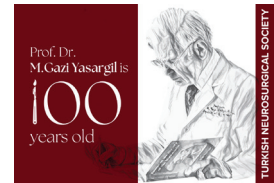




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Prediction and Analysis of Risk Factors for Lower Extremity Deep Vein Thrombosis After Craniotomy in Patients with Primary Brain Tumors: A Machine Learning Approach

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ABSTRACT

AIM: To explore the risk factors associated with the occurrence of lower extremity deep vein thrombosis (DVT) after craniotomy in patients with primary brain tumors, and to develop a predictive model using machine learning.

MATERIAL and METHODS: A prospective cohort study was conducted on 140 patients with primary brain tumors who underwent neurosurgical treatment at our hospital between March 2021 and September 2022. A logistic regression analysis was performed to identify independent risk factors associated with postoperative DVT. Additionally, multiple machine learning models were developed and evaluated to determine their predictive performance.

RESULTS: The incidence of lower extremity DVT after craniotomy was 27.9%. Logistic regression identified age [OR=1.07, 95% CI (1.03–1.11)], GCS score [OR=0.88, 95% CI (0.78–0.98)], D-dimer level [OR=1.08, 95% CI (1.02–1.15)], and mechanical ventilation (≥ 48 hours) [OR=3.83, 95% CI (1.21–12.15)] as independent risk factors ($P < 0.05$). The Gradient Boosting Machine (GBM) had the highest prediction accuracy among the assessed machine learning models, achieving an area under the curve (AUC) of 0.850, with a sensitivity of 56.44% and a specificity of 90.09%.

CONCLUSION: Age, D-dimer, and mechanical ventilation (≥ 48 hours) are independent risk factors for the development of lower extremity DVT after craniotomy in patients with primary brain tumors. The GCS score serves as a potential protective risk factor. The GBM model, with its high AUC and specificity, offers a promising tool for early identification of high-risk patients, potentially informing clinical decision-making and targeted interventions.

KEYWORDS: Brain tumor, Lower extremity, Machine learning, Venous thrombosis

ABBREVIATIONS: DVT: Deep vein thrombosis, BMI: Body mass index, AUC: Area under the curve, PE: Pulmonary embolism, LR: logistic regression, RF: Random forest, SVM: Support vector machine; GBM: Gradient boosting machine, NN: Neural network, LDA: Linear discriminant analysis; ROC: Receiver operating characteristic, GCS: Glasgow coma scale, VTE: venous thromboembolism

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■ INTRODUCTION

Research has indicated that individuals with primary brain tumors are susceptible to developing deep vein thrombosis (DVT) in their lower limbs. This is mostly attributable to factors such as surgical interventions, lengthy surgical durations, prolonged postoperative bed rest, limb hemiplegia, and hypercoagulable states (6,9,15). DVT is a prevalent and severe vascular condition primarily affecting the deep veins of the lower limbs. The formation of a blood clot, known as a thrombus, in these veins impedes venous blood flow, leading to localized circulation obstruction. Common symptoms encompass swelling, pain, skin discoloration, and varicose veins in the affected limb. If not treated promptly, DVT may result in emboli dislodging and migrating to the pulmonary artery, causing pulmonary embolism (PE), a severe and potentially fatal complication. This is a major contributor to the development of PE. PE is the most severe complication of DVT, manifesting as abrupt chest pain, dyspnea, palpitations, and hypoxemia. In extreme cases, PE can be fatal, with a mortality rate ranging from 9% to 50%, presenting a substantial threat to the patient's life (3,4,10). Research indicates that approximately 50% of PEs are caused by thrombi detaching from the venous wall and passing through the heart to the pulmonary artery (10). Therefore, prompt intervention and preventive measures are essential to reduce the risk of lower extremity DVT in patients with primary brain tumors after craniotomy.

The objective of this study was to identify the risk factors associated with the development of lower extremity deep vein thrombosis (DVT) following craniotomy in patients with primary brain tumors and to develop a predictive model using machine learning techniques. This work seeks to improve the precision of detecting high-risk patients by integrating multiple machine learning models. Early detection and intervention for these patients can diminish the occurrence of DVT, enhance clinical outcomes, and promote improved patient safety and quality of life. The findings of this study provide healthcare professionals with valuable references to guide clinical decision-making and improve postoperative care.

