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Risk Estimation of Deep Venous Thrombosis in Polytrauma Patients with Traumatic Brain Injury: A Nomogram Approach

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Background: Deep venous thrombosis (DVT), known to be a major factor in poor outcomes and death rates, is common after polytrauma with traumatic brain injury (TBI). In this study, a nomogram will be developed to predict the risk of DVT in polytrauma patients with TBI, since there is currently no specific and convenient diagnostic method.

Methods: A retrospective and observational trial was conducted between November 2021 and May 2023. The predictive model was created using a group of 349 polytrauma patients with TBI in a training set, with data collected between November 2021 and August 2022. A nomogram was presented after using multivariable logistic regression analysis to create the predictive model. Validation of the model was conducted internally. A separate group for validation included 298 patients seen consecutively between August 2022 and May 2023.

Results: A total of 647 trauma patients were included in the study. Out of these, 349 individuals were part of the training group, while 298 were part of the validation group. Training cohorts reported 32.1% and validation cohorts reported 31.9% DVT. Age, Smoking, Injury Severity Score (ISS), Glasgow Coma Scale (GCS), D-dimer, Mechanical ventilation (MV) and Application of Vasoactive Drugs (AVD) comprised the individualized prediction nomogram. The model exhibited strong discrimination, achieving a C-index of 0.783 and a statistically insignificant result (P=0.216) following the Hosmer–Lemeshow test. Nomogram calibration plots and decision curve analysis showed the nomogram's utility in predicting DVT.

Conclusion: Our study characterized the incidence of DVT in polytrauma patients with TBI and further emphasized that it represented a substantial health concern, as evidenced by its frequency. Using this nomogram, it is possible to predict DVT in polytrauma patients with TBI based on demographics and clinical risk factors.

Keywords: polytrauma, traumatic brain injury, deep venous thrombosis, nomogram

Introduction

Polytrauma, defined as injuries with an Abbreviated Injury Scale (AIS) score of 3 or higher in at least two body regions (2AIS $\geq$ 3), is a complex condition associated with poor outcomes and high mortality rates resulting from severe damage and complicated complications, making it a persistent health concern.[1,2] A growing amount of proof indicates that over half of polytrauma patients present with a concomitant traumatic brain injury (TBI), which greatly affects their chances of long-term survival.[3] Virchow's Triad, consisting of trauma-induced stasis, a hypercoagulable state, and endothelial injury, is a common primary factor leading to high early mortality rates (30–50%) after injury, with deep venous thrombosis (DVT) being a pathological result of coagulation dysfunction.[4] Up to 20% of polytrauma patients suffer lower extremity DVT, which is a leading cause of death for those who survive the initial trauma.[5,6] Direct venous injury, increased blood clotting, and skeletal fixation all contribute to polytrauma patients' high DVT rates. Additionally, TBI patients are also at higher risk for blood clot complications because of immobility resulting from neurologic injuries, as well as sedatives and neuromuscular blocking agents.[7–10] It is consistent with our own clinical practice experience that polytrauma patients with TBI are at a greater risk than polytrauma patients without TBI of developing DVT.

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Managing bleeding and blood clotting presents a crucial and formidable challenge in instances of polytrauma, particularly in cases of traumatic brain injury (TBI), where surgeons must carefully weigh the risks of ongoing brain hemorrhage against the development of secondary thrombotic events such as deep venous thrombosis (DVT).[11] The commencement of chemical DVT prophylaxis may be postponed in polytrauma patients with TBI due to the concern of exacerbating intracranial hemorrhage. This delay in prophylaxis may elevate the likelihood of morbidity and mortality attributable to DVT.[1] The decision to initiate low-molecular-weight heparin or unfractionated heparin is typically made by the neurosurgery or trauma team in an acute care hospital.[12] However, due to the lack of definitive guidelines, chemical prophylaxis is usually initiated in response to stable bleeding conditions observed by repeated head CT scans or based on physician clinical expertise.[9]

It is essential to promptly recognize polytrauma patients with TBI who are at risk of developing DVT in order to provide effective treatment and optimize resource allocation. At present, the diagnosis of DVT depends on evaluating D-dimer (DD) concentrations and performing Venous Doppler ultrasound (VDU).[13] However, DD testing has limited specificity in diagnosing DVT, especially in polytrauma patients who have complicating factors like infection. Moreover, polytrauma patients in need of mechanical ventilation may not have easy access to VDU.[14] This study is focused on creating a nomogram to predict the likelihood of DVT in polytrauma patients with TBI due to the absence of a simple and specific diagnostic tool.

