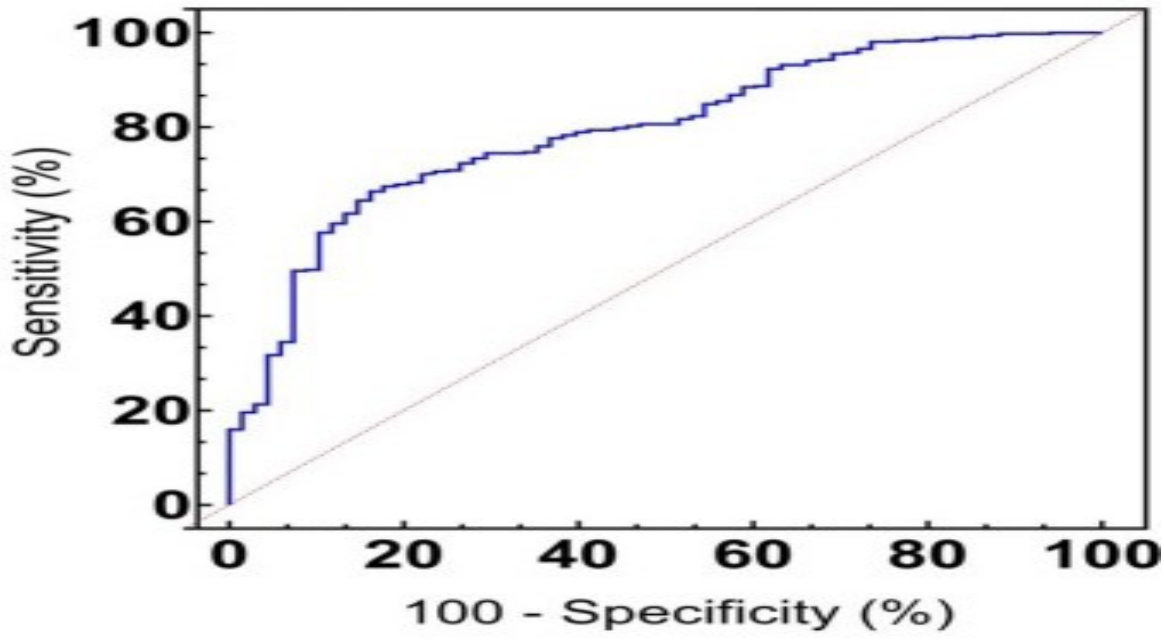

Figure 2. ROC curve analysis for the logistic regression model.