■ MATERIAL and METHODS

Ethics approval and consent to participate:

All procedures performed in studies were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval for this study was approved by the Ethical Committee of Shanghai Pudan Hospital (Approval No. SHSY-IEC-5.0/22K26). All patients gave their written informed consent.

Study Design and Participants

This prospective cohort study included 140 patients with primary brain tumors who underwent craniotomy at the Neurosurgery Department of our hospital between March 2021 and September 2022. Patients were enrolled based on the following inclusion criteria: i. age ≥ 18 years; ii. no thrombi detected by Doppler ultrasound examination of the lower extremities upon admission to the Neurosurgery Department; iii. sched-

uled for craniotomy for brain tumor resection. Exclusion criteria: i. refusal to participate in the trial; ii. abnormal coagulation function; iii. prior treatment with anticoagulants or thrombus removal before admission; iv. presence of psychiatric disorders.

Collected clinical data included demographic information on gender, age, Body Mass Index (BMI), hypertension, diabetes, Glasgow Coma Scale (GCS), types of brain tumor, duration of stay in the Neurosurgery Department, D-dimer levels on the third day after craniotomy, Caprini score, APACHE II score, mechanical ventilation, deep vein catheterization, muscle strength assessment, presence of infection, and use of vasopressors.

DVT Screening and Diagnosis

All patients received bilateral lower extremity Doppler ultrasound examinations twice a week during hospitalization using the P40 Pro Doppler ultrasound system (SonoScape Medical Corp, P. R. China). DVT was diagnosed based on the following criteria: i. incomplete venous compression under probe pressure; ii. a noticeably enlarged diameter of the thrombosed vein segment, exhibiting varying echo levels from the intraluminal blood clot; iii. color Doppler ultrasound showed color flow imaging during embolization, indicating vein thinning or a lack of blood flow; iv. the pulsed Doppler indicates the absence of a blood flow signal in the thrombus segment, with no respiratory variation observed in the distal thrombus blood flow; v. abnormal Valsalva maneuver.

All Doppler ultrasound diagnoses were performed using P40 Pro (SonoScape Medical Corp, CN) (Figure 1). To ensure diagnostic reliability, all ultrasound examinations were performed by two board-certified radiologists blinded to clinical data.

Statistical Analysis

Data entry was conducted independently by two research nurses and subsequently verified by a third researcher. Continuous variables were expressed as mean $\pm$ standard deviation (SD) and assessed using t-tests, whereas categorical variables were denoted as percentages and analyzed with Fisher's exact test or chi-square tests. Univariate logistic regression identified possible risk variables ($p < 0.05$), followed by multivariate logistic regression to determine independent predictors, reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Missing data ($< 5\%$) were handled by multiple imputation. A significance level of $p < 0.05$ was applied, and statistical analyses were performed using Stata 15.0 SE (Texas, USA).

Machine Learning Model Development

Six machine learning algorithms were employed in Orange 3.27.1 (Ljubljana, Slovenia) to construct predictive models for postoperative DVT: logistic regression (LR), random forest (RF), support vector machine (SVM), gradient boosting machine (GBM), neural network (NN), and linear discriminant analysis (LDA). Feature selection was based on clinical relevance and statistical significance, including 10 variables: age, GCS score, APACHE II score, Caprini score, duration of neurosurgical stay (days), D-dimer levels, muscle strength, hypertension,

mechanical ventilation (≥ 48 hours), and infection. The model's performance was evaluated using 10-fold cross-validation, focusing on metrics such as area under the curve (AUC), classification accuracy, precision (positive predictive value), recall (true positive rate), sensitivity, and specificity.

