Original Article

A predictive model for postthrombotic syndrome in proximal deep vein thrombosis patients

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Background: Postthrombotic syndrome (PTS) is the most common long-term complication of deep vein thrombosis (DVT). Predictive models for PTS after hospitalized DVT patients, especially those with proximal DVT for whom preventative intervention decisions need to be made, are rare. We aimed to develop and externally validate a clinical predictive model for PTS in patients with proximal DVT.

Methods: This study was a retrospective, single-center, case-control study. The data used in our model were retrospectively collected from a prospective registry database in which 210 (derivation) and 90 (validation) consecutive patients were first diagnosed with proximal DVT. We developed a nomogram using the multivariate logistic regression model. External validation of our predictive model and previous predictive models in our validation set was assessed by discrimination, calibration, and clinical utility.

Results: Of the 30 candidate predictors, 5 were significantly associated with PTS in our final multivariable model, including the number of signs and symptoms (OR 1.33, 95% CI: 1.17 to 1.53, P<0.001), male sex (OR 1.79, 95% CI: 1.07 to 3.06, P=0.028), varicose vein history (OR 3.02, 95% CI: 1.04 to 7.60, P<0.001), BMI (OR 1.06, 95% CI: 1.00 to 1.12, P=0.052), and chronic DVT (OR 2.66, 95% CI: 1.49 to 4.79, P<0.001). The area under the curve was 0.724 in our predictive model, indicating suitable external performance.

Conclusions: A simple-to-use nomogram effectively predicts the risk of PTS in patients with proximal DVT. This predictive model may be considered for use in clinical care.

Keywords: Postthrombotic syndrome (PTS); deep vein thrombosis (DVT); clinical prediction rule; logistic models

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Introduction

Postthrombotic syndrome (PTS) is the most common long-term complication of deep vein thrombosis (DVT). The incidence of PTS ranges from 20% to 50% in DVT patients (1,2). Surgical treatment of PTS is attempted when conservative treatment fails. However, there is a lack of evidence to support that the existing treatment options improve the quality of life and costs of care of patients with PTS (3-8). Therefore, prevention is a key measure for managing PTS. Due to the development of endovascular

techniques, a large proportion of proximal DVT patients undergo endovascular therapy to prevent PTS development (9,10), and proximal DVT accounts for the vast majority of hospitalized DVT patients who undergo endovascular therapy (11).

Predictive models have been accepted as reliable tools to quantify risk for prognostic analyses. Although numerous predictors have been identified as risk factors for PTS (12-15), confirming the combined factors to develop a prediction model that predicts the development of PTS after DVT remains a challenge. Because of the high proportion of proximal DVT among hospitalized DVT patients, we believe that the derivation of an easy-to-use PTS predictive model for patients with proximal DVT who are hospitalized may be beneficial in daily clinical practice. Furthermore, we externally validated our model and existing PTS prediction rules to evaluate the calibration, discrimination and clinical utility of these predictive models. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3239).

Methods

Sampling design

This study was a retrospective, single-center, case-control study. The data used in our model were retrospectively collected in a prospective registry database. This registry was launched in June 2016 and prospectively collected consecutive patients who were diagnosed with DVT at the Vascular Center of Shanghai Jiaotong University (Shanghai Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the registration number of Medical Ethics Committee of Shanghai Ninth People's Hospital (No.: SH9H-2020-T314-2) and individual consent for this retrospective analysis was waived. The DVT registry at the Vascular Center of Shanghai Jiaotong University collected the demographics of patients, treatment details, preoperative and postoperative laboratory tests, and postdischarge follow-ups, including telephone follow-up and/or outpatient follow-up. The missing data in the database was excluded.

The inclusion criteria were adult inpatients with a first diagnosis of proximal DVT. Proximal DVT was defined as a thrombus involving the iliac and/or common femoral veins, with or without extension to the inferior vena cava and with or without concomitant PE. There were no exclusion criteria. The included cases were randomly divided into derivation and validation sets according to a 7:3 ratio. The presence of PTS was defined as a Villalta score of ≥5 (16). A Villalta score at 6 months post-DVT was used to assess the incidence of PTS, as determined by a medical doctor.

