Article

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The Role of Iron Metabolism Markers in Predicting Deep Vein Thrombosis After Joint Replacement in Patients With Rheumatoid Arthritis

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Background: Patients with rheumatoid arthritis (RA) are at increased risk of deep vein thrombosis (DVT) after joint replacement, but the predictive value of iron metabolism markers remains unclear. This study aimed to investigate the predictive value of serum iron metabolism-related indicators for DVT after joint replacement in patients with RA, and to construct and internally validate a combined prediction model.

Methods: A total of 180 RA patients who underwent joint replacement in our hospital from January 2019 to December 2023 were retrospectively enrolled. According to postoperative confirmed DVT, the patients were divided into a DVT group (n = 45) and a non-DVT group (n = 135). The general data, preoperative iron metabolism indices (serum iron, ferritin, total iron binding capacity), D-dimer, and DAS28 score were collected. Univariate and multivariate Logistic regression identified independent risk factors for postoperative DVT. The Box-Tidwell test was used to assess linearity; variables that violated the linearity assumption were categorized into quartiles, while variables that satisfied the linearity assumption were entered as continuous variables. Model discrimination was evaluated using Receiver Operating Characteristic (ROC) curve analysis, internal validation was performed using bootstrap resampling, calibration was performed using a calibration curve, and clinical utility was assessed using decision curve analysis (DCA).

Results: The Box-Tidwell test showed that ferritin ($p = 0.03$) and D-dimer ($p < 0.01$) violated the linearity assumption, while DAS28 score ($p = 0.41$) satisfied it. Consequently, ferritin and D-dimer were categorized into quartiles, and the DAS28 score was entered as a continuous variable. Logistic regression analysis showed that ferritin (Q2: odds ratio (OR) = 10.19, 95% confidence interval (CI): 2.00–51.96, $p < 0.01$; Q3: OR = 15.53, 95% CI: 3.16–76.28, $p < 0.01$; Q4: OR = 15.09, 95% CI: 2.90–78.45, $p < 0.01$), D-dimer (Q3: OR = 6.97, 95% CI: 1.85–26.25, $p < 0.01$; Q4: OR = 9.16, 95% CI: 2.51–33.38, $p < 0.01$), and DAS28 score (OR = 1.66, 95% CI: 1.19–2.31, $p < 0.01$) were independent risk factors for postoperative DVT. Trend tests confirmed significant dose-response relationships for both ferritin and D-dimer (p for trend < 0.01 and <0.01, respectively). The area under the ROC curve of the model based on the above three indicators for predicting postoperative DVT was 0.83 (95% CI: 0.76–0.90). The calibration curve indicated good agreement between predicted and observed probabilities, with a calibration slope of 1.02 (95% CI: 0.94–1.11) and an intercept of –0.005 (95% CI: –0.026 to 0.015) (Hosmer-Lemeshow test $p > 0.05$). DCA demonstrated that the prediction model simultaneously outperformed both the 'treat all' and 'treat none' strategies within the clinically relevant threshold range of 15% to 60%.

Conclusions: Preoperative ferritin, D-dimer, and DAS28 score are independent risk factors for DVT after joint arthroplasty in RA patients. The model based on the above indicators has good predictive performance and clinical utility, which can provide a reference for the formulation of clinical individualized thrombosis prevention strategies.

Keywords: rheumatoid arthritis; joint replacement; deep vein thrombosis; iron metabolism

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder featuring chronic synovitis and progressive joint destruction. With the progression of the disease, RA patients often suffer from irreversible destruction of articular cartilage and subchondral bone, leading to joint deformity and loss of function, seriously reducing the quality of life [1,2]. Total hip and knee arthroplasty are effective treatments for end-stage joint disease that significantly relieve pain, correct deformity, and restore joint function [3]. However, as a major orthopedic operation, the risk of deep vein thrombosis (DVT) after joint replacement cannot be ignored [4]. DVT is defined as abnormal blood clotting in the deep veins, resulting in venous obstruction and impaired return. It most commonly affects the lower limbs and can be life-threatening in severe cases [5].

