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Original Article

Risk factors and clinical strategies for lower extremity deep vein thrombosis following breast cancer surgery

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Abstract: Objective: To analyze the risk factors and clinical strategies for lower extremity deep vein thrombosis (LEDVT) following breast cancer (BC) surgery. Methods: From August 2022 to August 2025, 139 BC patients who underwent surgical treatment at The Second Affiliated Hospital of Chengdu Medical College, Nuclear Industry 416 Hospital were selected for the study. Patients were grouped into the LEDVT group (n = 56) and the non-LEDVT group (n = 83) based on the presence of postoperative LEDVT. Clinical information were collected from both groups for comparative analysis, including baseline data (age, disease duration, body mass index [BMI], menopause status, concomitant hypertension, diabetes, hyperlipidemia, and smoking status), surgery-related parameters (surgery duration, surgical approach, use of adjuvant chemotherapy, diagnostic method), and pathological data (pathological stage, pathological pattern, lymphatic tumor embolus, histological grade, D-dimer [D-D], fibrinogen [FIB], thrombomodulin [TM]). Binary logistic regression analysis was performed to identify factors influencing the occurrence of LEDVT in patients after BC surgery. Results: Neoadjuvant chemotherapy, lymphatic tumor thrombus, and elevated levels of D-D, FIB, and TM were closely associated with postoperative LEDVT, whereas other indicators showed no significant correlation. Multivariate analysis further confirmed that high D-D (≥ 68 ng/L), high FIB (≥ 4.84 g/L), and high TM (≥ 30.00 μg/L) were independent risk factors for LEDVT after BC surgery. A nomogram based on multivariate analysis results was constructed to identify patients at moderate-to-high risk (30-90% risk) for postoperative LEDVT. It demonstrated favorable predictive accuracy and good calibration across low- and high-risk groups. Further evaluation revealed that the area under the curve (AUC) for predicting postoperative LEDVT after BC surgery was 0.732 for D-D, 0.784 for FIB, 0.752 for TM, and 0.889 for the joint prediction of all three factors. Conclusion: These findings suggest that elevated levels of D-dimer (≥ 68 ng/L), FIB (≥ 4.84 g/L), and TM (≥ 30.00 μg/L) increase the risk of LEDVT following BC surgery, and the combination of these markers demonstrates superior predictive performance for LEDVT after BC surgery.

Keywords: Breast cancer, surgery, lower extremity deep vein thrombosis, risk factors, clinical strategies

Introduction

Breast cancer (BC) is one of the most common malignancies in women, accounting for nearly one-third of all new cancer cases, with an increasing incidence trend [1]. According to BC-related statistics in 2024, the disease shows a higher incidence among women under 50 years old, and the overall mortality has dropped by 44% since 1989 [2]. The development of BC is a complex process driven by genetic and environmental factors. It progresses from precancerous lesions to carcinoma in situ through cumulative genetic mutations and acquires invasive and metastatic capabilities through interactions between genetic alterations and the tumor microenvironment, ultimately advancing to invasive cancer [3]. Deep vein thrombosis (DVT) is a severe postoperative complication in BC patients, with lower extremity deep vein thrombosis (LEDVT) being the most common type (80% of all cases) [4]. LEDVT is characterized by chronic pain, swelling, and skin ulcers, which impair patients' mobility and quality of life and increase the risk of post-thrombotic syndrome, posing a potential life-threatening risk [5, 6]. In BC patients, LEDVT represents a life-threatening complication second only to tumor progression and is associated with poorer prognosis and shorter

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overall survival [7]. Although BC patients generally have a lower thrombotic risk than patients with other malignancies, the high incidence rate and multiple risk factors (e.g., radical surgery, chemotherapy, and endocrine therapy) lead to a higher absolute number of LEDVT cases [8]. Additionally, LEDVT increases the medical burden of BC patients, manifesting as more outpatient/emergency visits, higher frequency of hospitalization, and increased healthcare costs [9]. Current risk prediction tools for postoperative LEDVT in BC patients (e.g., Caprini score, Khorana score) demonstrate limited sensitivity, specificity, or applicability [10, 11]. Therefore, it is necessary to further explore the risk factors for LEDVT following BC surgery to improve prevention and management strategies and to formulate targeted clinical strategies aimed at improving survival outcomes for BC patients.