Predictor variables

A standardized data form was created to retrieve all relevant information on demographics [sex, age, and body mass index (BMI)], potential DVT risk factors (hospitalization for surgery, active cancer, trauma/fracture, nursing home confinement, hospitalization due to nonsurgical illness, and idiopathic DVT), comorbidities [hypertension, heart disease, diabetes, neurological disease, prior varicose vein, and pulmonary embolism (PE)], classification of DVT (limbs of DVT, acute/chronic DVT), and signs or symptoms of DVT at baseline (pain, cramps, heaviness, pruritus, paresthesia, edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression, venous ulcers, and the number of signs and symptoms). There were 30 variables in the study, and 18 candidate predictors were finally analyzed. For instance, 10 venous signs and symptoms were combined to a candidate predictor of "number of signs and symptoms". The selection of candidate predictors was based on previous studies, and we also considered clinically observed variables with potential impact. The potential DVT risk factors mentioned above are defined as factors that occurred within 3 months before the onset of DVT. Acute DVT is defined from onset to treatment <14 days, and chronic DVT is defined from onset to treatment ≥14 days. As there were too many signs or symptoms of DVT at baseline, we used the number of signs and symptoms as a variable.

Sample size

According to the literature, the incidence of PTS is 20–50% (1,2); thus, we estimated the incidence of PTS to be 35% for the sample size calculation. We first selected 100 samples and found that 7 variables were significant after univariate analysis. We followed the suggested sample size calculation for logistic regression, where p is the smallest of the proportions of negative or positive cases in the population and k is the number of independent variables;

then, the minimum number of cases to include is N=10 k/p. The minimum number of cases required of the derivation set is therefore N=10 * 7/0.35 = 200.

Statistical analysis

All model creation steps were based only on the derivation set. First step, univariate logistic regression was used to evaluate the factors associated with PTS. Second step, a multivariate logistic regression model was performed with selected variables that were significant in the univariate analysis (P<0.05). The final multivariable model was constructed by removing variables with a P value >0.1. The odds ratio (OR) for each independent variable was determined with a 95% confidence interval (CI). To facilitate the ease of use in the clinical setting, a nomogram was generated on the basis of the final predictive model.

We externally validated our predictive model, the SOX-PTS predictive model, and the SWITCO-PTS predictive model in our set. We calculated the score or the predicted probabilities based on the score and the model coefficients presented in the original publication. A receiver operating characteristic (ROC) curve of each predictive model was generated using a validation set, and predictive discriminations were evaluated by calculating the area under the curve (AUC) (17). The overall accuracy and calibration of each predictive model were visualized by calibration curves that compared the predicted versus actual probabilities, including a bias correction for overfitting (18). A decision curve analysis (DCA) was performed to assess the clinical utility of using each of these 3 predictive models to guide the decision (19,20). Data were analyzed with R version 3.5.3.

Results

In total, 349 consecutive patients with proximal DVT were registered in our registry database from June 2016 to June 2018. We excluded patients without 6 months of follow-up (n=32) and those who died before the 6-month visit (N=17). Finally, 300 patients were enrolled in this study. A total of 210 patients were used as the derivation set and 90 as the validation set. The characteristics of the patients in the derivation set and validation set are presented in *Table 1*. Among those in the derivation set, 126 patients were diagnosed with PTS after 6 months, accounting for 42.0%. Participation at each stage is shown in a flow diagram (*Figure 1*).