RA patients are considered to be a high-risk group of DVT, and epidemiological studies have shown that the risk of DVT in RA patients is significantly higher than that in the general population [6]. The mechanism involves multiple factors, such as vascular endothelial injury in a chronic inflammatory state, imbalance of the coagulation-fibrinolysis system, platelet activation, and long-term bed rest or activity limitation. In a chronic inflammatory state, proinflammatory factors continue to increase, which can upregulate the expression of tissue factor and activate the exogenous coagulation pathway. At the same time, inflammatory mediators can inhibit the anticoagulant system and damage vascular endothelial function, thus jointly creating a prothrombotic environment [7–9]. When RA patients receive joint replacement, surgical trauma further aggravates the local and systemic inflammatory response as well as coagulation activation, together with postoperative immobilization, resulting in a significant superposition of DVT risk [10]. It is of great clinical significance to accurately identify individuals at risk of DVT and implement individualized prevention strategies in RA patients during the perioperative period.

At present, commonly used clinical DVT risk assessment tools are mostly developed based on the general surgical population or patients undergoing major orthopedic surgery. Although these tools can be used in RA patients to some extent, they often fail to fully consider the unique pathophysiological characteristics of RA disease, especially the interaction between chronic inflammation and metabolic disorders. With the deepening understanding of the mechanism of thrombosis, the relationship between iron metabolism and thrombosis has gradually become a research hotspot [11,12]. Iron, an essential trace element, participates in diverse physiological processes including oxygen transport, Deoxyribonucleic Acid (DNA) synthesis, and mitochondrial respiration. The maintenance of iron homeostasis in the body depends on the precise coordination of iron absorption, storage, recycling, and regulation. Disorders of iron metabolism, whether iron overload or iron deficiency, are closely related to the occurrence and development of a variety of diseases. Iron metabolism disorders are particularly common in RA patients [13,14], which may promote deep vein thrombosis through a variety of mechanisms. Research has confirmed that iron overload can induce mitochondrial damage and apoptosis in endothelial cells, release endothelial microparticles carrying tissue factor, and promote thrombosis [15]. Additionally, iron can directly affect platelet function. Iron ions have been shown to enhance platelet activation and aggregation, thereby increasing thrombophilia [16].

Ferritin, serum iron, and total iron binding capacity (TIBC) are among the most commonly used clinical parameters for assessing iron metabolism. As an acute-phase reactant, ferritin reflects both iron storage status and systemic inflammatory burden, making it particularly relevant in RA patients who often experience chronic inflammation [17,18]. Serum iron and TIBC provide complementary information regarding circulating iron availability and iron-binding capacity, both of which are frequently altered in inflammatory conditions such as RA due to hepcidin-mediated iron sequestration [18,19]. Given the complex interplay between chronic inflammation, endothelial dysfunction, and coagulation activation in RA-related thrombosis, these three markers serve as practical and readily available indicators for assessing iron metabolism.

However, there is a lack of systematic studies on the value of iron metabolism markers in predicting DVT after joint replacement in RA patients. This study aims to explore the relationship between preoperative iron metabolism-related indicators and postoperative DVT by retrospectively analyzing the clinical data from RA patients undergoing joint replacement in our hospital, to identify the independent risk factors of postoperative DVT, and to construct a prediction model. The results of this study are expected to identify new biomarkers for the risk assessment of DVT in RA patients after joint replacement and to provide a reference for the formulation of perioperative anticoagulation strategies in clinical practice.

Methods

Subjects

This was a single-center retrospective study involving RA patients undergoing joint replacement at our hospital between January 2019 and December 2023. The study protocol complied with the Declaration of Helsinki and received approval from the Ethical Review Board of Hangzhou Geriatric Hospital (approval number: ZN-2024317-01). Written informed consent was obtained. Inclusion criteria: (1) RA patients diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis, undergoing total hip/knee arthroplasty; (2) complete medical history and laboratory examinations. Exclusion criteria: (1) coexistence of other rheumatic diseases, such as osteoarthritis or ankylosing spondylitis; (2) patients with incomplete main clinical data; (3) presence of tuberculosis or other infectious diseases; (4) history of joint infection, bone tumor, hemophilia, or previous joint reconstruction surgery; (5) active malignancy; (6) known thrombophilia; and (7) ongoing anticoagulant therapy prior to surgery. A total of 200 RA patients undergoing joint replacement during the study period were initially identified. After applying the inclusion and exclusion criteria, 20 patients were excluded: 14 had incomplete key clinical data (e.g., missing preoperative ferritin or D-dimer measurements), 4 had active malignancies, and 2 were on ongoing anticoagulant therapy prior to surgery. Consequently, 180 patients were included in the final analysis, with no missing data for any of the variables under investigation.