Materials and methods

Patient information

From August 2022 to August 2025, 139 BC patients who underwent surgical treatment at The Second Affiliated Hospital of Chengdu Medical College, Nuclear Industry 416 Hospital were retrospectively screened as the study subjects according to predefined inclusion and exclusion criteria. This study was approved by the ethics committee of The Second Affiliated Hospital of Chengdu Medical College, Nuclear Industry 416 Hospital. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Inclusion criteria: Pathologically diagnosed with BC [12]; diagnosed with LEDVT via bilateral lower limb venous color Doppler ultrasound [13]; no anticoagulant therapy received within 6 months prior to surgery; complete clinical data available, with no deliberate concealment of medical history.

Exclusion criteria: Complicated with hematologic disorders (e.g., hemophilia, thrombocytopenia) or immune disorders; presence of other malignancies; cardiac, pulmonary, or renal insufficiency; history of radiotherapy or chemotherapy; failure to attend timely postoperative follow-up resulting in severe wound infection.

Methods

Through on-site surveys, patients completed standardized forms based on their own conditions, with physicians providing explanations of technical terms to ensure accuracy. Baseline data were collected from both groups for comparative analysis, including age, disease duration, body mass index (BMI), menopausal status, concomitant hypertension, diabetes and hyperlipidemia, and smoking history. Surgery-related parameters primarily included surgical duration, surgical approach, use of neoadjuvant chemotherapy, and diagnostic method. Pathological data included pathological stage, pathological type, lymphatic tumor embolus, histological grade, D-dimer (D-D), fibrinogen (FIB), and thrombomodulin (TM). Fasting venous blood (5 mL) was drawn from each patient and centrifuged to separate serum. D-D and FIB levels were determined using a fully automated coagulation analyzer, while TM levels were measured using enzyme-linked immunosorbent assay (ELISA; Shanghai Fusheng Industrial Co., Ltd., China, A127625).

Statistical treatment

SPSS 24.0 statistical software was adopted for data analysis. All continuous variables were tested for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation (SD). Comparisons between groups were conducted using the independent t-test. Categorical variables were presented as number/percentage (n/%), with intergroup comparisons conducted using the X^2 test. Binary logistic regression analysis was performed to identify factors influencing the occurrence of LEDVT after BC surgery. A nomogram was subsequently constructed based on multivariate regression results and verified using 1000 Bootstrap resamples and calibration curves. The receiver operating characteristic (ROC) curve analysis was applied to evaluate the predictive performance of each indicator for postoperative LEDVT. A P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

No significant differences were observed between the two groups in baseline characteris-

Table 1. Comparison of baseline characteristics between the two groups

	LEDVT group (n = 56)	Non-LEDVT group (n = 83)	χ^2/t/Z	P
Age (years)			1.546	0.214
< 60	23 (41.07)	43 (51.81)		
≥ 60	33 (58.93)	40 (48.19)		
Average age (years)	58.88±6.37	57.58±8.35	0.987	0.325
Disease duration (years)			0.634	0.408
< 2	23 (41.07)	40 (48.19)		
≥ 2	33 (58.93)	43 (51.81)		
Average disease duration (years)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	-0.748	0.455
BMI (Kg/m^2)			2.316	0.128
< 23	21 (37.50)	42 (50.60)		
≥ 23	35 (62.50)	41 (49.40)		
Average BMI (kg/m^2)	23.00 (22.00, 24.00)	22.00 (21.00, 24.00)	-0.925	0.355
Menopausal	37 (66.07)	46 (55.42)	1.577	0.209
Concomitant hypertension	22 (39.29)	25 (30.12)	1.255	0.263
Concomitant diabetes	25 (44.64)	33 (39.76)	0.328	0.567
Concomitant hyperlipidaemia	14 (25.00)	15 (18.07)	0.972	0.324
Smoking	24 (42.86)	37 (44.58)	0.040	0.841

Note: LEDVT, lower extremity deep vein thrombosis; BMI, body mass index.

Table 2. Comparison of surgery-related parameters between the two groups

	LEDVT group (n = 56)	Non-LEDVT group (n = 83)	χ^2/Z	P
Surgical duration (h)			3.237	0.072
< 2	23 (41.07)	47 (56.63)		
≥ 2	33 (58.93)	36 (43.37)		
Average surgical duration (h)	2.10 (1.80, 2.60)	1.90 (1.70, 2.60)	-1.111	0.267
Surgical method			0.583	0.445
Breast-conserving surgery	20 (35.71)	35 (42.17)		
Radical surgery	36 (64.29)	48 (57.83)		
Neoadjuvant chemotherapy	36 (64.29)	37 (44.58)	5.208	0.023
Diagnostic methods			0.387	0.534
Surgical biopsy	30 (53.57)	40 (48.19)		
Core needle biopsy	26 (46.43)	43 (51.81)		

Note: LEDVT, lower extremity deep vein thrombosis.

tics, including age, disease duration, BMI, menopausal status, concomitant hypertension, diabetes, hyperlipidemia, or smoking history (P > 0.05; **Table 1**).