Derivation of the predictive model

Table 2 presents the characteristics of the derivation set. The univariable associations between PTS and potential predictors are listed in *Table 2*. Of the 18 candidate predictors, 6 were significantly associated with PTS in our final multivariable model (*Table 3*). The independent predictors of PTS based on the derivation set were the number of signs and symptoms (OR 1.33, 95% CI: 1.17 to 1.53, P<0.001), male sex (OR 1.79, 95% CI: 1.07 to 3.06, P=0.028), varicose vein history (OR 3.02, 95% CI: 1.04 to 7.60, P<0.001), BMI (OR 1.06, 95% CI: 1.00 to 1.12, P=0.052), and chronic DVT (OR 2.66, 95% CI: 1.49 to 4.79, P<0.001). A nomogram incorporating the 5 independent predictors in the derivation set was established (*Figure 2*).

External validation and comparison with other models

The validation set was used in the external validation of our predictive model, the SOX-PTS predictive model, and the SWITCO-PTS predictive model. The discriminative ability of the models is represented as the AUC. The AUC was highest for our predictive model (AUC 0.724) (*Figure 3*); the AUC for the SOX-PTS and SWITCO-PTS predictive models was 0.606 and 0.579, respectively. The difference between AUC of our model and SOX-PTS model was not statistically significant (Z=1.707, P=0.088), and the difference between AUC of our model and SWITCO-PTS model was statistically significant (Z=2.556, P=0.011). The calibration curves are presented in *Figure 3*, showing good overall agreement between the predicted and observed risk of PTS in our predictive model, whereas the risk of PTS was systematically overestimated in both the SOX-PTS predictive model and SWITCO-PTS predictive model (*Figure 4*). The clinical utility of our predictive model, the SOX-PTS predictive model, and the SWITCO-PTS predictive model is presented in a DCA (*Figure 5*). The DCA graphically shows the clinical usefulness of each model based on a continuum of potential thresholds for PTS risk (x axis) and the net benefit of using the model to risk stratify patients (y axis) relative to assuming that no patient will have a PTS. In this analysis, our predictive model was associated with the highest net benefit within threshold probabilities of 20%-95% for the prediction of PTS.

Table 1 Characteristics of the patients in the derivation set and validation set

Variable	Derivation set, N=210, n (%)	Validation set, N=90, n (%)
Age (years)	57.40±15.71	58.93±14.60
Men	125 (59.5)	52 (57.8)
BMI (kg/m^2)	24.43±4.77	24.36±4.57
Potential DVT risk factors		
Hospitalization for surgery	59 (28.1)	21 (23.3)
Active cancer	20 (9.5)	5 (5.6)
Trauma/fracture	13 (6.2)	9 (10.0)
Nursing home confinement	28 (13.3)	11 (12.2)
Hospitalization due to non-surgical illness	18 (8.6)	4 (4.4)
Idiopathic DVT	83 (39.5)	42 (46.7)
Comorbidity		
Hypertension	54 (25.7)	26 (28.9)
Heart disease	46 (21.9)	22 (24.4)
Diabetes	11 (5.2)	7(7.8)
Neurological disease	11 (5.2)	5 (5.6)
Varicose vein	16 (7.6)	11 (12.2)
PE	10 (4.8)	6 (6.7)
Limbs of DVT		
Right	44 (21.0)	21 (23.3)
Left	153 (72.9)	66 (73.3)
Bilateral	13 (6.2)	3 (3.3)
Chronic DVT	49 (23.3)	25 (27.8)
Proximal DVT	242 (71.6)	68 (75.6)
Signs/symptoms of DVT		
Pain	115 (54.8)	48 (53.3)
Cramps	14 (6.7)	10 (11.1)
Heaviness	143 (68.1)	63(70.0)
Pruritus	22 (10.5)	3 (3.3)
Paraesthesia	153 (72.9)	66 (73.3)
Oedema	197 (93.8)	81 (90.0)
Skin induration	11 (5.2)	11 (12.2)
Hyperpigmentation	50 (23.8)	29 (32.2)
Venous ectasia	42 (20.0)	24 (26.7)
Redness	30 (14.3)	18 (20.0)
Pain during calf compression	69 (32.9)	34 (37.8)
Venous ulcer	27 (12.9)	14 (15.6)
No. of signs and symptoms	4.16±1.96	4.46±2.25

The potential DVT risk factors mentioned above are defined as factors that occurred within 3 months before the onset of DVT. Acute DVT is defined from onset to treatment <14 days, and chronic DVT is from onset to treatment ≥14 days. BMI, body mass index; DVT, deep vein thrombosis; VKAs, vitamin K antagonists; NOACs, newer oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs.