According to the occurrence of postoperative DVT, patients were divided into a DVT group (n = 45) and a non-DVT group (n = 135).

Data Collection

Patient data were extracted from the hospital's electronic medical record system, including: (1) general demographic characteristics: age, history of hypertension, gender, diabetes, and smoking history, Body mass index (BMI); (2) Clinical and laboratory indicators: fasting venous blood samples were collected before operation to detect iron metabolism related indicators (ferritin, serum iron, total iron binding capacity) and coagulation related indicators (D-dimer). The duration of RA, morning stiffness time, and DAS28 score were recorded; (3) Surgical and postoperative data: joint replacement site (knee joint/hip joint); (4) Outcome indicators: postoperative DVT was defined as the presence of thrombus in the deep veins of the lower extremity detected by routine color Doppler ultrasound within 7 days after surgery, regardless of clinical symptoms. Both proximal DVT (involving the popliteal, femoral, or iliac veins) and distal DVT (involving the calf veins) were included. All ultrasound examinations were performed by certified radiologists, and the diagnosis of DVT was confirmed by a second, independent radiologist who was blinded to the patients' clinical data. In cases of disagreement, a consensus was reached through discussion. Patients were then divided according to the diagnosis results. Patients with incomplete key clinical data were excluded to ensure no missing data in the final analysis dataset.

Statistical Analysis

SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Categorical variables were presented as n (%) and compared using the chi-square or Fisher's exact test (if expected frequency <5). Continuous variables were tested for normality; normally distributed data were expressed as mean ± SD and compared using the independent *t*-test, whereas non-normally distributed data were presented as M (Q_1, Q_3) and compared using the Mann-Whitney U test. Univariate Logistic regression was used to screen candidate predictors. Variables with $p < 0.05$ were included in multivariate Logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Prior to multivariate analysis, the Box-Tidwell test was employed to assess the linearity assumption between continuous variables and the logit transformation of the dependent variable; a p value < 0.05 indicated a violation of the linearity assumption. For variables exhibiting nonlinearity, quartile categorization was applied for model entry, with the lowest quartile serving as the reference group. Trend tests (p for trend) were performed using the median values of each quartile to evaluate dose-response relationships. Collinearity was assessed using the variance inflation factor (VIF >10 indicating severe multicollinearity). A prediction model was constructed based on the identified independent factors. Model discrimination was evaluated using the ROC curve (AUC), and calibration was assessed by the Hosmer-Lemeshow goodness-of-fit test ($p > 0.05$ indicating good calibration) and calibration curves, with internal validation via bootstrap resampling (1000 replicates). The calibration slope was calculated using a bootstrap-based grouped method (10 deciles, weighted by group size, 1000 resamples), with a value of 1.0 indicating perfect calibration. Clinical utility was assessed using decision curve analysis (DCA). All tests were two-tailed, with $p < 0.05$ considered statistically significant.

Results

Baseline Characteristics of the Study Population

Among 180 RA patients undergoing joint replacement, postoperative DVT occurred in 45 (25.0%), forming the DVT group versus the non-DVT group (n = 135). No significant differences were found between groups in age, BMI, sex, hypertension, diabetes, smoking history, thrombosis history, surgical site, RA duration, or morning stiffness ($p > 0.05$). The DVT group had significantly higher D-dimer ($p < 0.01$) and ferritin levels ($p < 0.01$), but similar serum iron and TIBC ($p > 0.05$). DAS28 score ($p < 0.01$) was also higher in the DVT group (Table 1).