Patients and Methods

Study Design and Patients

This study was conducted with approval from the Institutional Review Board and involved retrospective observation with informed consent from participants. From November, 2021 to May, 2023, every patient was hospitalized in the Traumatic Intensive Care Unit (TICU) at the Advanced Trauma Center located in Tongji Hospital (Wuhan). A total of 647 patients in a row were eligible and categorized into DVT and N-DVT groups. Patients meeting the criteria from November 2021 to August 2022 were selected for the training group to create the nomogram, while those from August 2022 to May 2023 were assigned to the validation group. This approach adheres to established machine learning methodologies, where in the training dataset is employed to construct the predictive model, while the independent validation dataset is utilized to rigorously evaluate its performance. By employing temporally distinct cohorts, this design minimizes potential biases associated with overlapping data and ensures robust assessment of the nomogram's predictive accuracy. This strategy enhances the model's generalizability and reliability, facilitating its applicability in diverse real-world clinical settings. Approval for the current research was granted by the ethics committee of Tongji Hospital under the reference TJIRB20200720. Patients and their legal representatives gave their consent to the collection of their data. The entry criteria were as follows: 1) Diagnosed as polytrauma with TBI; 2) Admission to the hospital within 24 hours after trauma; 3) age over 18 years. The exclusion criteria were as follows: 1) Pregnancy;2) A history of VTE or received antithrombotic/anticoagulant therapy prior to admission; 3) Previous cerebrovascular accident history, including hemorrhagic and ischemic; 4) Admission after 24h post-trauma. All participants were administered venous thromboprophylaxis treatment and management in accordance with current guidelines.[15] Specifically, on the basis of preventing further injury and progressive cerebral hemorrhage, patients received early venous thromboprophylaxis, including chemical prophylaxis (either low molecular weight heparin or nadroparin calcium, administered once daily).[16]

Data Collection

Baseline clinical features were collected within 48 hours of admission by retrieving information from electronic medical and nursing files. The data contained details about the population, such as demographic information (eg age, sex), medical history (eg Injury Severity Score (ISS), Glasgow coma scale (GCS), cause and location of injury), laboratory results (eg D-dimer levels, lactate levels, APTT), and details of the hospital course (eg use of mechanical ventilation). Further, a VDU evaluation of the deep venous system and detection of DVT was performed on the lower extremities.

Diagnosis

The updated "Berlin criteria" for polytrauma now includes a patient with a score of 3 or higher on the Abbreviated Injury Scale (AIS) in at least two body regions (2AIS ≥ 3) along with at least one additional parameter such as hypotension, unconsciousness, acidosis, coagulopathy, or being over 70 years old.[17] DVT was characterized by abnormalities detected on VDU, like dilated veins that cannot be compressed or shadows within the vein that indicate thrombosis.[18] TBI was characterized by the detection of subdural hemorrhage, epidural hemorrhage, focal contusion, subarachnoid hemorrhage on computed tomography (CT) and diffuse axonal injury on clinical symptoms and magnetic resonance imaging (MRI) according to recommended guidelines.[19,20] Obesity is defined as a body mass index of 30 or greater.[21] Every subject who was enrolled received uniform treatment and care according to established guidelines for traumatic brain injury and polytrauma.[22] Chemical prophylaxis involves the initiation of low-molecular-weight heparin following admission, while the application of vasoactive drugs entails the use of norepinephrine and dopamine throughout the patient's hospitalization. The specification of the drugs used was according to the existing research.[23]