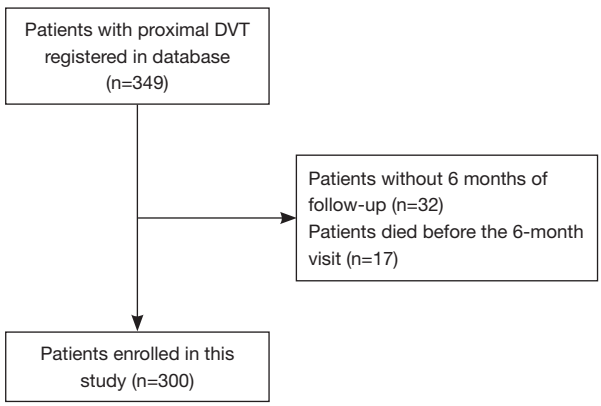

Figure 1 Flow diagram of participation.

Discussion

PTS is a common, late complication of DVT that reduces the quality of life and increases the financial burden of patients (1-3). Due to the lack of effective prevention and treatment, PTS occurs in 20% to 50% of DVT patients, even with effective anticoagulation (1,2). Previous studies have revealed a number of risk factors for PTS (12-15,21), but identifying patients at a high risk of PTS by a single risk factor is difficult. Several previous models of PTS have attempted to predict the development of PTS by combining risk factors (12-14). However, most of these studies adopted cohorts from randomized controlled trials, excluding young people and chronic cases, among others, populations that are common in clinical practice. Therefore, whether these predictive models have practical value and repeatability in clinical work is debatable. Additionally,

Table 2 Characteristics of the derivation set

Variable	PTS, N=84, n (%)	No PTS, N=126, n (%)	P value
Age (years)	58.36±14.56	56.76 ±15.59	0.457
Men	57 (67.9)	68 (54.0)	0.046
BMI (kg/m^2)	25.22±5.42	23.90±4.22	<0.050
Potential DVT risk factors			
Hospitalization for surgery	27 (32.1)	32 (25.4)	0.347
Active cancer	7 (8.3)	13 (10.3)	0.811
Trauma/fracture	5 (6.0)	8 (6.3)	1.000
Nursing home confinement	15 (17.9)	13 (10.3)	0.147
Hospitalization due to non-surgical illness	8 (9.5)	10 (7.9)	0.802
Idiopathic DVT	26 (31.0)	57 (45.2)	0.044
Comorbidity			
Hypertension	19 (22.6)	35 (27.8)	0.425
Heart disease	26 (31.0)	20 (15.9)	0.011
Diabetes	6 (7.1)	5 (4.0)	0.354
Neurological disease	6 (7.1)	5 (4.0)	0.354
Prior varicose vein	10 (11.9)	6 (4.8)	0.066
PE	4 (4.8)	6 (4.8)	1.000
Limbs of DVT			0.968
Right	17 (14.9)	27 (22.1)	
Left	62 (73.8)	91 (72.2)	
Bilateral	5 (6.0)	8 (6.3)	
Chronic DVT	24 (28.6)	25 (19.8)	0.183
Signs/symptoms of DVT			
Pain	42 (50.5)	73 (57.9)	0.262
Cramps	12 (14.3)	2 (1.6)	<0.001
Heaviness	60 (71.4)	83 (65.9)	0.451
Pruritus	16 (19.0)	6 (4.8)	0.002
Paraesthesia	66 (78.6)	87 (69.0)	0.155
Oedema	81 (96.4)	116 (92.1)	0.251
Skin induration	10 (11.9)	1 (0.8)	0.001
Hyperpigmentation	30 (35.7)	20 (15.9)	0.002
Venous ectasia	27 (32.1)	15 (11.9)	0.001
Redness	15 (17.9)	15 (11.9)	0.235
Pain during calf compression	20 (23.8)	49 (38.9)	0.025
Venous ulcer	22 (26.2)	5 (4.0)	<0.001
No. of signs and symptoms	4.77±2.23	3.75±1.63	<0.001