RESULTS

Comparison of Clinical Data Between Two Groups

This study included a cohort of 140 patients diagnosed with primary brain tumors. Among them, 39 experienced lower extremity DVT, while 101 patients did not develop DVT. The thrombosis group had a markedly higher mean age of 59.51 years in contrast to the non-thrombosis group, which had a mean age of 49.78 years. No significant correlations were

found between gender or BMI and the risk of DVT ($p=0.5822$, $p=0.7466$, respectively). The thrombosis group exhibited substantially higher values for the APACHE II score ($p=0.001$), Caprini score ($p=0.0367$), length of stay in the neurosurgery department ($p=0.0066$), and D-dimer levels ($p=0.0354$) compared to the non-thrombosis group. The Glasgow Coma Scale (GCS) score ($p=0.0023$) was significantly higher in the non-thrombosis group than in the thrombosis group. The thrombosis group had greater proportions of muscle strength ≤ 3 ($p=0.0965$), hypertension ($p=0.0769$), mechanical ventilation (≥ 48 hours) ($p=0.0011$), and infection ($p=0.0465$) compared to the non-thrombosis group. No significant difference in tumor types was noted between the thrombosis and non-thrombosis groups ($p=0.697$), with gliomas being the predominant tumor type (Table I).

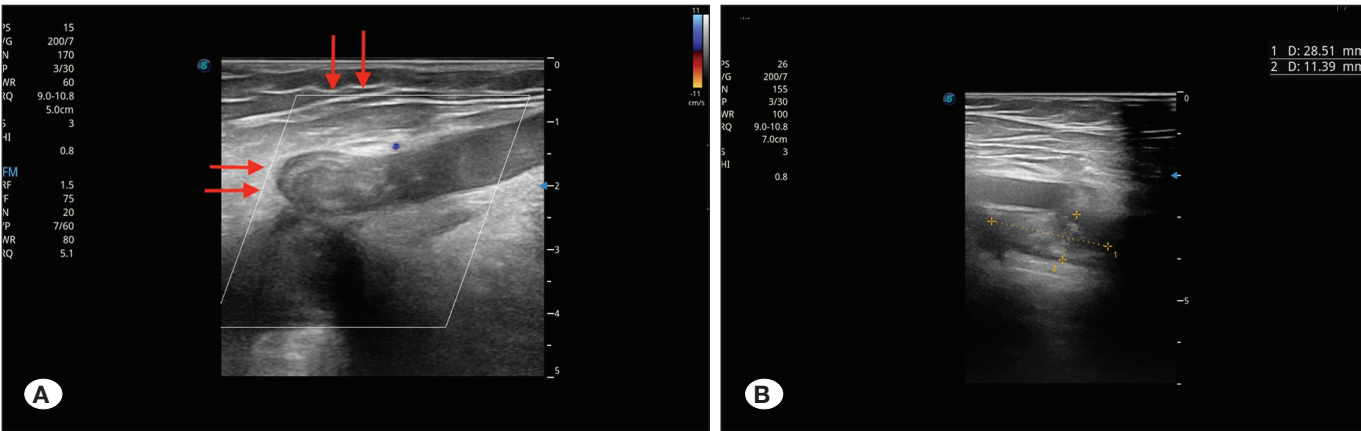


Figure 1: Ultrasound of venous embolism in a 67-year-old female patient. A) Color flow Doppler imaging profile image. B) Ultrasound transverse profile image.

Table I: Comparison of Clinical Data Between Two Groups

Item	Thrombosis Group (n=39)	Non-thrombosis Group (n=101)	t-value	p-value
Age [years, Mean (SD)]	59.51 (9.74)	49.78 (16.56)	-3.4427	<0.001
Gender [n(%)]			-0.5502	0.5822
Male	19 (48.72)	44 (43.56)		
Female	20 (51.28)	57 (56.44)		
GCS score [Mean (SD)]	8.82 (3.89)	11.19 (4.11)	3.1011	0.0023
APACHE II score [Mean (SD)]	14.10 (4.75)	10.08 (5.67)	-3.9292	0.001
APACHE—II A	3.31 (1.56)	2.25 (1.92)	-3.0830	0.0025
APACHE—II B	1.67 (1.27)	1.67 (1.32)	0.0273	0.9783
APACHE—II C	6.18 (3.90)	3.81 (4.10)	-3.1011	0.0023
APACHE—II D	2.95 (2.63)	2.39 (2.32)	-1.2411	0.2167
Caprini score [Mean (SD)]	9.82 (2.41)	8.94 (2.13)	-2.1098	0.0367
Neurosurgery stay [Mean (SD)]	18.18 (13.30)	11.04 (13.88)	-2.7589	0.0066
D-dimer [ug/mL, Mean (SD)]	7.46 (7.97)	4.79 (6.09)	-2.1252	0.0354

Table I: Cont.