Univariate and Multivariate Logistic Regression Analyses Were Performed

The variables with $p < 0.05$ in univariate analysis (D-dimer, ferritin, and DAS28 score) were included in the multivariate Logistic regression model with the occurrence of postoperative DVT as the dependent variable (Table 2). The Box-Tidwell test results demonstrated nonlinear relationships with logit(p) for Ferritin ($\lambda = 0.84$, $p = 0.03$) and D-dimer ($\lambda = 0.38$, $p < 0.01$), with D-dimer showing more pronounced non-linearity. In contrast, the DAS28 score satisfied the linearity assumption ($\lambda = 0.69$, $p = 0.41$). Consequently, Ferritin and D-dimer were categorized into quartiles for subsequent analyses, while the DAS28 score was included as a continuous variable. Additionally, multicollinearity was assessed using the VIF, and all VIF values were below 2 (range: 1.01–1.57), indicating no significant multicollinearity among the predictors. Multivariate analysis revealed that ferritin (with the lowest quartile Q1 as reference, Q2: OR = 10.19, 95% CI: 2.0–51.96, $p < 0.01$; Q3: OR = 15.53, 95% CI: 3.16–76.28, $p < 0.01$; Q4: OR = 15.09, 95% CI: 2.90–78.45, $p < 0.01$), D-dimer (with the lowest quartile Q1 as reference, Q3: OR = 6.97, 95% CI: 1.85–26.25, $p < 0.01$; Q4: OR = 9.16, 95% CI: 2.51–33.38, $p < 0.01$), and DAS28 score (per 1-point increase: OR = 1.66, 95% CI: 1.19–2.31, $p < 0.01$) were independently as-

Table 1. Baseline characteristics of the study population.

Variables	Non-DVT group (n = 135)	DVT group (n = 45)	Statistic	*p*
Age (years)	66.90 ± 7.97	66.00 ± 8.01	$t = 0.66$	0.51
BMI (kg/m^2)	27.34 ± 3.99	27.69 ± 3.78	$t = –0.53$	0.60
TIBC (μmol/L)	51.08 ± 4.69	49.64 ± 6.42	$t = 1.38$	0.17
D-dimer (mg/L)	1.45 ± 0.53	1.71 ± 0.40	$t = –2.95$	<0.01
Serum iron (μmol/L), M (Q_1, Q_3)	10.50 (7.75, 16.35)	9.60 (6.10, 15.20)	Z = –1.33	0.19
Ferritin (μg/L), M (Q_1, Q_3)	108.00 (93.00, 155.00)	139.000 (118.00, 164.00)	Z = –3.80	<0.01
DAS28 score, M (Q_1, Q_3)	3.20 (2.30, 3.75)	3.70 (2.90, 4.60)	Z = –3.10	<0.01
RA duration, M (Q_1, Q_3)	5.00 (4.00, 7.00)	6.00 (4.00, 7.00)	Z = –0.35	0.73
Morning stiffness duration (min), M (Q_1, Q_3)	61.00 (48.00, 77.50)	60.00 (43.00, 74.00)	Z = –0.83	0.41
Gender, n (%)			$\chi^2 = 0.09$	0.77
Male	33 (24.44)	12 (26.67)		
Female	102 (75.56)	33 (73.33)		
Hypertension, n (%)			$\chi^2 = 0.48$	0.49
No	74 (54.82)	22 (48.89)		
Yes	61 (45.19)	23 (51.11)		
Diabetes, n (%)			$\chi^2 = 1.08$	0.30
No	98 (72.59)	29 (64.44)		
Yes	37 (27.41)	16 (35.56)		
Smoking history, n (%)			$\chi^2 = 0.04$	0.84
No	100 (74.07)	34 (75.56)		
Yes	35 (25.93)	11 (24.44)		
History of thrombosis, n (%)			$\chi^2 = 0.33$	0.57
No	123 (91.11)	39 (86.67)		
Yes	12 (8.89)	6 (13.33)		
Joint replacement site, n (%)			$\chi^2 = 0.50$	0.48
Knee	101 (74.82)	36 (80.00)		
Hip	34 (25.19)	9 (20.00)		

DVT, deep vein thrombosis; BMI, body mass index; TIBC, total iron binding capacity; RA, rheumatoid arthritis.

sociated with an increased risk of postoperative DVT in RA patients undergoing joint replacement (Table 3). Trend tests confirmed significant dose-response relationships for both ferritin and D-dimer (p for trend <0.01 and <0.01, respectively).