PTS, postthrombotic syndrome; BMI, body mass index; DVT, deep vein thrombosis; VKAs, vitamin K antagonists; NOACs, newer oral anticoagulants; NSAIDs, nonsteroidal anti-inflammatory drugs; INR, international normalized ratio.

with recent advances in endovascular technology, many endovascular interventions have been attempted in DVT patients, especially patients with proximal DVT, to reduce the development of PTS (9-11). Previous randomized controlled trials have revealed that endovascular therapy is associated with a PTS reduction compared with anticoagulation alone. Accordingly, there is a great demand for surgical decision-support tools in clinical work for patients with DVT who receive endovascular therapy. Our predictive model was derived by using a registry database of hospitalized proximal DVT patients. Our model was established by easily available variables such as information on demographics, potential DVT risk factors, comorbidities, classification, and signs or symptoms of DVT at baseline.

Factors such as male sex, chronic DVT, BMI, signs and symptoms at baseline, and prior varicose vein were incorporated into our predictive model as independent risk factors. These variables were also revealed to be independent risk factors in a previous analysis. In addition, previous PTS predictive models did not consider the risk factors of DVT included in our analysis. These variables are easily available in the electronic medical records of hospitalized patients, enhancing the ease of use of our predictive model.

The discrimination of our PTS predictive model, as highlighted by the AUC value, was higher than those of the SOX-PTS predictive model and the SWITCO-PTS predictive model, which were both derived from data from a prospective cohort. The calibration curve demonstrated very good agreement between the predicted and actual risk of PTS, which assures the repeatability and reliability of

Table 3 Final multivariable model of potential predictors

Parameter	OR (95% CI)	β-coefficient (95% CI)	P value
Intercept	0.028 (0.006 to 0.128)	–3.564 (–5.166 to –2.053)	<0.01
No. of signs and symptoms	1.329 (1.171 to 1.524)	0.285 (0.158 to 0.422)	<0.01
BMI	1.055 (1.000 to 1.115)	0.053 (–0.001 to 0.109)	0.05
Prior varicose vein	2.662 (1.112 to 6.604)	0.979 (0.106 to 1.888)	0.03
Chronic DVT	2.463 (1.397 to 4.393)	0.901 (0.334 to 1.480)	<0.01
Male sex	1.905 (1.144 to 3.213)	0.645 (0.134 to 1.167)	0.01

OR, odds ratio; BMI, body mass index; DVT, deep vein thrombosis.