Surgery-related parameters

No significant differences were observed in surgery duration, surgical approach, or diagnostic methods between the LEDVT and non-LEDVT groups (P > 0.05). However, the use of neoadjuvant chemotherapy was significantly higher in the LEDVT group compared with the non-LEDVT group (P = 0.023) (P = 0.023; **Table 2**).

Pathological data

There were no significant differences in pathological stage, pathological type, or histological grade between the two groups (P > 0.05). The LEDVT group showed significantly higher proportions of patients with lymphatic cancer embolus positivity (P = 0.015) and elevated D-D (P < 0.001), FIB (P < 0.001), and TM (P < 0.001) compared with the non-LEDVT group

Table 3. Comparison of pathological data between the two groups

	LEDVT group (n = 56)	Non-LEDVT group (n = 83)	χ^2	P
Pathological stage			0.671	0.413
I-II	39 (69.64)	63 (75.90)		
III-IV	17 (30.36)	20 (24.10)		
Pathological type			3.759	0.053
Carcinoma in situ	23 (41.07)	48 (57.83)		
Invasive carcinoma	33 (58.93)	35 (42.17)		
Lymphatic cancer embolus			5.967	0.015
Negative	24 (42.86)	53 (63.86)		
Positive	32 (57.14)	30 (36.14)		
Histological grade			2.377	0.123
II	32 (57.14)	58 (69.88)		
III	24 (42.86)	25 (30.12)		
D-D (ng/L)			12.051	< 0.001
< 68.00	15 (26.79)	47 (56.63)		
≥ 68.00	41 (73.21)	36 (43.37)		
FIB (g/L)			16.653	< 0.001
< 4.84	16 (28.57)	53 (63.86)		
≥ 4.84	40 (71.43)	30 (36.14)		
TM (μg/L)			12.934	< 0.001
< 30.00	17 (30.36)	51 (61.45)		
≥ 30.00	39 (69.64)	32 (38.55)		

Note: LEDVT, lower extremity deep vein thrombosis; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin.

Table 4. Assignment table

Item	Variable	Value
Neoadjuvant chemotherapy	X1	Absent = 0, present = 1
Lymphatic cancer embolus	X2	Negative = 0, positive = 1
D-D (ng/L)	X3	< 68 = 0, ≥ 68 = 1
FIB (g/L)	X4	< 4.84 = 0, ≥ 4.84 = 1
TM (μg/L)	X5	< 30.00 = 0, ≥ 30.00 = 1
LEDVT	Y	Absent = 0, present = 1

Note: LEDVT, lower extremity deep vein thrombosis; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin.

(**Table 3**). Consistently, the levels of D-D, FIB, and TM were notably higher in the LEDVT groups compared with those in the non- LEDVT group (all P < 0.001).

Factors influencing LEDVT in patients after BC surgery

Variables with significant intergroup differences in univariate analysis (neoadjuvant chemotherapy, lymphatic cancer embolus, D-D, FIB, and TM) were entered into binary logistic regression analysis, with assignment results detailed in **Table 4**. The multivariate analysis identified elevated levels of D-D (≥ 68 ng/L), FIB (≥ 4.84 g/L), and TM (≥ 30.00 μg/L) as independent risk factors for LEDVT after BC surgery (all P < 0.001), while neoadjuvant chemotherapy and lymphatic cancer embolus were not (P > 0.05) (**Table 5**).

Construction of a nomogram for predicting LEDVT after BC surgery

A nomogram was constructed based on independent risk factors (D-D, FIB, TM) identified in the multivariate analysis to predict the risk of post-operative LEDVT, particularly in patients at moderate-to-high risk (30-90%). Internal validation using 1000 bootstrap resamples yielded a C-index of 0.892 (95% CI: 0.831-0.946), indicating excellent discriminative capability. Further calibration curve analysis demonstrated high agreement between predicted and

Table 5. Multivariate analysis of factors influencing LEDVT after BC surgery

	B	SE	WALD	P	OR	95% CI
Neoadjuvant chemotherapy	0.649	0.487	1.772	0.183	1.913	0.736-4.974
Lymphatic cancer embolus	0.829	0.485	2.927	0.087	2.291	0.886-5.923
D-D (ng/L)	0.105	0.030	12.148	< 0.001	1.110	1.047-1.178
FIB (g/L)	0.496	0.130	14.622	< 0.001	1.641	1.273-2.116
TM (μg/L)	0.184	0.051	13.280	< 0.001	1.202	1.089-1.328

Note: LEDVT, lower extremity deep vein thrombosis; BC, breast cancer; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin.