Item	Thrombosis Group (n=39)	Non-thrombosis Group (n=101)	t-value	p-value
Muscle strength (Medical Research Council Scale) [cases (%)]			1.6622	0.0965
≥4	28 (71.79)	85 (84.16)		
≤3	11 (28.20)	16 (15.84)		
Hypertension [n(%)]			-1.7690	0.0769
Yes	16 (41.03)	26 (25.74)		
No	23 (58.97)	75 (74.26)		
Hyperglycemia [n(%)]			-1.0532	0.2922
Yes	2 (5.13)	11 (10.89)		
No	37 (94.87)	90 (89.11)		
Surgery [n(%)]			0.3079	0.7582
Yes	34 (87.18)	86 (85.15)		
No	5 (12.82)	15 (14.85)		
Central venous catheter [n(%)]			-1.0880	0.2766
Yes	39 (100)	98 (97.03)		
No	0	3 (2.97)		
Hemostatic drugs [n(%)]			1.5158	0.1296
Used	37 (94.87)	100 (99.01)		
Not used	2 (5.13)	1 (0.99)		
Vasopressors [n(%)]			0.8955	0.3705
Used	5 (12.82)	8 (7.92)		
Not used	34 (87.18)	93 (92.08)		
Sedatives/analgesics [n(%)]			1.1345	0.2566
Used	36 (92.31)	86 (85.15)		
Not used	3 (7.69)	15 (14.85)		
Mechanical ventilation (≥48 hours) [n(%)]			3.2758	0.0011
Yes	14 (35.90)	12 (11.88)		
No	25 (64.10)	89 (88.12)		
Infection [n(%)]			-1.9910	0.0465
Yes	14 (35.90)	20 (19.80)		
No	25 (64.10)	81 (80.2)		

GCS: Glasgow Coma Scale, **APACHE:** Acute Physiologic Assessment and Chronic Health Evaluation.

Univariate Logistic Regression Model

The univariate regression analysis identified several potential risk factors: patient age, APACHE II score, Caprini score, length of stay in the neurosurgery department, D-dimer levels,

hypertension, mechanical ventilation (≥48 hours), and infection. The GCS score and muscle strength of ≥4 were identified as potential protective factors (Table II).

Table II: Univariate Logistic Regression Model

Item	OR	p-value	95% CI
Age	1.05	0.002	(1.02, 1.09)
GCS score	0.87	0.003	(0.79, 0.95)
APACHE II score	1.14	<0.001	(1.06, 1.23)
Caprini score	1.21	0.041	(1.08, 1.45)
Neurosurgery stay	1.03	0.011	(1.01, 1.06)
D-dimer	1.06	0.040	(1.00, 1.11)
Muscle strength (Medical Research Council Scale)			
≤3	Ref		
≥4	0.24	0.001	(0.10, 0.53)
Hypertension			
No	Ref		
Yes	2.01	0.080	(0.92, 4.37)
Mechanical ventilation (≥48 hours)			
No	Ref		
Yes	4.15	0.002	(1.70, 10.11)
Infection			
No	Ref		
Yes	2.27	0.049	(1.00, 5.13)

GCS: Glasgow coma scale, **APACHE:** Acute physiologic assessment and chronic health evaluation.

Table III: Multivariate Logistic Regression Model

Item	OR	p-value	95% CI
Age	1.07	0.001	(1.03, 1.11)
GCS score	0.88	0.021	(0.78, 0.98)
D-dimer	1.08	0.009	(1.02, 1.15)
Mechanical ventilation (≥48 hours)			
No	Ref		
Yes	3.83	0.023	(1.21, 12.15)

GCS: Glasgow Coma Scale.

