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EDITED BY

Xiao Chen,
Second Military Medical University, China

REVIEWED BY

Jin Cui,
Second Military Medical University, China
Droc Ionel,
Central Military Hospital Bucharest Romania,
Romania

*CORRESPONDENCE

Jiaqi Wang
✉ wangjiaqidy2y@sina.com
Shufeng Li
✉ shufenglisd@126.com
Dapeng Feng
✉ rocfofw@163.com
Jian Wang
✉ jianwangmd@aliyun.com
Kai Li
✉ likai74418@126.com

[†]These authors have contributed equally to this work

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Development and validation of a newly developed nomogram for predicting the risk of deep vein thrombosis after surgery for lower limb fractures in elderly patients

Shuai Han^{1†}, Yunpeng Bai^{1†}, Kun Jiao^{1†}, Yongmin Qiu¹, Juhong Ding¹, Jun Zhang¹, Jingyun Hu², Haihan Song², Jiaqi Wang^{3*}, Shufeng Li^{4*}, Dapeng Feng^{3*}, Jian Wang^{1*} and Kai Li^{1*}

¹Department of Orthopedics, Shanghai Pudong New Area People's Hospital, Shanghai, China,

²Department of Orthopedics, The Second Hospital of Dalian Medical University, Dalian, China, ³Central Lab, Shanghai Key Laboratory of Pathogenic Fungi Medical Testing, Shanghai Pudong New Area People's Hospital, Shanghai, China, ⁴Department of Orthopedic Surgery, Shandong Key Laboratory of Rheumatic Disease and Translational Medicine, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, China

Background: Prevention of deep vein thrombosis (DVT) is indispensable in the treatment of lower limb fractures during the perioperative period. This study aimed to develop and validate a novel model for predicting the risk of DVT in elderly patients after orthopedic surgeries for lower limb fractures.

Methods: This observational study included 576 elderly patients with lower limb fractures who were surgically treated from January 2016 to December 2018. Eleven items affecting DVT were optimized by least absolute shrinkage and selection operator regression analysis. Multivariable logistic regression analysis was performed to construct a predictive model incorporating the selected features. C-index was applied to evaluate the discrimination. Decision curve analysis was employed to determine the clinical effectiveness of this model and calibration plot was applied to evaluate the calibration of this nomogram. The internal validation of this model was assessed by bootstrapping validation.

Results: Predictive factors that affected the rate of DVT in this model included smoking, time from injury to surgery, operation time, blood transfusion, hip replacement arthroplasty, and D-dimer level after operation. The nomogram showed significant discrimination with a C-index of 0.919 (95% confidence interval: 0.893–0.946) and good calibration. Acceptable C-index value could still be reached in the interval validation. Decision curve analysis indicated that the DVT risk nomogram was useful within all possibility threshold.

Conclusion: This newly developed nomogram could be used to predict the risk of DVT in elderly patients with lower limb fractures during the perioperative period.

KEYWORDS

nomograms, deep vein thrombosis, lower limb fractures, elderly patients, predictive factors

Introduction

Deep vein thrombosis (DVT) is a common complication in patients with lower limb fractures, which can result in fatal pulmonary embolism (PE) (1, 2). The incidence of DVT after surgery for lower limb fractures reported in previous studies ranges from 8.2 to 61.3% (3, 4). As most DVT cases are asymptomatic, early diagnosis is relatively

difficult. If not prevented in time, some of the asymptomatic DVT may progress to symptomatic DVT with clinical symptoms such as redness, leg swelling, and tenderness. The consequence of symptomatic DVT often indicates a poor outcome and increases the risk of PE and mortality, and it is therefore highly important to prevent DVT in patients with lower limb fractures during the perioperative period.

DVT diagnosis has traditionally depended on digital subtraction angiograph (DSA). As a gold standard for diagnosis, DSA is a traumatic examination. Hence color Doppler ultrasonography is more frequently used in identifying DVT (5). Considering the actual situation, the objective and timely diagnosis of DVT is frequently delayed in daily practice (6, 7). Ageno et al. found that it required 5 days from symptom onset to the DVT diagnosis for 47.1% of patients and >10 days for 22.6% of patients (6). Hence, there is an urgent need to identify patient at high risk based on the related risk factors or admission laboratory biomarkers. By far, substantial efforts have been made to address this in orthopedics or other fields. The risk factors for DVT include older age, gender, obesity, smoking, cardiovascular disease, a cancer history, fracture location, delay in surgery and so on (8–10). Given so many associated risk factors, early accurate prediction of DVT by utilizing risk factors may be difficult to manage. Although previous studies have demonstrated that many risk factors are associated with DVT after lower limb fractures, they failed to translate the findings into accurate predictive model to identify DVT in elderly patients with lower limb fractures (7, 11–13). Indeed, these identified factors either relied too heavily on the subjective judgment of the assessors, or lacked well-validated biomarkers (14–16). Therefore, it is almost impossible to use these “isolated” risk factors to determine the “intuitive” and “real” possibility that one patient develops a DVT.