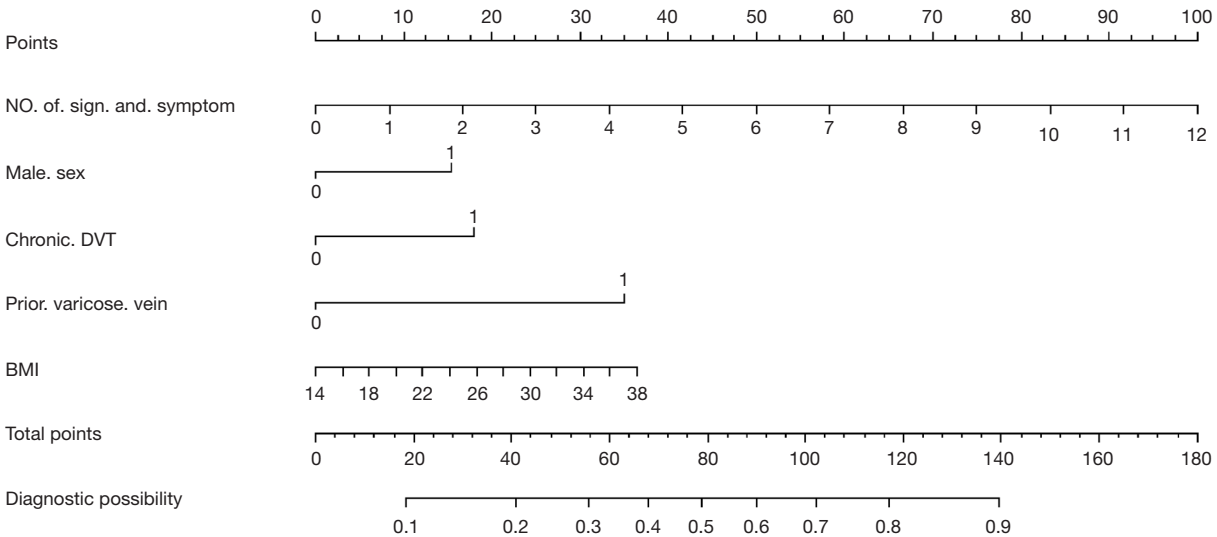

Figure 2 Nomogram of PTS predictive model. PTS, postthrombotic syndrome.

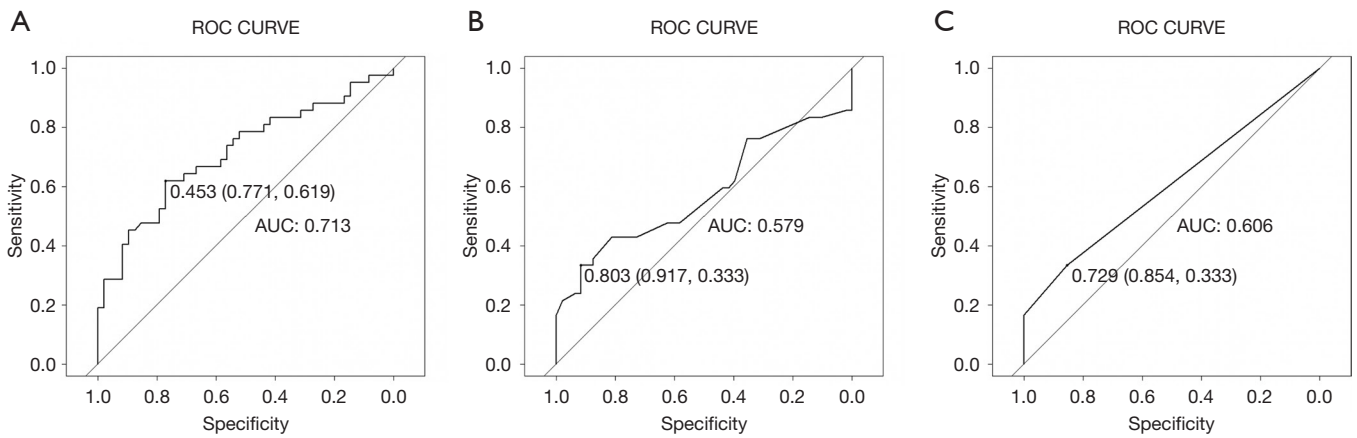

Figure 3 Receiver operating characteristic (ROC) curve of our PTS predictive model (A), SOX-PTS predictive model (B), and SWITCO-PTS predictive model (C). PTS, postthrombotic syndrome.