Multivariate Logistic Regression Model

In the multivariate regression model, we observed that the probability of post craniotomy lower extremity DVT increased by 7% for each additional year of patient age. For each one-point reduction in the Glasgow Coma Scale (GCS) score, the risk of lower extremity DVT after craniotomy decreased by 12%. Furthermore, we discovered that the incidence of lower extremity DVT after craniotomy rose by 8% with each unit increase in patient D-dimer (ug/mL) levels. Besides, patients

who underwent mechanical ventilation for over 48 hours exhibited a 2.83-fold increased risk of lower extremity DVT post-craniotomy in comparison to those ventilated for less 48 hours (Table III).

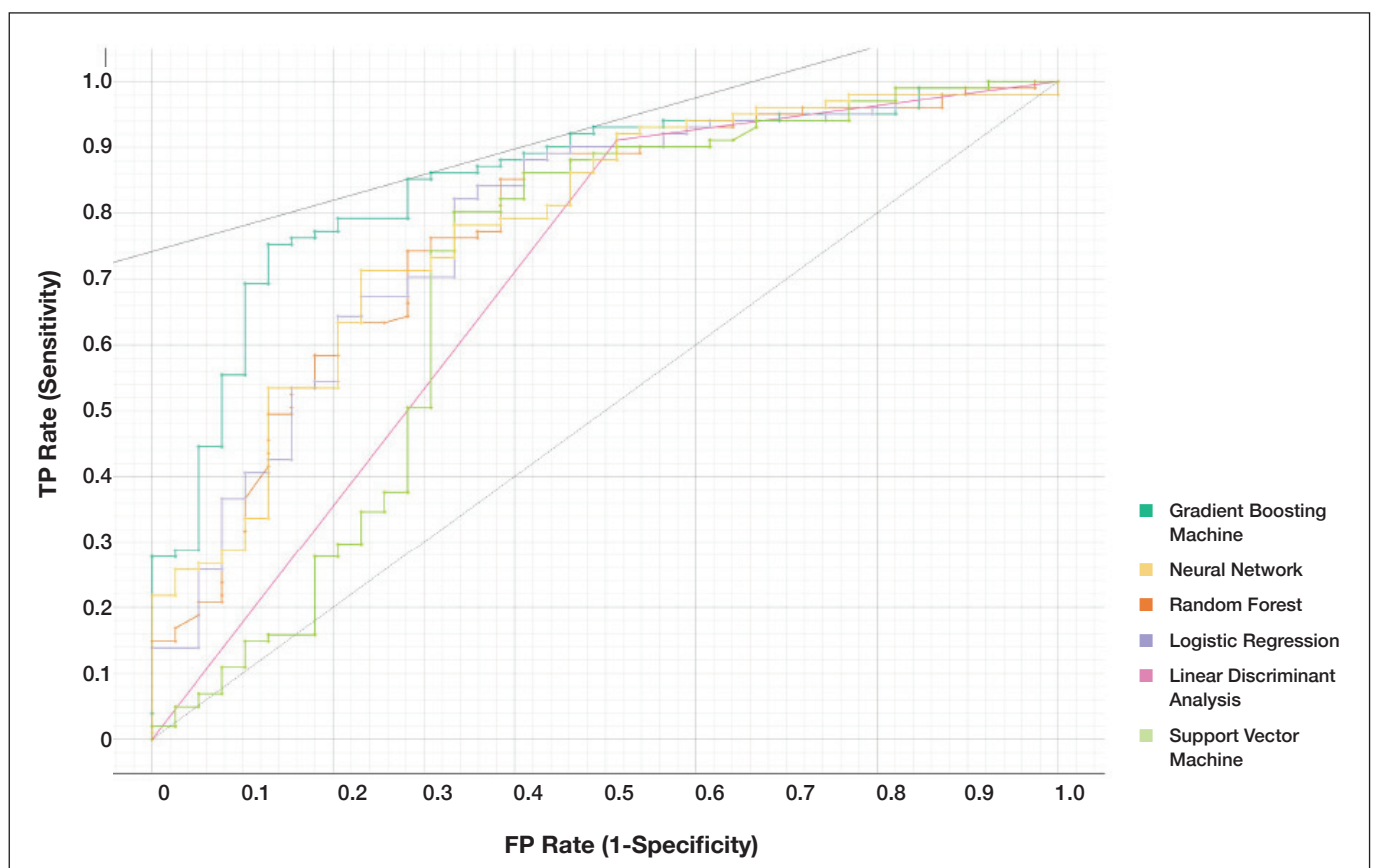
The 10-Fold Cross-Validation Performance of the Machine Learning Models