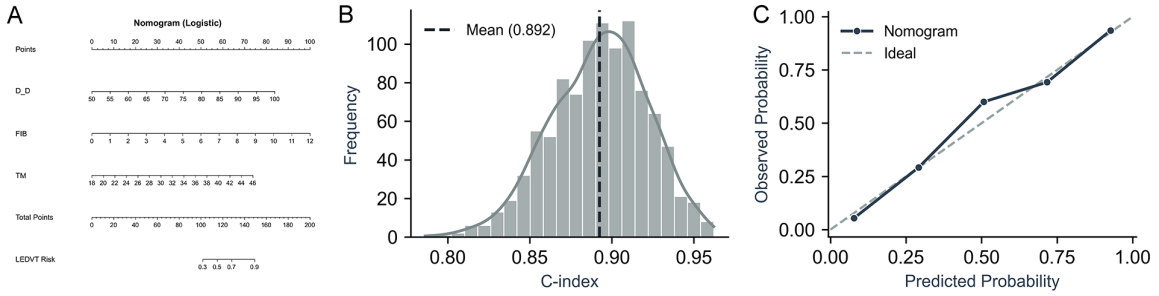

Figure 1. Construction and validation of a nomogram for predicting postoperative LEDVT. A. Construction of the nomogram for predicting LEDVT in patients after BC surgery. B. Internal validation of the nomogram using 1000 bootstrap resampling method. C. Calibration curve. Note: LEDVT, lower extremity deep vein thrombosis; BC, breast cancer; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin.

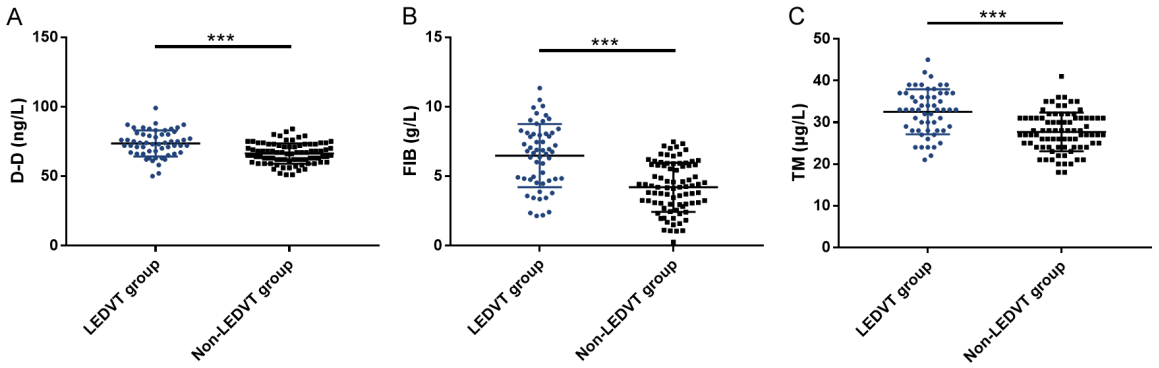

Figure 2. Comparison of D-D (A), FIB (B), and TM (C) levels between the two groups. Note: ***P < 0.001. LEDVT, lower extremity deep vein thrombosis; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin.

observed probabilities in both low- and high-risk zones, with minor underestimation in the intermediate-risk zone (**Figure 1**).

D-D, FIB, and TM levels in the two groups

The D-D, FIB, and TM levels in the LEDVT group were significantly higher than those in the non-LEDVT group (P < 0.001), as detailed in **Figure 2**.