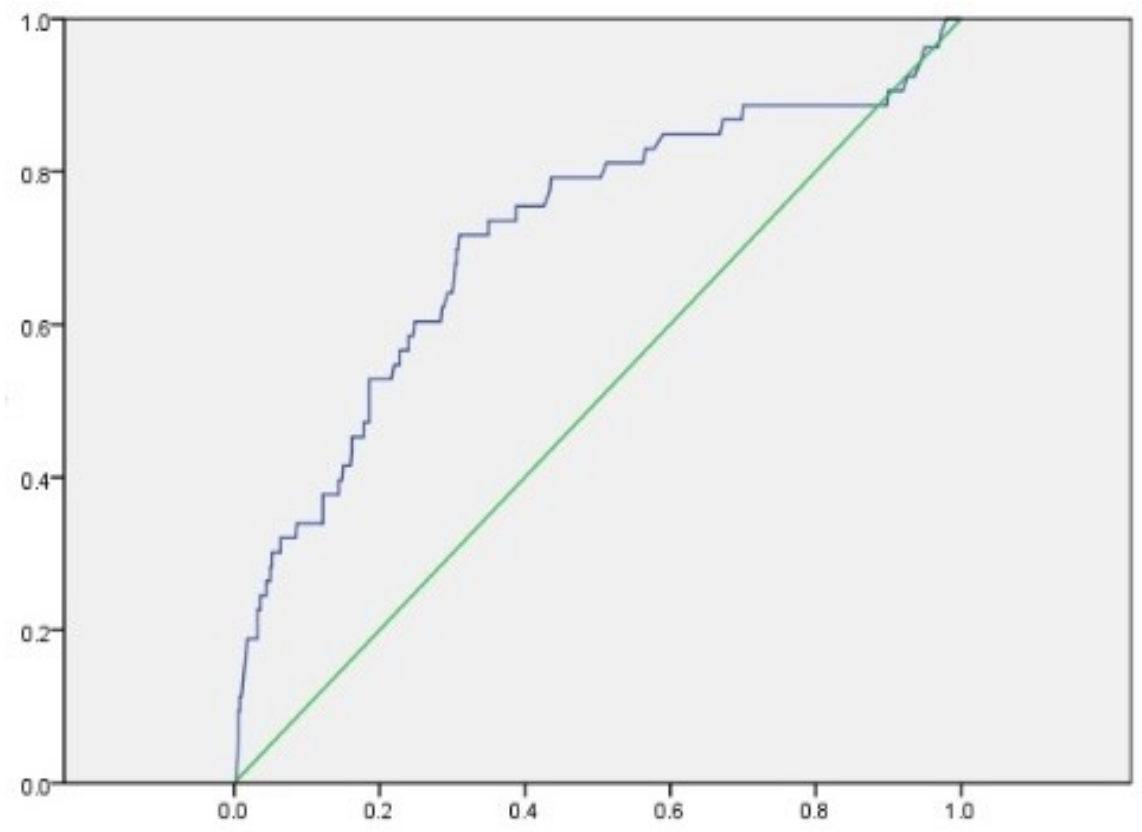

Figure 3. ROC curve analysis to evaluate the ability of D-Dimer
ROC = Receiver Operating Characteristic

rate is 6.7% (3.0%-30.4%), PPV is 20.3% (15.0%-22.9%), NPV is 99.0% (99.5%-99.7%), correct rate is 69.3% and Youden index is 40.7% (**Table 6**).

As for the compliance of anticoagulant medication for asymptomatic VTE, among the 53 patients, 2 were excluded due to contact being lost. After discharge from the hospital, a further 2 of these patients developed lower extremity pain, 1 patient developed lower extremity swelling, 1 patient had worsening hematuria (which improved 10 days after stopping rivaroxaban), and no patients developed dyspnea, chest pain, or other PE symptoms. The compliance of anticoagulant therapy after discharge was mainly evaluated as either "good" or "poor". Good compliance was defined if a patient took the anticoagulant drugs regularly and underwent re-examination at the vascular surgery clinic within the time specified by the doctor. Among 51 patients, 46 (90%) took rivaroxaban after discharge from hospital, 4 (8%) warfarin, and 1 (2%) aspirin. 27 patients (52.9%) had good compliance with anticoagulation therapy and 24 patients (47.1%) had poor compliance. From our univariate analysis, we found that patients with a poor awareness of VTE and its dangers (P = .001; 95%CI: 2.406-64.932), and patients who lived more than 1 hour away from the hospital (P = .033; 95%CI: 1.074-14.896), were more likely to have a poor compliance with anticoagulant therapy after discharge, the difference being statistically significant. (**Table 7**).

DISCUSSION

VTE is a serious complication during hospitalization, and its incidence of VTE in the nononcological unit of urology has still not received much attention, especially for asymptomatic VTE. We estimated the incidence and risk factors of asymptomatic VTE, and built an RAM for asymptomatic VTE in urological nononcological inpatients. Our results cast new light on the incidence of VTE in urological nononcological medium-high risk inpatients, with the RAM performing well and yielding good results.

Among the 573 inpatients who took part in our study, 73 (15.4%) were diagnosed with VTE, including 20 (4.2%) symptomatic and 53(11.2%) asymptomatic patients. We found that among asymptomatic VTE and symptomatic VTE patients, older patients were more likely to be asymptomatic (65.53 ± 10.08 vs 59.00 ± 12.61, P = .024). This result might be due to the low responsiveness and sensitivity of the older patients, or because the clinical manifestations were atypica,l hidden, or absent, and therefore could not truly reflect the condition.

A large number of clinical studies have shown that asymptomatic VTE remains common despite anticoagulant therapy[16]. For this reason, it is important to identify the risk factors associated with asymptomatic VTE to improve its early diagnosis. According to our multivariable logistic regression analysis, we found that prior VTE, administering anticoagulants or antiplatelet agents to patients before admission, or a D-dimer $\geq$ 1

were potential risk factors. Interestingly, older age was not a risk factor for asymptomatic VTE based on multivariable analysis even though age was independently associated with asymptomatic VTE in other studies[17]. Prior history of VTE is widely perceived to be a risk factor, regardless of whether it is symptomatic or asymptomati[18,19]. It is also easy to understand why administering anticoagulant or antiplatelet agent to paeitnes before admission is also a risk factor, as patients who need to take anticoagulants or antiplatelet agents are more vulnerable to VTE due to their hypercoagulable state of the blood. As for the D-dimer value, our results were similar to those of other studies, which found it to be significantly associated with asymptomatic VTE[20,21]. Interestingly, when D-dimer is considered to be a risk factor for asymptomatic VTE, its value is often higher than the prescribed abnormal value (0.5 μg/mL) (something to be discussed in more detail below). Furthermore, creatinine clearance levels between 60 and 90 mL/min were considered to be a protective factor for asymptomatic VTE patients, which is consistent with other research[22]. However, some OR estimates and confidence limits are inflated which suggesting sparse-data bias.The majority of data with missing or zero values are included in the data set. Quartile division or cutting off deletion value are used to modify proper data sets.