Caprini score has been frequently used to evaluate the risk of VTE in surgical patients. Although there is robust evidence to show its validity, it includes more than 30 risk factors in various aspects, which makes it too cumbersome and complex to allow for a rapid clinical diagnosis. Even worse, orthopedic surgeons were disappointed to find that elderly patients with lower limb fractures would always be classified as high-risk group (17–19). The purpose of this study was to develop a simple but valid predictive model to assess the risk of DVT in elderly patients with lower limb fractures, with the hope to provide a more accurate method for identifying and preventing DVT during the perioperative period.

Patients and methods

The research protocol for this study was approved by the local ethics committee of Shanghai Pudong New Area People’s Hospital. Patients were recruited from the Orthopedics Department from January 2016 to December 2018, and all the patients were diagnosed with new lower limb fractures. All participating patients signed informed consent.

The inclusion criteria were as follows: (1) age ≥ 60 years; (2) surgical treatment; and (3) internal implants. The exclusion

criteria were as follows: (1) pathological fracture; (2) old fracture; (3) open fracture; (4) multiple complicated injuries; (5) anti-coagulation before injury; (6) hematological system disease; and (7) insufficient clinical or follow-up data.

After admission, all patients were treated with low molecular weight heparin (LMWH, 4,000 IU/d) for prophylaxis 12 h after injury. If the patients were hemodynamically unstable, LMWH heparin was not administered until the condition became stable. DVT screening of the lower extremities was performed using color Doppler ultrasonography before and after surgery.

The following data were collected: (1) demographics: gender, age, comorbidities, smoking history, and the time from injury to surgery; (2) location of the fracture: hip, knee, ankle and foot, femoral shaft, tibia and fibula shaft; (3) anesthesia method; (4) time of operation; (5) blood transfusion; (6) implant type; and (7) D-dimer level.

Diagnostic methods and standards of DVT

Patients underwent venous color Doppler ultrasonography for DVT detection at 24 h after admission, 1 day before surgery, and 7 days after surgery. The deep veins of the proximal lower extremity were examined successively by using intermittent compression across the cross-section, from the femoral vein to the calf muscle venous plexus, and then successively along the longitudinal section of the above veins with the color doppler probe.

The diagnostic criteria of DVT (20): (1) the venous lumen could not be compressed; (2) the tone could be seen within the real echo; (3) the presence of blood flow signal filling defects in the lumen; (4) loss of phase in the blood flow spectrum; (5) incomplete obstruction of the vascular segment forming a “track” or “contour”; (6) no blood flow signal detectable in the vein segment or the presence of only a small amount of blood flow signal; and (7) pulse Doppler showing no blood flow or spectral changes with respiration.

Statistical analysis

R version 4.2.1 (www.r-project.org) was used for statistical analysis. All data was presented as count (%). The least absolute shrinkage and selection operator (LASSO) regression, which is suitable for generating a relatively lower dimension model from high dimensional data, was used to select the potential prediction features in risk factors from patients with DVT in this study (21). In the LASSO model, features with nonzero coefficients were selected as significant predictors (22). Multivariable logistic regression analysis was utilized to build a predicting model. The potential features were evaluated by an odds ratio (OR), 95% confidence interval (CI) and corresponding *P*-values. Predictors with *P*-value < 0.05 were considered statistically significant and involved in the model (23). Calibration curves were used to assess the calibration of this nomogram. Harrell’s C-index was applied to quantify the discrimination performance of this prediction nomogram. The relative C-index was corrected by

bootstrapping validation (1,000 bootstrap resamples). Decision curve analysis was used to evaluate the clinical effectiveness of the DVT nomogram by comparing the net benefit under different threshold probabilities in the cohort of elderly patients with lower limb fracture (24). The net benefit was calculated by subtracting the proportion of false positive patients from the proportion of the true positive patients to identify who would really benefit from intervention by applying this nomogram.