Statistical Analysis

Before conducting the analysis, the data was checked for normal distribution and equality of variance. Frequency counts and percentages were used to analyze categorical variables, while median/IQR or mean ± SD were utilized to assess continuous variables. Statistical analyses were conducted using the Student's *t*-test, Mann–Whitney *U*-test, and the two-tailed test. To determine the independent factors linked to DVT in polytrauma with TBI, a multivariate logistic regression analysis was performed. Following this, a nomogram was created using the findings from the multivariable logistic regression analysis and the rms software in the R coding language. The C-index was employed for evaluating model accuracy, bootstrap validation for detecting overfitting, calibration plot for assessing nomogram performance, and ROC curve analysis for predictive accuracy. Data analysis was conducted using R software (version 3.6.3) and GraphPad Prism software 9.3.1.

Results

Sociodemographic Characteristics, Laboratory Parameters and Events of the Hospital Course in Trauma Patients

A total of 647 trauma patients meeting the inclusion criteria were included in the study cohort. Out of these, 349 individuals were part of the training group, while 298 were part of the validation group. Table 1 provides patient characteristics for both the training and validation cohort. The prevalence of DVT shows no significant differences between the two cohorts (P= 0.99). In the training and validation cohorts, the occurrence of DVT was 32.1% and 31.9%, respectively. The clinical characteristics did not show any notable discrepancies between the training and validation cohorts, whether in the DVT and N-DVT groups, supporting their selection as training and validation cohorts.

In univariate analysis, Age, Obesity, Smoking, D-dimer levels, ISS score, GCS score, Mechanical ventilation, First day of chemical prophylaxis ≤3d and Application of vasoactive drugs were risk factors for DVT in the training cohort. Notably, delayed initiation of chemical prophylaxis was found to be particularly risky for developing DVT in this group. Emerging studies highlight the delicate balance between preventing thrombotic complications and managing bleeding risks in patients with TBI after polytrauma. The initiation of chemical prophylaxis is often delayed due to concerns about the potential progression of intracranial hemorrhage, with repeated head CT scans typically required to confirm stable bleeding conditions. While this cautious approach is essential for minimizing bleeding risks, inconsistencies in clinical practice frequently result in further delays, thereby increasing the risk of deep vein thrombosis (DVT), as observed in our cohort. Table 1 contains important predictors for DVT.

Multivariate Analyses of Relative Factors for DVT

Following univariate examination, variables with a P value <0.05 in the training cohort were chosen for multivariate analysis utilizing a stepwise multiple regression approach. Multivariate logistic regression analysis indicated that a higher Age (OR1.725, 95% CI 1.215–5.314, P=0.016), Smoking (OR 1.976, 95% CI1.142–4.642, P=0.003), ISS (OR 3.612,

Table 1 Comparison of Sociodemographic Characteristics, Laboratory Parameters and Events of the Hospital Course Between DVT (+) and DVT (−) in Training and Validation Cohorts