As far as we are concerned, there are no specific anticoagulation strategy in the current guidelines for urological nononcological asymptomatic VTE, and there are few randomized clinical trials evaluating the effectiveness and safety of anticoagulation for asymptomatic DVT. Yugo et al retrospectively evaluated 300 patients with asymptomatic lower extremity DVT and found that most asymptomatic DVT patients had undergone long-term anticoagulation therapy, due to the risk of major bleeding[23].

Our RAM assessed the risk of asymptomatic VTE was based on the D-dimer value, which was recommended to predict VTE in the guidelines of the American College of Chest Physicians[15]. D-dimer is produced during the endogenous fibrinolysis of blood clots and plays an important role in the diagnosis algorithm to rule out VTE. It is considered to be the best biomarker for the early screening of VTE due to its high sensitivity but does have a poor specificity, and thus false-positive D-dimer results may occasionally occur[24]. Balogun et al found that, a D-dimer cut-off point of 1660 ng/mL in the 48 hours following a stroke could effectively distinguish the asymptomatic VTE patients, with a diagnosis rate of 72% (13/18)[25]. This suggests D-dimer might be a sensitive predictor for asymptomatic VTE. In our study, we noticed that D-dimer $\geq$ 1 μg/mL was a risk factor for asymptomatic VTE, and that it might increase the likelihood of asymptomatic VTE by about 4.6 times. However, a D-dimer level < 1 μg/mL had no statistical difference when compared with a level < 0.5 μg/mL. In our RAM, the threshold value of D-Dimer was determined when the sum of sensitivity and specificity was at its maximum and the cut-off point was 1.785. The sensitivity of this RAM was 71.7%, specificity 69%, and NPV 95.8%. Other studies have used D-dimer to assess the risk of VTE. For instance, Shi et al. reported in a study of gynecologic malignancy inpatients that the D-dimer threshold needed to be raised to 1.5 μg/ml, with a sensitivity of 87.5%, a specificity 93.8%, and NPV 99.2% in patients with gynecologic malignancies[26]. Another study indicated that D-dimer $\geq$ 0.89 μg/mL might be more suitable for urological oncological patients, reporting a sensitivity of 83.9%, and a specificity of 80.0%[27].

Different groups of people have their own suitable cutoff values. Nevine et al stratified the D-dimer cutoff according to age, and found that sensitivity was compromised in patients older than 80 years[28]. Douma et al. defined a new D-dimer cutoff value as patient's age x 10 in patients aged > 50 years and greatly increased the proportion of older patients in whom PE could be safely excluded[29]. Our own aim was to build a RAM for the early detection of asymptomatic VTE in urological nononcological inpatients.

Our study found that only 27 (52.9%) patients with nontumor VTE in the urology department received anticoagulation therapy according to the requirements of the medical advice after discharge. This ratio was far lower than the ratio of good compliance with postoperative preventive anticoagulant therapy reported in other literature[12,30]. Among our 51 VTE patients, 14 (27.0%) patients did not understand what VTE was and what its dangers were. Combining the experience of clinical work and the analysis of data, we found that this was mainly due to 2 reasons.[1] Urinary nontumor patients, all were hospitalized because of urological diseases. During the hospitalization period, they were found to have VTE by accident. VTE was not the main reason for their visit.[2] Apart from 15.7% of patients had an undergraduate and junior college degree, with the education level of the remaining patients being low, limiting their understanding of the disease.

Our research also found that patients who spend more than 1 hour on the journey to hospital had poor compliance with re-examination at vascular surgery within the time specified by the doctor. This made the length of the journey an important indicator affecting patient compliance[12,30]. Long distances increase the cost of travel and require more time, reducing the willingness of patients to undergo re-examination. Furthermore, after visiting a higher-level hospital, patients were also unwilling to visit a lower-level hospital closer to their homes.

It is also important to mention that our study had certain limitations. First, it was a single-center, retrospective analysis, and retrospective bias might be present. Second, the study only enrolled urological nononcological inpatients admitted to hospital from January 1, 2017, to June 30, 2019, restricting the sample size through an insufficient time span. Third, VTE in some asymptomatic patients might have gone undetected due to the patients' normal D-dimer value or due to their being evaluated as low risk by the in-hospital VTE risk assessment team. Despite the above limitations, we were still able to use some risk factors, such as D-dimer, to build a RAM for the early screening of asymptomatic VTE.

CONCLUSIONS

We found that prior VTE, use of anticoagulants or antiplatelet agents before admission, or a D-dimer $\geq$ 1 were potential risk factors for the patients in our study. We also found that the more appropriate threshold of D-dimer (at least in Chinese urological nononcological inpatients) for asymptomatic VTE should be elevated to 1.785. In addition, patients with asymptomatic VTE

have low compliance with anticoagulation therapy after discharge. Urologists should strengthen hospitalization education, carry out targeted instructions, and follow-up regularly after discharge.

CONFLICT ON INTEREST

There are no conflicts of interest.

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