Results

Patient characteristics

576 patients with lower limb fractures who received surgical treatment in our hospital from January 2016 to December 2018 were enrolled in this study, of whom 68 were diagnosed with DVT by color Doppler ultrasonography. The prevalence of DVT was 11.81%. All these 68 patients presented with asymptomatic DVT, and none of them developed PE. All the 576 patients were divided into a DVT group and a non-DVT group. All data of the patients including the demographics, disease and treatment features in the two groups are given in [Table 1](#).

Feature selection

11 features of the demographics, disease, and treatment features were reduced to 7 potential predictors on the basis of 576 patients in the cohort by LASSO regression model ([Figures 1A,B](#)). These features included age, smoking, time from injury to surgery, operation time, blood transfusion, implant type, and level of D-dimer.

Development of an individualized prediction model

The results of the logistic regression analysis among age, smoking, time from injury to surgery, operation time, blood transfusion, implant type, and level of D-dimer are given in [Figure 2](#). Based on the results of the forest plots, we removed age factor, and merged the non-significant sub group in the other factors. Then these adjusted predictors were incorporated into the nomogram as shown in [Figure 3](#).

Apparent performance of the DVT risk nomogram in the cohort

The calibration curve of the DVT risk nomogram for the prediction of DVT risk in elderly patients with lower limb fractures demonstrated good agreement in this cohort ([Figure 4](#)). The C-index for the prediction nomogram was 0.919 (95%CI: 0.893–0.946) for the cohort, and was confirmed to be 0.9195 through bootstrapping validation, suggesting that the model had

TABLE 1 Differences between demographic and clinical characteristics of DVT and non-DVT groups.