Evaluation of the Predictive Performance of the Combined Model

The predicted probability of postoperative DVT can be calculated using the following logistic regression equation (apparent model): logit(p) = –6.45 + 2.32 × I(Ferritin = Q2) + 2.74 × I(Ferritin = Q3) + 2.71 × I(Ferritin = Q4) + 0.66 × I(D-dimer = Q2) + 1.94 × I(D-dimer = Q3) + 2.22 × I(D-dimer = Q4) + 0.51 × (DAS28 score), where I(condition) is an indicator variable that equals 1 if the condition is true and 0 otherwise. The reference groups are Ferritin Q1 (<93 μg/L) and D-dimer Q1 (<1.1 mg/L). The predicted risk is then $p = 1 / (1 + e^{-logit(p)})$. The optimal cutoff value determined by the Youden index was 0.24. This means that patients with a predicted probability of postoperative DVT ≥0.24 (24%) should be classified as high-risk, while those with a predicted probability <0.24 are considered low-risk. Using this threshold, the model achieved a sensitivity of 0.84 (95% CI: 0.74–0.95) and a specificity of 0.75 (95% CI: 0.68–0.82). Clinicians may also implement this equation as a simple spreadsheet-based calculator for routine clinical use. The combined model based on the independent risk factors (ferritin, D-dimer, and DAS28 score) identified through multivariate regression analysis, a prediction model was constructed to estimate the risk of DVT in RA patients after joint replacement. The AUC of the model for predicting postoperative DVT was 0.83 (95% CI: 0.76–0.90) (Fig. 1). After internal validation using the bootstrapping method, the bias-corrected AUC was 0.83 (95% CI: 0.75–0.89).

Model Calibration Evaluation

A calibration curve was used to evaluate the prediction accuracy of the combined model (Fig. 2). In the figure, the bias-corrected represents the prediction performance of the model after correction using the Bootstrapping internal validation, and the “ideal” line represents the reference line in the ideal case (the predicted probability is completely consistent with the observed event probability). The results showed that the calibration curve after correction basically coincided with the ideal diagonal. The calibration slope was

Table 2. Univariate Logistic regression analysis of risk factors for postoperative DVT.

Variables	β	S.E	Z	p	OR (95% CI)
Gender					
Male					1.00 (Reference)
Female	–0.12	0.39	–0.30	0.77	0.89 (0.41∼1.92)
Hypertension					
No					1.00 (Reference)
Yes	0.24	0.35	0.69	0.49	1.27 (0.65∼2.49)
Diabetes					
No					1.00 (Reference)
Yes	0.38	0.37	1.04	0.30	1.46 (0.71∼3.00)
Smoking history					
No					1.00 (Reference)
Yes	–0.08	0.40	–0.20	0.84	0.92 (0.42∼2.02)
History of thrombosis					
No					1.00 (Reference)
Yes	0.46	0.53	0.86	0.39	1.58 (0.56∼4.48)
Joint replacement site					
Knee					1.00 (Reference)
Hip	–0.28	0.42	–0.71	0.48	0.74 (0.33∼1.70)
Age (years)	–0.01	0.02	–0.66	0.51	0.99 (0.94∼1.03)
BMI (kg/m^2)	0.02	0.04	0.53	0.60	1.02 (0.94∼1.12)
Ferritin (per 10 µg/L)	0.02	0.01	3.39	<0.01	1.02 (1.01∼1.03)
Serum iron (µmol/L)	–0.05	0.04	–1.31	0.19	0.96 (0.89∼1.02)
TIBC (µmol/L)	–0.06	0.03	–1.60	0.11	0.95 (0.89∼1.01)
D-dimer (mg/L)	1.03	0.36	2.82	0.01	2.79 (1.37∼5.70)
DAS28 score	0.42	0.14	3.03	<0.01	1.52 (1.16∼2.00)
RA duration	0.04	0.10	0.35	0.72	1.04 (0.85∼1.26)
Morning stiffness duration (min)	–0.01	0.01	–0.86	0.39	0.99 (0.98∼1.01)

Table 3. Multivariate Logistic regression analysis of risk factors for postoperative DVT.

Variables	β	S.E	Z	p	OR (95% CI)	VIF
Ferritin group						
Q1 (≤93)					1.00 (Reference)	
Q2 (94–122)	2.32	0.83	2.79	0.01	10.19 (2.00∼51.96)	1.47
Q3 (123–160)	2.74	0.81	3.38	<0.01	15.53 (3.16∼76.28)	1.47
Q4 (>160)	2.71	0.84	3.23	<0.01	15.09 (2.90∼78.45)	1.48
D-dimer group						
Q1 (≤1.1)					1.00 (Reference)	
Q2 (1.2–1.5)	0.66	0.70	0.94	0.35	1.94 (0.49∼7.71)	1.50
Q3 (1.6–1.9)	1.94	0.68	2.87	<0.01	6.97 (1.85∼26.25)	1.57
Q4 (>1.9)	2.22	0.66	3.36	<0.01	9.16 (2.51∼33.38)	1.48
DAS28 score	0.51	0.17	2.99	<0.01	1.66 (1.19∼2.31)	1.02

1.02 (95% CI: 0.94–1.11), with an intercept of –0.005 (95% CI: –0.026 to 0.015), and the Hosmer-Lemeshow test indicated no significant lack of fit ($\chi^2 = 15.07$, $p = 0.06$).