Variables	Training (n=349)		*P*	Validation (n=298)		*P*
	DVT (+,112)	DVT (−,237)		DVT (+,95)	DVT (−,203)	
Age	56.1±12.3	47.6±11.3	< 0.01	57.3±11.5	46.2±10.4	< 0.01
Male	84 (75.0)	177 (74.7)	0.95	70 (73.7)	153 (75.4)	0.87
Obesity	20 (17.9)	19 (8.0)	< 0.01	18 (18.9)	16 (7.9)	< 0.01
Hypertension	21 (18.9)	41 (17.3)	0.86	17 (17.9)	37 (18.2)	0.93
Hyperlipidemia	28 (25.0)	65 (27.4)	0.73	24 (25.3)	49 (24.1)	0.95
Smoking	76 (67.9)	86 (36.3)	< 0.01	67 (70.5)	84 (41.4)	< 0.01
Cause of injury	–	–	0.21	–	–	0.25
Traffic accident	79 (70.5)	165 (69.6)	–	69 (72.6)	151 (74.4)	–
High-energy fall	26 (23.2)	55 (23.2)	–	21 (22.1)	41 (20.2)	–
Other	7 (6.3)	17 (7.2)	–	5 (5.3)	11 (5.4)	–
Anatomical location of injury	–	–	0.32	–	–	0.44
Thoracic injury	58 (51.8)	129 (54.4)	–	51 (53.7)	114 (56.2)	–
Abdominal injury	50 (44.6)	94 (39.7)	–	45 (47.4)	104 (51.2)	–
Pelvic and limbs fracture	81 (72.3)	116 (48.9)	–	73 (76.8)	124 (61.1)	–
ISS	32.8±6.9	30.4±6.1	< 0.01	33.5±6.5	31.2±7.1	< 0.01
GCS	8.2±2.1	10.4±1.7	< 0.01	8.9±2.4	10.1±1.8	< 0.01
Location of brain injury			0.07			0.08
Subdural hemorrhage	42 (37.5)	60 (25.3)		37 (38.9)	53 (26.1)	
Epidural hemorrhage	24 (21.4)	68 (28.7)		20 (21.1)	55 (27.1)	
Focal contusion	71 (63.4)	113 (47.7)		61 (64.2)	100 (49.3)	
Subarachnoid hemorrhage	48 (42.9)	99 (41.8)		39 (41.1)	82 (40.4)	
Blood transfusions	–	–	0.12	–	–	0.16
Red cells	39 (34.8)	56 (23.6)	–	34 (35.8)	46 (22.7)	–
Platelets	13 (11.6)	21 (8.9)	–	9 (9.5)	15 (7.4)	–
Fresh frozen plasma	27 (24.1)	30 (12.7)	–	25 (26.3)	19 (9.4)	–
Lactate	1.9±0.8	1.8±0.7	0.24	1.7±0.6	1.8±0.8	0.28
PT	15.1±2.4	14.5±3.2	0.08	16.3±2.6	16.7±2.4	0.19
APTT	40.1±11.8	38.6±10.5	0.23	41.6±12.5	39.8±11.3	0.22
D-dimer	15.3±6.2	3.6±1.3	< 0.01	17.6±6.4	3.7±1.8	< 0.01
Mechanical ventilation	34 (30.4)	19 (8.2)	< 0.01	33 (34.7)	13 (6.4)	< 0.01
First day of chemical prophylaxis ≤3d	25 (22.3)	140 (60.1)	< 0.01	27 (28.4)	126 (62.1)	< 0.01

(*Continued*)

Table 1 (Continued).

Variables	Training (n=349)		*P*	Validation (n=298)		*P*
	DVT (+,112)	DVT (−,237)		DVT (+,95)	DVT (−,203)	
Application of vasoactive drugs (norepinephrine or dopamine)	42 (37.5)	11 (4.7)	< 0.01	33 (34.7)	7 (3.4)	< 0.01
Skeletal traction	34 (30.4)	60 (25.3)	0.39	32 (33.7)	55 (27.1)	0.30
Operation	89 (79.5)	165 (69.6)	0.07	71 (74.7)	133 (65.5)	0.14
Craniotomy	35 (31.3)	69 (29.1)	0.78	27 (28.4)	52 (25.6)	0.71
Internal fixation of fractures	45 (40.2)	81 (34.2)	0.33	36 (37.9)	68 (33.5)	0.54
Others	9 (8.0)	15 (6.3)	0.72	8 (8.4)	13 (6.4)	0.70

Notes: All values are presented as mean ± standard deviation or number (percentage); P < 0.05 is statistically significant.
Abbreviations: DVT, deep vein thrombosis; GCS, Glasgow coma scale; ISS, injury severity score.

95% CI1.354–8.437, P=0.006), D-dimer (OR2.847, 95% CI 1.243–6.831, P = 0.014), Mechanical ventilation (OR 1.824, 95% CI, 1.011–5.835, P = 0.024), Application of vasoactive drugs (OR 2.018, 95% CI 1.164–6.312, P =0.013) and a lower GCS (OR0.425 95% CI 0.237–0.863, P=0.009) were all linked to an increased risk of DVT (Table 2).