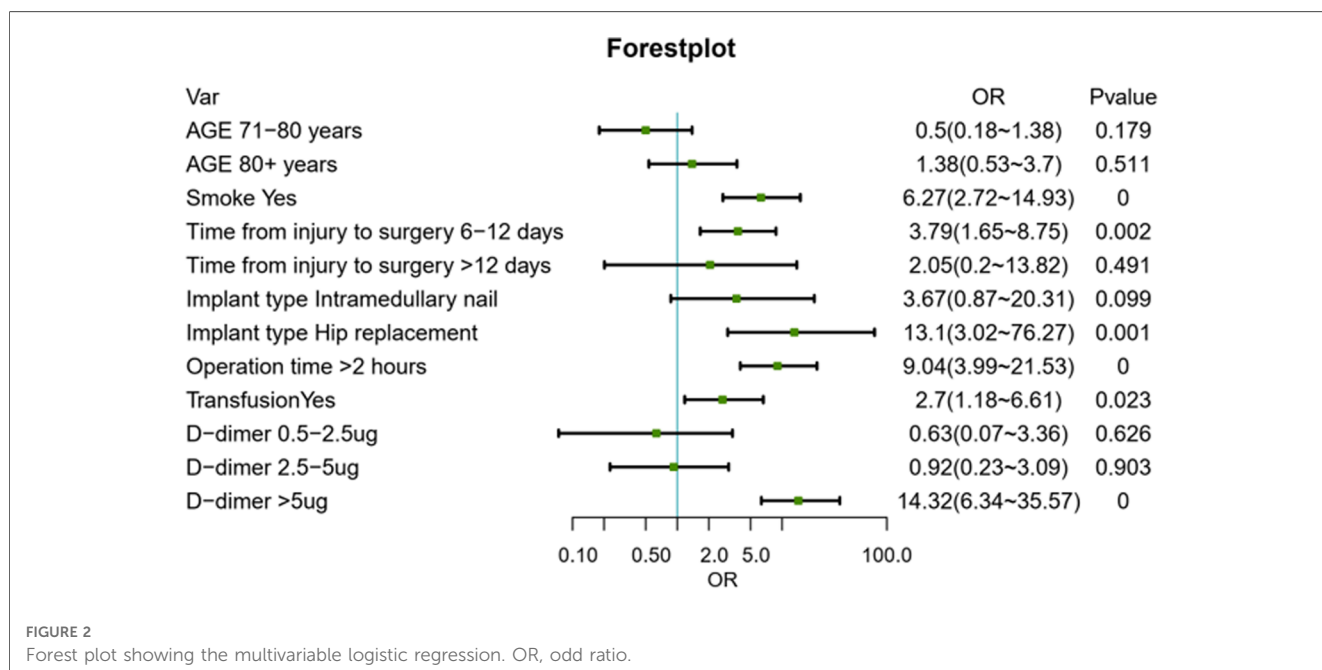
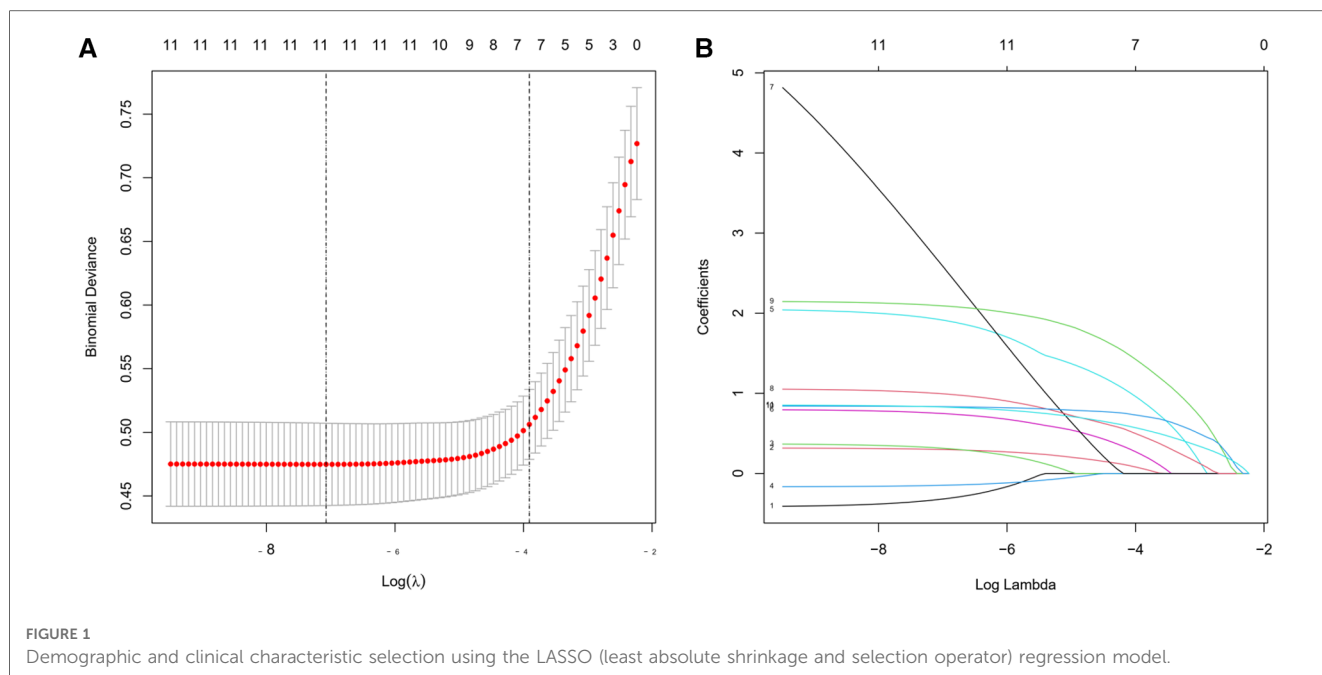
Clinical characteristics	non-DVT (N = 508)	DVT (N = 68)	P-value
Sex			
Female	329 (64.8%)	42 (61.8%)	0.726
Male	179 (35.2%)	26 (38.2%)	
Age			
60–70 years	225 (44.3%)	14 (20.6%)	<0.001*
71–80 years	159 (31.3%)	16 (23.5%)	
80 + years	124 (24.4%)	38 (55.9%)	
Fracture site			
Hip	457 (90.0%)	63 (92.6%)	0.078
Knee	29 (5.7%)	0 (0%)	
Ankle	22 (4.3%)	5 (7.4%)	
Disease			
None	224 (44.1%)	34 (50.0%)	0.743
Hypertension	15 (3.0%)	1 (1.5%)	
Diabetes	186 (36.6%)	22 (32.4%)	
Both	83 (16.3%)	11 (16.2%)	
Smoke			
No	441 (86.8%)	46 (67.6%)	<0.001*
Yes	67 (13.2%)	22 (32.4%)	
Time from injury to surgery			
0–6 days	425 (83.7%)	47 (69.1%)	0.014*
6–12 days	75 (14.8%)	19 (27.9%)	
>12 days	8 (1.6%)	2 (2.9%)	
Anesthetization			
Combined Spinal-Epidural	329 (64.8%)	42 (61.8%)	0.726
General	179 (35.2%)	26 (38.2%)	
Surgery			
Other	216 (42.5%)	3 (4.4%)	<0.001*
Intramedullary nail	124 (24.4%)	18 (26.5%)	
Hip replacement	168 (33.1%)	47 (69.1%)	
Operation time			
≤2 h	449 (88.4%)	40 (58.8%)	<0.001*
>2 h	59 (11.6%)	28 (41.2%)	
Transfusion			
No	329 (64.8%)	13 (19.1%)	<0.001*
Yes	179 (35.2%)	55 (80.9%)	
D-dimer level			
<0.5 ug	331 (65.2%)	18 (26.5%)	<0.001*
0.5–2.5 ug	35 (6.9%)	2 (2.9%)	
2.5–5 ug	59 (11.6%)	4 (5.9%)	
>5 ug	83 (16.3%)	44 (64.7%)	