Predictive value of D-D, FIB, and TM for LEDVT

ROC curve analysis showed that D-D demonstrated an AUC of 0.732 (95% CI: 0.646-0.819) for predicting post-operative LEDVT, with the sensitivity, specificity, and accuracy at 67.86%, 69.88%, and 69.06%, respectively, at the best cut-off value of 70.50 ng/L; FIB had an AUC of 0.784 (95% CI: 0.704-0.864), with sensitivity 60.71%, specificity 87.95%, and accuracy

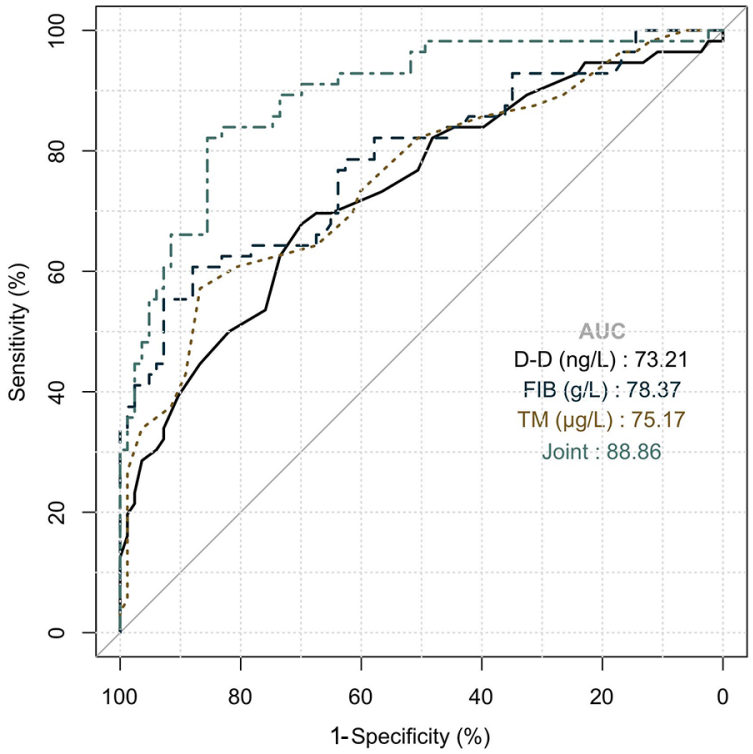

Figure 3. ROC curves for D-D, FIB, TM and their combination in predicting postoperative LEDVT. Notes: LEDVT, lower extremity deep vein thrombosis; BC, breast cancer; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin; AUC, area under the curve; ROC, Receiver Operating Characteristic.

76.98% at a cut-off value of 6.26 g/L; and TM demonstrated an AUC of 0.752 (95% CI: 0.668-0.836), with sensitivity 57.14%, specificity 86.75%, and accuracy 74.82% at a cut-off value 32.50 μg/L. The combined model achieved an AUC of 0.889 (95% CI: 0.832-0.945) with sensitivity 82.14%, specificity 85.54%, and accuracy 84.17% at a cut-off value of 0.40. See **Figure 3** and **Table 6** for details.

Discussion

We first conducted univariate analyses across three sets of indicators to preliminarily assess potential predictors associated with LEDVT following BC surgery. Results revealing significant associations were observed for the following factors: use of neoadjuvant chemotherapy, lymphatic cancer embolus, D-D, FIB, and TM. Multivariate analysis further revealed that elevated levels of D-D (≥ 68 ng/L), FIB (≥ 4.84 g/L), and TM (≥ 30.00 μg/L), rather than use of neoadjuvant chemotherapy and lymphatic cancer embolus, were independent risk factors for LEDVT in patients after BC surgery.

For BC patients not receiving neoadjuvant chemotherapy, post-operative administration of chemotherapeutic drugs may induce platelet aggregation, placing the body in a hypercoagulable state and slowing venous return from the lower limbs, thereby potentially increasing the risk of LEDVT [14, 15]. In our multivariate analysis, neoadjuvant chemotherapy was not an independent risk factor, which may be attributed to its effects being masked by stronger independent risk factors, such as elevated D-D, FIB, and TM, or influenced by confounding variables including chemotherapy regimen, treatment course, and individual coagulation status. Although lymphatic embolus formation may indirectly increase the risk of LEDVT by disrupting lymphatic return and inducing local inflammatory responses, it likely interacts with other independent risk factors, exhibiting synergistic or confounding effects, which may explain why it did not emerge as an independent determinant [16, 17].