Construction of the Risk Score and Nomogram-Based Calculator

A nomogram, serving as a visual aid, displays the importance of different factors in a model and can assist in predicting the likelihood of certain results. The training cohort utilized these risk factors that were independently linked to create a nomogram to estimate DVT risk. When employing the nomogram, it is essential to identify the position of each factor on the corresponding axis, draw a line connecting the points axis based on the assigned number of points, calculate the total points accumulated from all factors, and trace a line from the total points axis to determine the probabilities of DVT at the lowermost section of the nomogram (Figure 1). Through the training process, the model was internally validated. Based on the calibration curve, the prediction and observation of DVT were in good agreement in the training cohort because of a closer ft to the diagonal dashed line that represents an ideal evaluation by a perfect model. The Hosmer-Leme exhibition examination resulted in a statistically insignificant finding (P=0.216), indicating that there was no

Table 2 Multivariable Logistic Regression Model for Predicting Development of Deep Venous Thrombosis in Polytrauma Patients with Traumatic Brain Injury in the Training Cohort

Variables	B	OR	Odds Ratio (95% CI)	*P*
Age	0.532	1.725	1.215–5.314	0.016
Obesity	0.974	1.125	0.894–1.436	0.152
Smoking	1.026	1.976	1.142–4.642	0.003
ISS	1.283	3.612	1.354–8.437	0.006
GCS	−0.856	0.425	0.237–0.863	0.009
D-dimer	1.206	2.847	1.243–6.831	0.014
Mechanical ventilation	0.601	1.824	1.011–5.835	0.024
First day of chemical prophylaxis ≤3d	1.263	1.783	0.354–3.742	0.073
Application of vasoactive drugs	0.702	2.018	1.164–6.312	0.013