**P < 0.05.

good discrimination. In the DVT risk nomogram, apparent performance manifested a good prediction capability.

Clinical use

The decision curve analysis for the DVT nomogram is presented in [Figure 5](#). The decision curve shows that within all threshold possibility, more benefits could be gained by using this nomogram to predict DVT, compared with the scheme.



Discussion

A nomogram is a multi-index graphical calculating device and has been widely used as a prognostic device in cancer research and medicine, and it is a good tool to increase the accuracy of predicting prognosis and makes it more convenient to reach a clinical decision (25–27). To the best of our knowledge, this study might be the first applied to DVT of lower limb fracture in elderly patients.

Lasso logistic regression is a useful alternative for variable reduction when collinearity is present. With this advantage, we developed and validated this predictive model for DVT risks in

elderly patients with lower limb fractures by merely using these six easily available variables. Of all the collective factors, smoking, time from injury to surgery, operation time, blood transfusion, implant type, and D-dimer level were selected by multivariate logistic analysis to form the nomogram to facilitate the DVT individualized prediction of elderly patients with lower limb fractures. Good discrimination and high internal validation of this nomogram were assessed by the C-index. The high C-index value in the interval validation demonstrated that this nomogram might be useful and accurate during clinical practice. For such a high predictive performance of our model, overfitting