D-D is a fibrin degradation product, and elevated levels reflect a hypercoagulable state, serving as a biomarker for high-risk postoperative LEDVT in BC patients. FIB, as a core circulating coagulation protein, may be overexpressed under stimuli such as inflammation. Upon activation by thrombin, FIB participates in fibrin network formation, potentially leading to abnormal clot structure, possibly inducing hypercoagulability, obstructing venous return from lower limbs, and consequently increasing the risk of LEDVT following the BC surgery [18]. TM, a novel thrombotic biomarker, functions as a high-affinity thrombin-binding receptor protein that regulates vascular homeostasis. Its association with DVT may relate to DNA methylation in its promoter region and regulation of DNA (Cytosine-5)-Methyltransferase 1 (DNMT1) and DNA (Cytosine-5)-Methyltransferase 3 Beta (DNMT3B) protein levels [19]. Other studies have reported similar results. For

Table 6. Predictive performance of D-D, FIB, TM, and their combination for LEDVT after BC surgery

Item	AUC	95% CI	Optimal cutoff value	Sensitivity	Specificity	Accuracy
D-D (ng/L)	0.732	0.646-0.819	70.50	67.86%	69.88%	69.06%
FIB (g/L)	0.784	0.704-0.864	6.26	60.71%	87.95%	76.98%
TM (μg/L)	0.752	0.668-0.836	32.50	57.14%	86.75%	74.82%
Joint	0.889	0.832-0.945	0.40	82.14%	85.54%	84.17%

Note: LEDVT, lower extremity deep vein thrombosis; BC, breast cancer; D-D, D-dimer; FIB, fibrinogen; TM, thrombomodulin; AUC, area under the curve; 95% CI, 95% confidence interval.

example, Tang et al. [20] identified D-D as an independent risk factor for LEDVT in patients after urological surgery. Pan et al. [21] indicated that FIB independently predicted DVT in patients with epithelial ovarian cancer. Based on our multivariate analysis, a predictive nomogram for postoperative LEDVT was constructed. This model can specifically assess the risk of postoperative LEDVT in BC patients at moderate-to-high risk (30-90%). Internal validation demonstrated good discriminatory ability, with predicted values in the low- and high-risk zones showing high concordance with observed outcomes. However, predictions in the medium-risk zone were systematically underestimated.

Furthermore, the LEDVT group exhibited significantly elevated levels of D-D, FIB, and TM, suggesting a close association between the pathological process of LEDVT in post-BC surgery patients and these markers. This finding is in line with the report by Pang et al. [22], who also observed increased plasma D-D and TM levels in BC patients after surgery. ROC curve analysis revealed that among individual markers, D-D showed the highest sensitivity (67.86%) for predicting postoperative LEDVT, whereas FIB demonstrated the highest diagnostic performance (AUC = 0.784), specificity (87.95%), and accuracy (76.98%). The combination of the three markers further improved predictive performance, achieving an AUC of 0.889, while maintaining high sensitivity (82.14%), specificity (85.54%), and accuracy (84.17%). Lu et al. [23] reported that combining D-D with the Caprini score increased the AUC to 0.812 for predicting postoperative DVT in gynecological patients. In comparison, a higher AUC was seen in the present study through the joint prediction model. Similarly, Hong et al. [24] indicated that joint prediction using TM, prothrombin time (PT), and age achieved the highest sensitivity (83.0%) and specificity (89.7%) for thrombosis in patients with antiphospholipid syndrome, which is similar to the diagnostic performance of the joint prediction model in this study. Additionally, previous studies have suggested that preoperative systemic immune-inflammation index (SII) levels may serve as a potential independent predictor of postoperative LEDVT in BC patients, with an AUC of 0.714 [5].

Based on these findings, we recommend incorporating the joint detection of D-D, FIB, and TM into the thrombus risk assessment system for patients after BC surgery. Specifically, D-D ≥ 70.50 ng/L, FIB ≥ 6.26 g/L, or TM ≥ 32.50 μg/L should be considered as a high-risk warning signal for LEDVT, and enhanced monitoring should be initiated. For patients identified as moderate-to-high risk (30-90%) according to the nomogram model, prophylactic anticoagulants (e.g., low molecular weight heparin) may be considered in addition to routine physical prevention measures, after assessing bleeding risk, along with extended monitoring and health education [7]. It should be noted that the model may underestimate risk within the moderate-risk zone when it is used in clinical practice; therefore, a dynamic, comprehensive assessment incorporating clinical presentation is recommended.

Conclusion

Elevated D-D, FIB, and TM levels are independent risk factors for postoperative LEDVT after BC surgery. The nomogram predictive model constructed based on these factors demonstrates favorable discriminatory performance, though a systematic underestimation is observed in the moderate-risk zone. Combined assessment of these three factors significantly enhances predictive performance, providing clinical guidance for early screening and targeted intervention in patients at moderate-to-high risk for postoperative LEDVT.

Disclosure of conflict of interest

None.

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