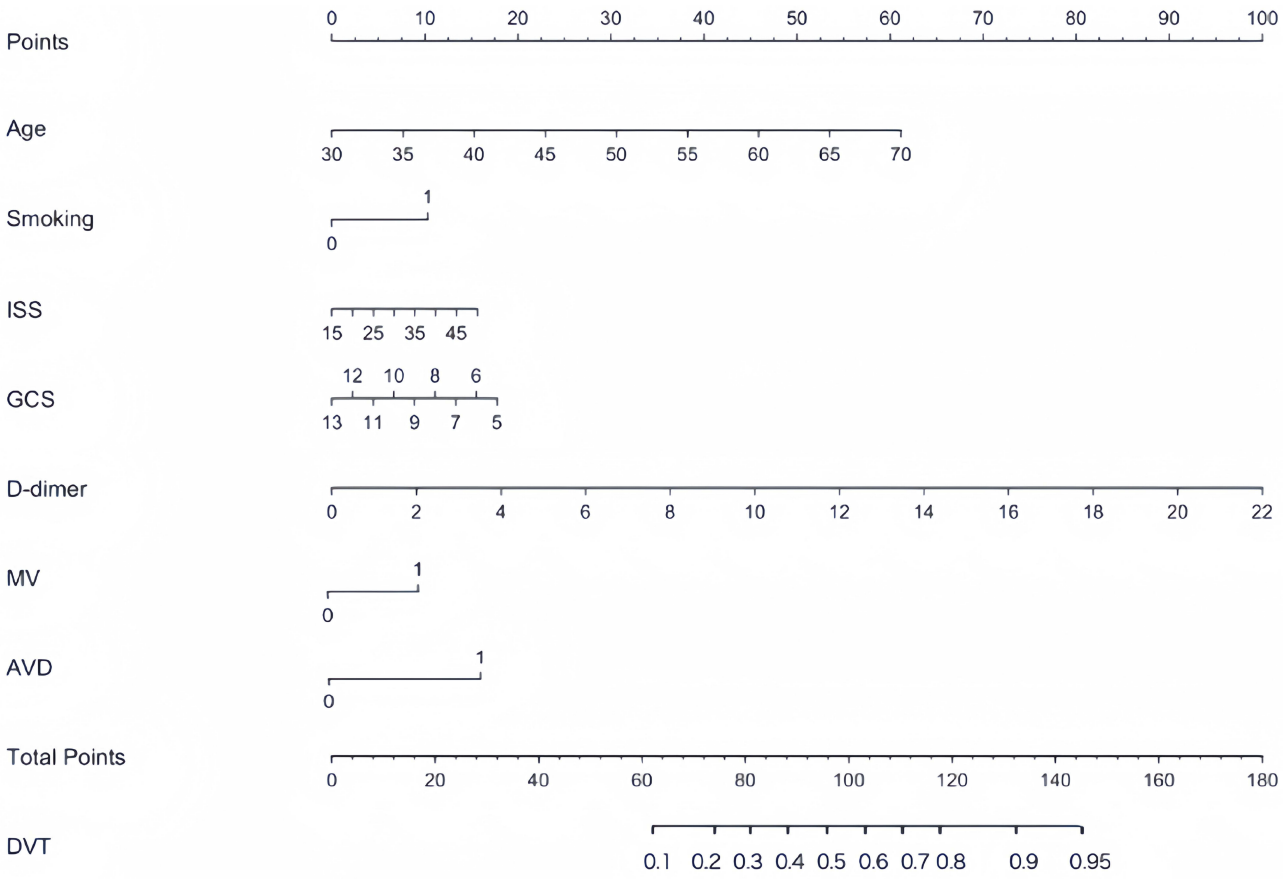

Figure 1 Developed DVT-predicting nomogram. Developed DVT-predicting nomogram. The DVT-predicting nomogram was developed in the training cohort.
Abbreviations: MV, Mechanical ventilation; AVD, Application of vasoactive drugs.

deviation from ideal alignment (Figure 2A). The nomogram had an AUC of 0.783 in the training group when analyzing the ROC curve (Figure 2B). Additionally, the training model's net benefit rate closely matched the validation model's within the threshold range of 0.0–1.0 (Figure 2C).

Discussion

DVT is classically caused by stasis, hypercoagulability, and endothelial injury, called Virchow's Triad, which occurs frequently in polytrauma patients.[24] Meanwhile, in cases of multiple traumatic injuries, bleeding can result in the activation of blood clotting factors, potentially resulting in DVT.[25] Following the initial survival of the acute phase on day one, the primary worries for these individuals involve severe complications that could be dangerous to life, such as DVT.[26] The occurrence of DVT in trauma cases ranges from 7% to 60%, varying based on patient characteristics, detection techniques, and preventive measures.[27,28] In our literature, the incidences of DVT were 32.1% in polytrauma patients with TBI. In our previous literature, significant difference in the DVT rate between polytrauma patients with TBI and those with isolated TBI (31.9% vs 20.2%, P<0.05), despite similar GCS scores. Polytrauma patients with TBI had a higher DVT rate than polytrauma patients without TBI (31.9 versus 22.0%, P<0.05), even though ISS was not different.[1] A possible explanation for this might be that many people who suffer TBIs have immobility, weakness, and bed rest, as well as other injuries that can increase their risk of venous stasis.[12] DVT is three to four times more likely to occur in people suffering from traumatic brain injury (TBI) according to a 2009 study.[29]

Our study identified older age, smoking, elevated D-dimer levels, higher ISS scores, lower GCS scores, mechanical ventilation, and increased use of vasoactive drugs as independent risk factors for DVT in polytrauma patients with TBI. Among these, age emerged as a particularly critical determinant, consistent with existing evidence highlighting the