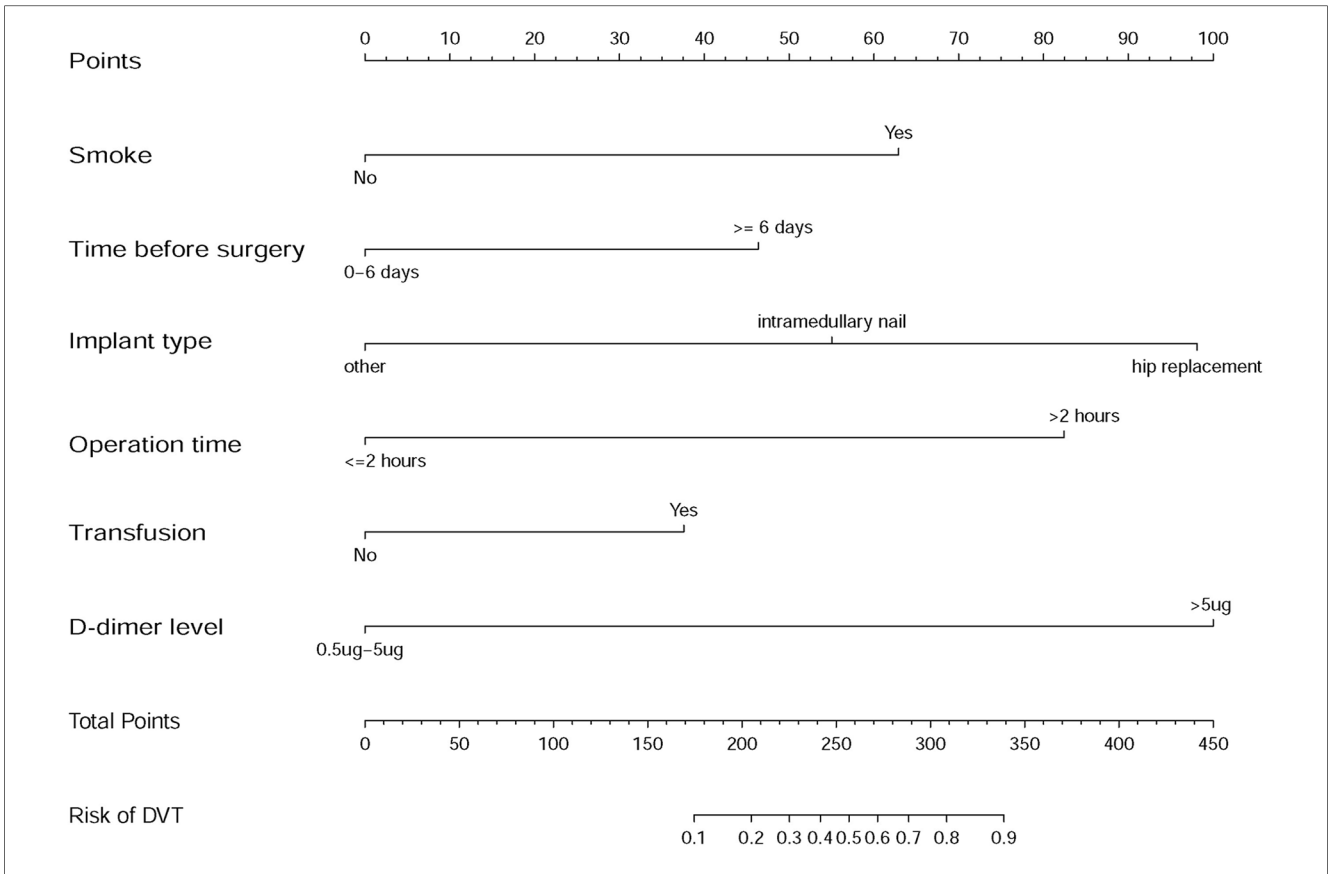


FIGURE 3 Developed DVT prediction nomogram. The sum of the scores of each predictor corresponds to the risk of DVT.