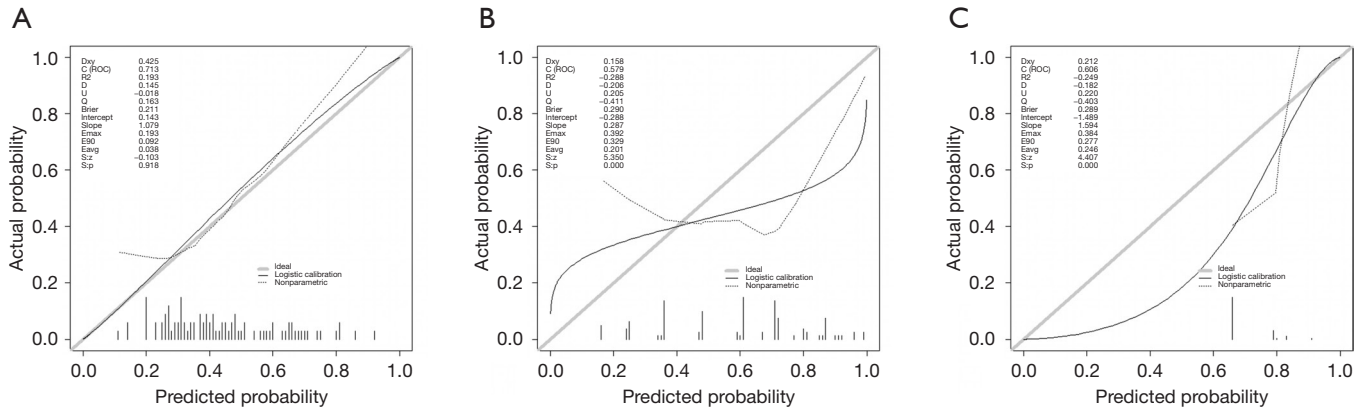

Figure 4 Calibration curves of our PTS predictive model (A), SOX-PTS predictive model (B), and SWITCO-PTS predictive model (C). PTS, postthrombotic syndrome.

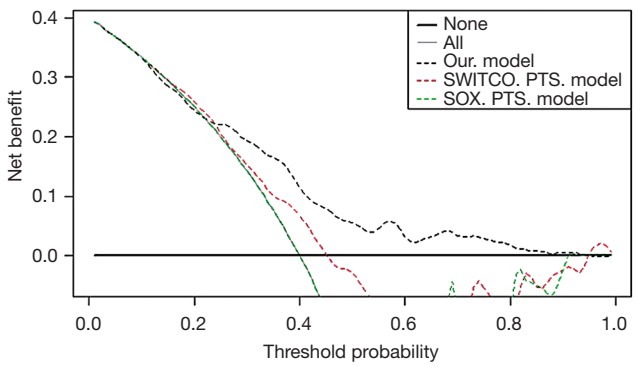

Figure 5 Decision curve analysis of our PTS predictive model, SOX-PTS predictive model, and SWITCO-PTS predictive model. PTS, postthrombotic syndrome.

our PTS predictive model. At the same time, the calibration curves of previous predictive models showed either a systematic overestimation or systematic underestimation. Moreover, we used DCA to evaluate the clinical utility of the predictive models. In DCA, the net benefit is determined by calculating the difference between the expected benefit and the expected harm associated with each predictive model (19,20). The DCA for our validation set showed that the net benefit was maximized with threshold probabilities of 0–25% by the "predict all" approach; with threshold probabilities of 25–90%.

Our study may support clinical decision making. Our model may offer personalized patient PTS risk estimates and facilitate clinical counseling for both patients and doctors. Identifying subgroups of DVT patients at different risk for PTS might have an impact on treatment or care options. Furthermore, this predictive model may also provide information for patient stratification in the design of clinical studies, gaining better equivalence between study arms.

As with any observational population-based study, our study has some limitations. First, our model was derived from data for hospitalized DVT patients and did not include outpatient DVT patients. Moreover, our institution is a famous venous center in China, and we received many DVT patients who were referred from local institutions, and these patients may have had severe DVT. Therefore, when applying this model in specific centers with different DVT populations, some inconsistencies between the predicted and actual PTS risks may be observed. Finally, future predictive models with better methodologies are needed to assist in clinical decision making and to guide future research.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-3239

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-3239

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3239). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the registration number of Medical Ethics Committee of Shanghai Ninth People's Hospital (No.: SH9H-2020-T314-2) and individual consent for this retrospective analysis was waived.

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