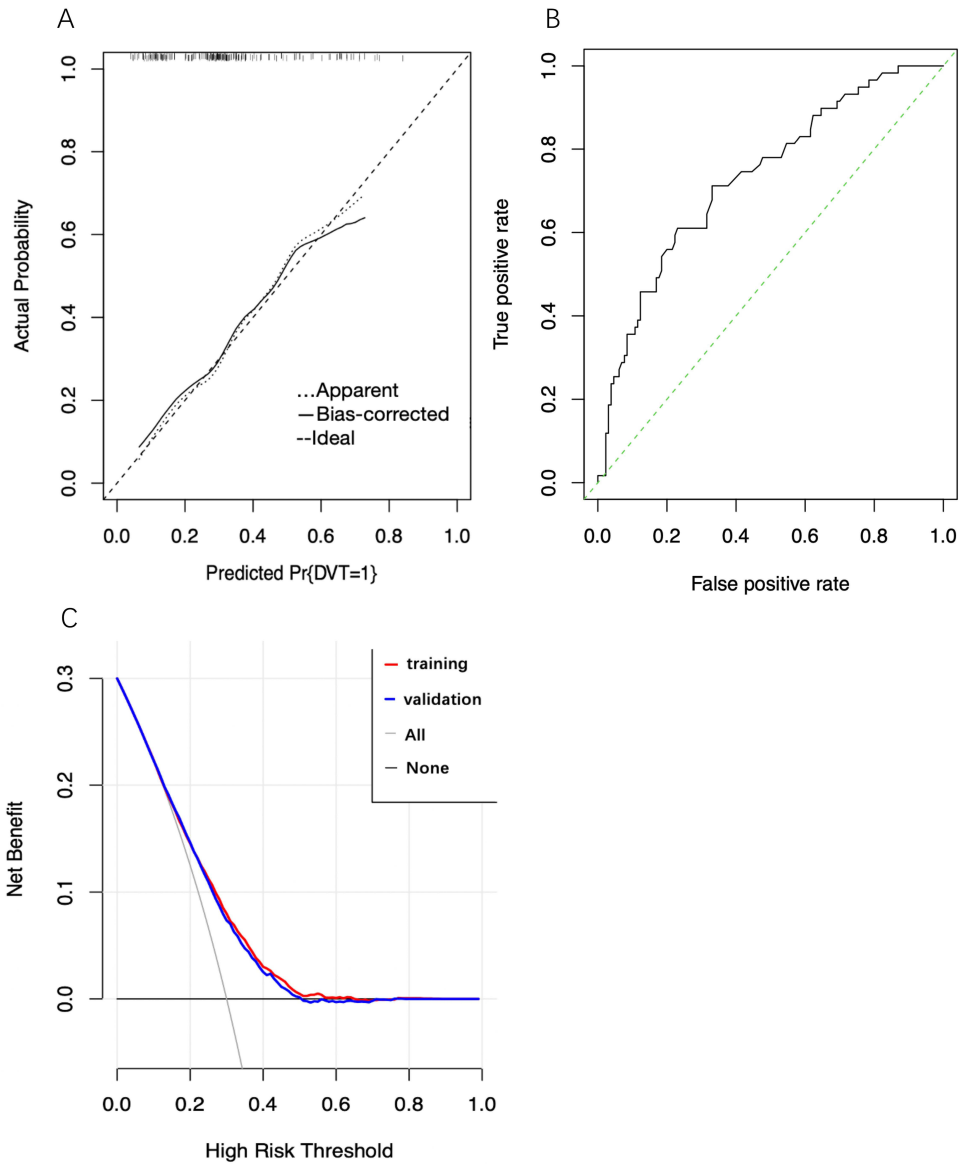

Figure 2 Calibration curves, ROC curve analysis for the sensitivity and specificity and decision curve analysis of the DVT-predicting nomogram. (**A**) Calibration curves of the DVT-predicting nomogram. Calibration curves depict the agreement between the predicted risks of DVT and observed outcomes of DVT. (**B**) ROC curve analysis for the sensitivity and specificity of the nomogram in the training cohort. (**C**) Decision curve analysis for the DVT-predicting nomogram. The y-axis measures the net benefit. The pink line represents the nomogram of training cohort. The blue line represents the nomogram of validation cohort. Thin black line represents the assumption that no patients have DVT. The net benefit was calculated by subtracting the proportion of all patients who are false-positive from the proportion who are true positive.