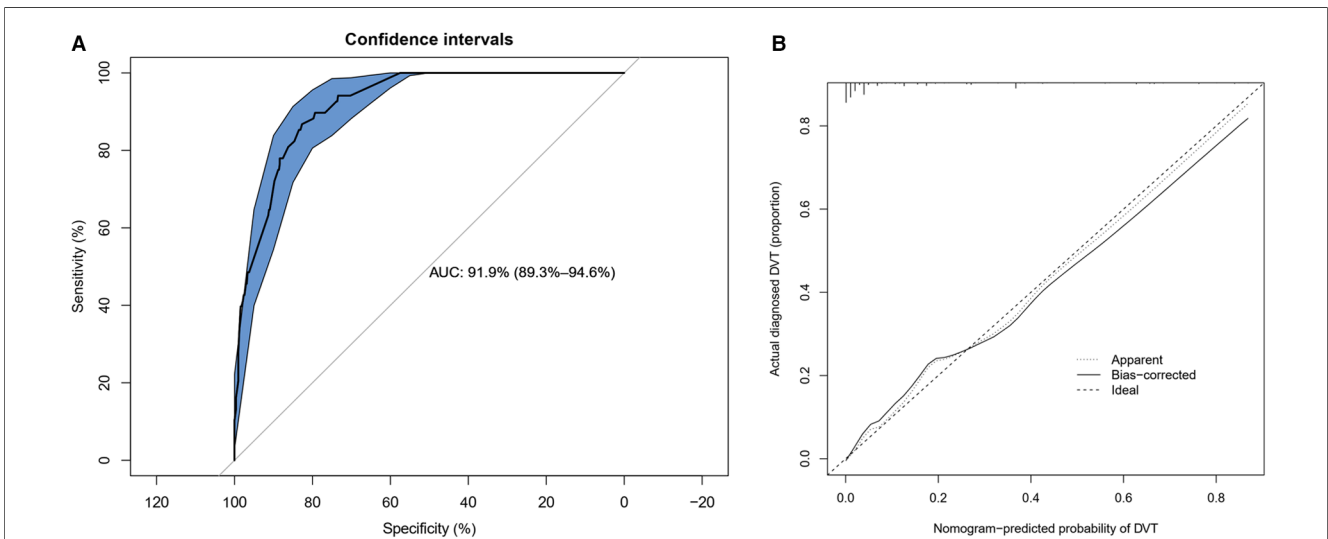
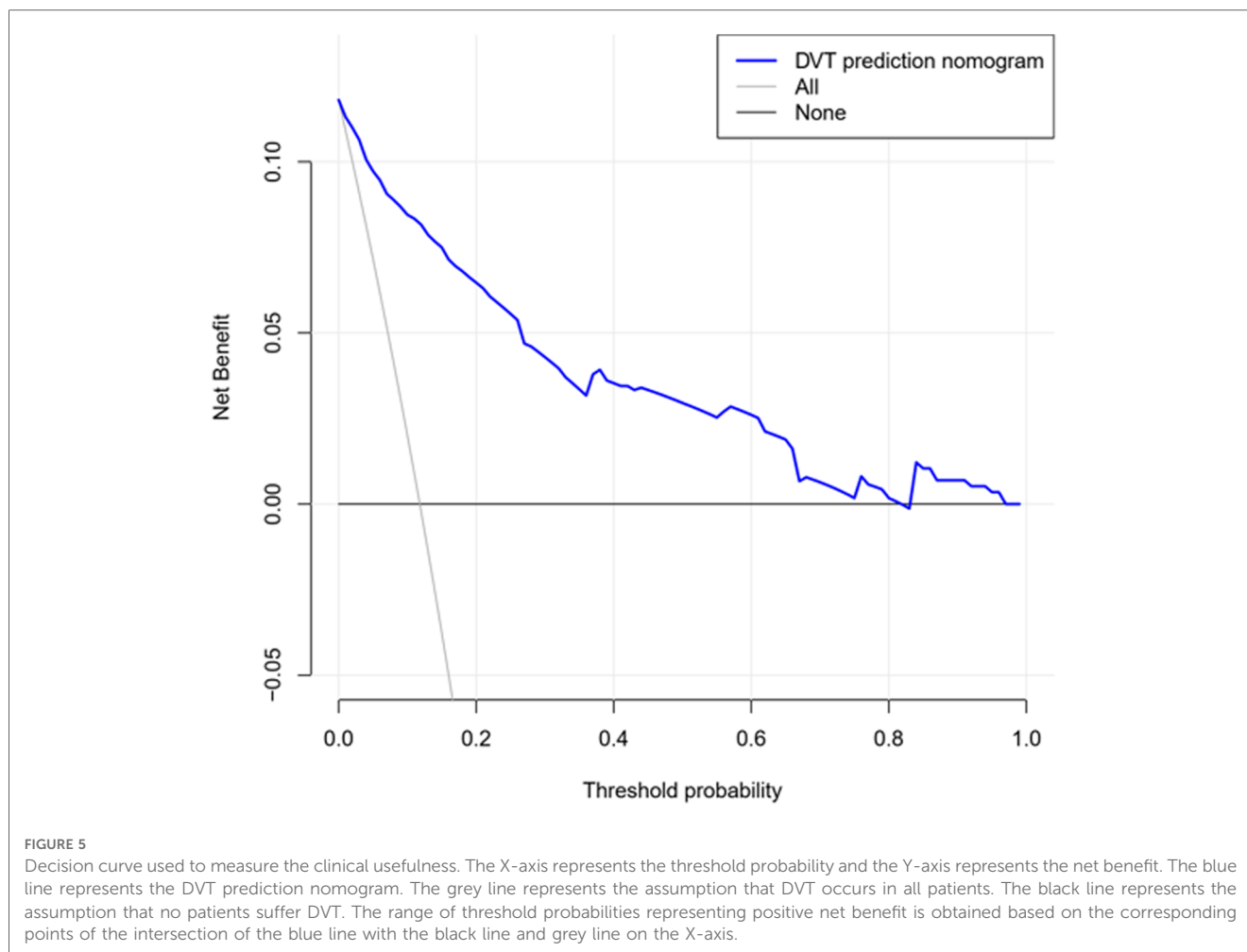


FIGURE 4 Calibration curves and ROC (receiver operating characteristic) curves of predicting DVT in the cohort. (A) ROC curves plotted to measure the discriminative capacity of nomogram. The area under curve (AUC) is positively correlated with the predictive accuracy of the nomogram. (B) Calibration curves of the DVT nomogram prediction in the cohort. In the calibration curve, the higher the overlap between the predicted curve and the ideal curve, the better the consistency between the predicted probability and the true probability.

must be a top concern (28–30). Regrettably, we were not able to find suitable publicly available datasets to verify this issue. The bootstrapping technique was thus used to perform internal

validation and our model demonstrated quite stable performance, reflecting its ability to avoid overfitting (11, 31). Given the fact that there are only 6 predictors in our model and they are easy



to implement, we are hoping that these results can be further validated by using clinical datasets from other investigators.

In the present study, 68 patients out of 576 were examined as asymptomatic proximal DVT by color Doppler ultrasonography above the popliteal vein, and the overall incidence of DVT was 11.81%. During the perioperative period of patients with lower limb fractures, many demographic, traumatic, and treatment features might be associated with the development of DVT. Our nomogram demonstrated that patients who had smoking history, delayed surgery, prolonged operation time, blood transfusion during operation, arthroplasty, and D-dimer level ≥ 5 $\mu\text{g/ml}$ might be more likely to develop DVT (32).