Table IV displays the results of 10-fold cross validation of machine learning models including LR, RF and SVM. It

Table IV: The 10-Fold Cross-Validation Performance of the Machine Learning Models

Model	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity	AUC	CA
GBM	22	10	91	17	56.44%	90.09%	0.850	0.807
RF	18	9	92	21	46.15%	91.09%	0.809	0.786
NN	19	11	90	20	48.72%	89.11%	0.781	0.779
LR	17	10	91	22	43.59%	90.09%	0.779	0.771
SVM	13	7	94	26	33.33%	93.07%	0.698	0.764
LDA	19	10	91	20	48.72%	90.09%	0.694	0.786

GBM: Gradient boosting machine, **RF:** Random forest, **NN:** Neural network, **LR:** Logistic regression, **SVM:** Support vector machine, **LDA:** Linear discriminant analysis.

**Figure 2:** Area under the receiver-operating characteristic curves of machine learning algorithms.

illustrates that all models achieved a specificity of 85%; however, their sensitivity was generally low, with only the Gradient Boosting Machine (GBM) exceeding 50%. The GBM model had the highest AUC (0.850), making it the optimal model in our analysis (Figure 2).

DISCUSSION

This study revealed a 27.9% incidence of lower extremity DVT in patients with primary brain tumors after craniotomy, comparable to the 31.1% incidence reported by Guo et al.

(4). Among the 140 patients, those who developed lower extremity DVT were significantly older than those who did not ($p < 0.001$). Multivariate analysis indicated that the age ($OR = 1.07$, 95% $CI = 1.03-1.11$) was an independent risk factor for lower extremity DVT in patients with primary brain tumors who had craniotomy. This finding is in line with prior research (3,12). Older patients have heightened vulnerability to DVT due to decreased vascular elasticity, augmented endothelial roughness, weakened muscle pump function, and concomitant diseases such as hypertension, diabetes, and

hyperlipidemia. These factors lead to endothelial damage and elevated levels of various coagulation factors (4,8,11,18).

The study demonstrated a substantial decrease in GCS scores in the DVT group as compared to the non-DVT group ($p < 0.002$). Additionally, the multivariate logistic regression model indicated that higher GCS scores ($OR = 0.88$, 95% $CI = 0.78-0.98$) serve as protective factors against lower extremity DVT. This may be attributed to the fact that patients with lower GCS scores are more likely to experience consciousness disorders, limb movement disorders, and prolonged bed rest, leading to slower blood circulation and subsequent DVT development (2). According to literature, D-dimer is a soluble degradation product of cross-linked fibrin generated by the fibrinolytic system, with elevated levels occurring as a result of thrombus fibrinolysis during thrombosis (1). Continuous monitoring of D-dimer levels can signify the patient's hypercoagulable status and act as a sensitive predictor for venous thromboembolism (VTE). Timely recognition of increased D-dimer levels can facilitate the promptly diagnosing DVT in the lower extremities (13,16). Logistic regression analysis in this study identified elevated D-dimer levels (odds ratio = 1.040, 95% $CI = 1.008-1.074$) as an independent risk factor for lower extremity DVT. This implies that, in the context of clinical treatment, it is crucial to meticulously monitor D-dimer levels and thoroughly evaluate the results in patients having craniotomy for primary brain tumors. Besides, this study identified mechanical ventilation (≥ 48 hours) as an independent risk factor for lower extremity DVT after craniotomy. Furthermore, the risk of developing DVT rises with the duration of mechanical ventilation. Prolonged utilization of mechanical ventilation results in extended periods of bed rest and limited physical activity. This leads to a decrease in blood flow rate in the veins of the lower extremities. Moreover, it raises the risk of developing DVT due to potential endothelial damage and a hypercoagulable state. In addition, prolonged mechanical ventilation may result in additional issues such as infection and inflammatory reactions, which further raise the likelihood of DVT occurring (17,19).