heightened risk of venous thromboembolism (VTE) in older populations. Studies indicate a near doubling of DVT risk for every additional decade of life, particularly in individuals over 40 years of age.[30] Age-related physiological changes, including reduced venous compliance, endothelial dysfunction, and an enhanced prothrombotic state, likely contribute to this increased vulnerability. These findings underscore the need for more aggressive thromboprophylaxis strategies in older patients, who may also have coexisting comorbidities, further predisposing them to thrombotic events.[31] Smoking amplifies the hypercoagulable state in trauma patients through endothelial dysfunction, platelet activation, and systemic inflammation. Its interaction with high ISS scores suggests a synergistic effect, exacerbating coagulation activation in severely injured individuals. Addressing smoking cessation, particularly in pre-hospital and rehabilitation settings, could mitigate thrombotic complications and improve outcomes.[32] Elevated D-dimer levels, a biomarker of fibrin turnover, also demonstrated a strong association with DVT risk. Recent bioinformatics analyses validate the predictive value of D-dimer in neurosurgical patients, with findings indicating that its measurement can reliably identify patients at high

risk for VTE.[33] In polytrauma patients with TBI, where clinical symptoms may be masked or nonspecific, D-dimer could serve as a critical adjunct for early risk stratification and targeted prophylactic interventions. Mechanical ventilation further compounds the risk of DVT by promoting venous stasis through prolonged immobility, a hallmark of Virchow's triad. Patients requiring extended ventilatory support are particularly susceptible to thrombus formation due to restricted mobility and altered hemodynamics.[34] Moreover, the use of vasoactive drugs, often reflective of hemodynamic instability, underscores the severity of the underlying trauma and its contribution to a hypercoagulable state.[35]

A nomogram was created and validated internally to predict DVT on an individual basis in polytrauma patients with TBI. The nomogram incorporates seven items of the Age, Smoking, ISS, GCS, D-dimer, MV and AVD. The risk score's performance was deemed satisfactory in the training cohort, achieving an accuracy of 0.78 based on AUC. Utilize the nomogram for predicting DVT to assess the likelihood of DVT in a patient admitted to the hospital. Typically, the seven necessary variables for assessing the risk of DVT are easily accessible. As shown in Figure 1, the nomogram aligns well with our everyday clinical practice and is user-friendly. The calibration graphs and decision curve analysis of the nomogram for predicting DVT underscore its strong potential for clinical applicability. The calibration plot demonstrated excellent concordance between predicted risks and actual observed outcomes, with the predicted values closely following the diagonal line, thereby confirming the model's robust reliability and precision. Furthermore, the decision curve analysis revealed that the nomogram offers superior net benefit over a range of threshold probabilities when compared to the simplistic strategies of assuming either universal or no DVT treatment. These results affirm the nomogram's substantial value in facilitating informed risk stratification and optimizing clinical decision-making in polytrauma patients. In cases where the patient's likelihood of developing DVT is deemed low, the healthcare provider may opt for observation, while high-risk assessments could warrant intensive treatment or hospitalization in the ICU.

Although our study provides valuable insights, its retrospective design inherently limits the ability to establish causal relationships and control for all confounding factors. Additionally, DVT detection was primarily based on ultrasound examinations conducted during the hospital stay, which may have resulted in missed cases of DVT that developed after discharge or in those with subclinical symptoms. This method of detection may not capture the full spectrum of DVT incidence, particularly minor cases that were asymptomatic. Another limitation is the inclusion of both surgical and non-surgical patients, which could introduce variability in patient outcomes and treatment approaches, potentially influencing the results. Lastly, while the nomogram exhibited strong internal validation, the generalizability of its findings to broader populations remains uncertain, necessitating multicenter validation studies to assess its external applicability and robustness across different clinical settings.

Conclusion

Our research investigated the frequency of DVT in polytrauma patients with TBI and highlighted its significant impact on health outcomes. Additionally, we developed a nomogram that incorporates relevant factors to aid in the personalized prediction of DVT in this patient population.

Institutional Review Board Statement

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committee at Tongji Hospital (approval date: 22 July 2020).

Data Sharing Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical, legal and privacy issues.

Informed Consent Statement

Informed consent was obtained from each patient or the patient's legally authorized representative involved in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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