As shown by previous studies (33, 34), smoking was associated with the occurrence of DVT, but whether it was an independent risk factor was also controversial (35, 36). Our study suggested that patients who had smoking habit in our series had a higher incidence of DVT, and the logistic regression analysis found smoking to be an independent predictor in this nomogram. Many previous studies indicated that delayed hip fracture operation on the elderly could significantly increase the incidence of DVT (2, 37–39). However, clinical practice shows that elderly patients often have other concomitant diseases, especially those

over 80 years old, and eliminating the contraindications before operation often delays the operation. In our nomogram, a six-day or longer waiting before operation is an important factor contributing to the higher risk of DVT. Similar to the finding of previous studies (33, 40), longer operation time increased the risk of developing DVT, and more than two hours' operation time significantly increased the rate of DVT after lower limb fracture operation. In addition, intra-operative blood transfusion may also increase the risk of DVT, especially when the transfusion amount is more than 800 ml (41–44). The implant type also has impact on the risk of DVT. The implants used in this study included the plate and screw, intramedullary nail and artificial joint, of which the artificial joint was half hip or total hip replacement for femoral neck fracture. The incidence of DVT in hip replacement was higher than that in the internal fixation system, which was consistent with the previous reports (45). Previous studies demonstrated (46, 47) that the elevated level of D-dimer showed a significant association with DVT in patients with lower extremity fractures. In clinical practice, D-dimer is usually used as a reliable screening tool to predict DVT. But the precise level of D-dimer is still not clear (48, 49). It was found in our study that the rate of DVT significantly increased when the level of D-dimer exceeded 5 $\mu\text{g/ml}$.

The pathogenesis of DVT includes slow blood flow, a hypercoagulable state of blood and injury of the venous wall (50). The factors which can influence these pathological pathways may have impact on the risk of DVT. In traumatic orthopedics, fracture-associated peripheral capillary injury is often the initial factor of DVT formation. It is acknowledged that the incidence of DVT in lower limb fractures is much higher than that in other parts of the body, which is mainly related to the injury mechanism and the long-term bed confinement required for previous treatment (51). The incidence of DVT in elderly patients is significantly higher than that in the young patients due to their decreased motor function and cardiovascular function.

Several scoring systems have been built to help to predict the risk of DVT for general patients, such as Padua score and Caprini score (17–19). Unfortunately, elderly patients with lower limb fractures were all at the highest level according to above mentioned scoring systems (17–19). Based on this criterion alone, it is difficult for surgeons to make an effective and balanced decision and to know which patient should be focused on. That is why we not only made an incidence and risk factor analysis of DVT but also developed this nomogram of prediction model. For instance, the total points of a simple hip replacement patient were 98 and the incidence of DVT was much smaller than 10%, but if the patient had a smoking history and a high D-dimer level (>5 mg/ml), the total points would be $260(98 + 62 + 100)$ and the incidence of DVT would be almost 50%. Our model makes it possible to select patients who need early evaluation and intervention. We hope our work will provide an effective approach to improve accuracy and efficiency of predicting DVT so as to improve the prognosis of elderly patients with lower limb fracture.

There are several limitations in this study. First, our data were collected between January 2016 and December 2018, which might cause some selective bias. Second, we only collected the DVT consequence in the injury limbs and ignored the asymptomatic DVT in the uninjured leg. Third, we only performed color Doppler ultrasonography up to 7 days, and did not study long-term DVT results. Finally, although we have used bootstrap testing to examine internal validation of our nomogram, we are not sure whether this nomogram can be used universally in other hospitals or centers because of lack of external validation. Further studies are required to evaluate the long-term efficacy of this nomogram in larger-sample studies.

Conclusion

This study has developed a relatively accurate nomogram to assess the risk of DVT in elderly patients with lower limb fractures. In clinical practice, surgeons can use this nomogram to estimate the risk of DVT of individual patients, and perform relevant prophylaxis to prevent the development of DVT. Nevertheless, external validation is needed to determine whether individual interventions based on this nomogram can reduce the DVT risk.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Shanghai Pudong New Area People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SH, YB, KJ, JW, SL, DF, JW, KL: designed the study; SH, YB, KJ, YQ, JD, JZ, JH, and HS: analyzed the data; SH, YB, KJ, JW, SL, DF, JW, and KL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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