In Jin et al.'s study on cancer-related DVT prediction models, logistic regression emerged as the optimal model, but its AUC was relatively low at 0.773 (5). Qiao et al.'s research on major sellar region tumors, linear discriminant analysis (LDA) was reported as the best-performing model ($AUC = 0.869$) (14). This model is limited in scope, as it only predicts DVT occurrence following surgery in the sellar region and cannot be generalized to brain tumors in other areas (14).

In contrast, our machine learning model offers broader applicability by predicting DVT after craniotomy across various brain tumor types while maintaining high accuracy. However, akin to the models in both Jin et al.'s and Qiao et al.'s studies, our model similarly shows relatively low sensitivity. This issue likely arises from imbalanced datasets, wherein the quantity of non-DVT cases substantially exceeds DVT cases, leading the model to favor the majority class (non-DVT) to enhance overall accuracy. Machine learning models often encounter difficulties with class imbalances, adversely affecting their capacity to reliably predict minority outcomes such as DVT.

The risk prediction model for lower extremity deep vein thrombosis established in this work holds great significance. Neurosurgical intensive care unit (ICU) physicians occasionally refrain from early anticoagulant administration due to the potential risks of new or worsening bleeding in numerous patients. A study on trauma patients revealed that the utilization of anticoagulants resulted in a 13-fold increase in the probability of clot enlargement (7). Currently, there are no conclusive international guidelines for the administration of anticoagulants in neurosurgical ICU patients. This study aims to identify the risk variables associated with DVT in individuals receiving neurosurgery. The objective is to aid physicians in assessing the probability of lower extremity DVT in ICU patients and promptly identifying individuals at elevated risk for proactive anticoagulant therapy.

Nevertheless, this study is subject to specific limitations. First, the sample utilized to examine lower extremities DVT following craniotomy in patients with primary brain tumors was sourced from a single institution (a tertiary hospital in Shanghai), potentially constraining the generalizability of the results. Second, the selection of model features and data quality were constrained by the hospital's records and measurement standards. Although the model emphasizes predictive performance, it may overlook causal relationships and the dynamic nature of DVT risk over time. Third, the potential influence of the surgical team, including variations in surgical techniques, intraoperative management, and postoperative care, was not considered, thus introducing unmeasured confounding. The lack of multi-center validation further restricts the model's applicability to broader populations. Future studies should focus on validating the model with multi-center datasets, integrating new critical factors, amalgamating traditional statistical techniques to improve interpretability, and investigating time-series analyses to identify temporal variations in risk. Acknowledging these limitations will improve the transparency and efficacy of the research.

■ CONCLUSION

Using logistic regression analysis, our study identified advanced age, GCS score, D-dimer levels, and prolonged mechanical ventilation (≥ 48 hours) as independent risk factors for lower extremity DVT after craniotomy in patients with primary brain tumors. Furthermore, a machine learning-based model was developed to predict DVT risk. The integration of machine learning enhances predictive accuracy and serves as a valuable tool for early identification of high-risk patients, potentially guiding clinical decision-making and tailored therapies. However, given the study's limitations, including the single-center design, future research should prioritize validating the model with multi-center datasets and exploring other clinical variables to further improve its performance and generalizability.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: LW, YZ, XL, XZ

Data collection: LW, YZ, XL

Analysis and interpretation of results: LW, YZ, GY, XL, XZ

Draft manuscript preparation: LW, YZ, GY, XL, XZ

Critical revision of the article:

Other (study supervision, fundings, materials, etc.): GY

All authors (LW, YZ, GY, XL, XZ) reviewed the results and approved the final version of the manuscript.

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