Clinical Utility Evaluation of the Model

Decision curve analysis showed that the prediction model simultaneously outperformed both the 'treat all' and 'treat none' strategies across threshold probabilities ranging from 15% to 60%. Within this range, the model demonstrated stable and clinically meaningful net benefit. Thresholds above 60% were not considered clinically relevant for postoperative DVT prevention, as net benefit became minimal and such high thresholds are not typically used in clinical decision-making for thromboprophylaxis (Fig. 3).

Discussion

RA patients are at high risk of thrombosis due to the chronic inflammatory state, and the surgical trauma associated with joint replacement further increases the risk of

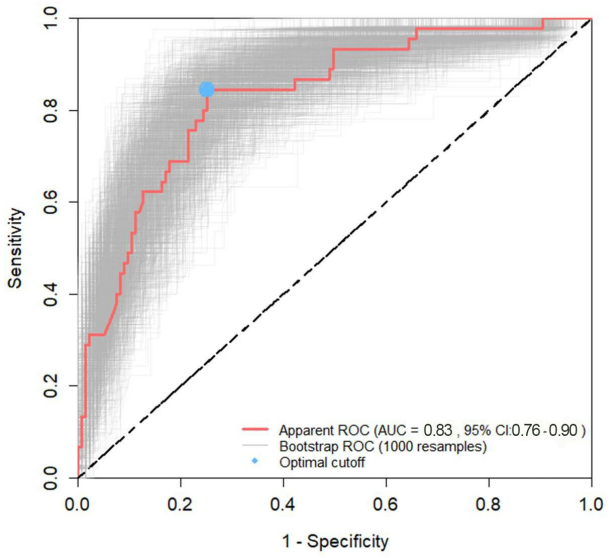

Fig. 1. Model bootstrap ROC curve for predicting postoperative DVT.

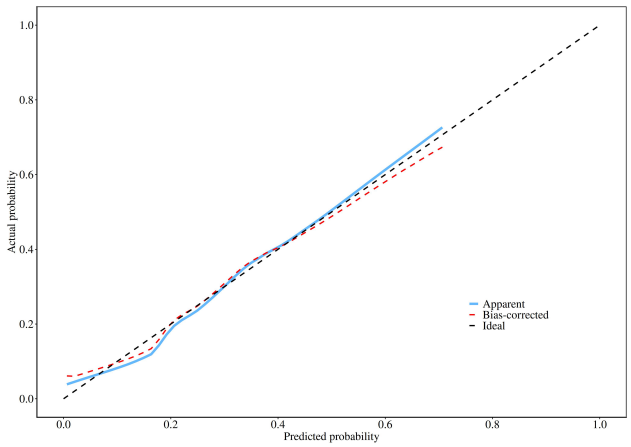

Fig. 2. Calibration curve.

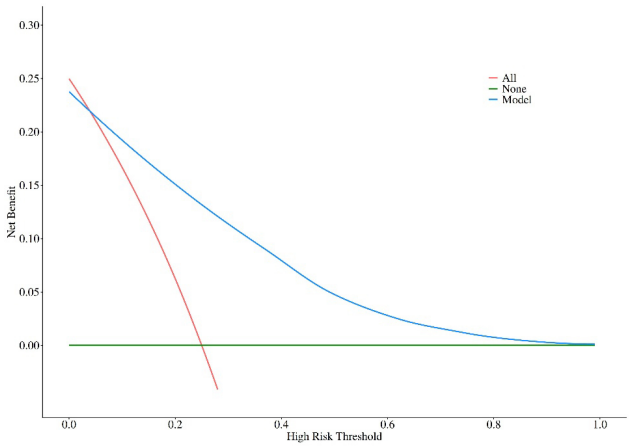

Fig. 3. Decision curve analysis.

DVT. Therefore, accurate identification of high-risk individuals during the perioperative period is of great clinical significance. The present study found that preoperative ferritin level was an independent risk factor for DVT after joint replacement in RA patients, suggesting that iron metabolism disorders may play an important role in RA-related thrombosis. In addition, D-dimer and DAS28 scores were also confirmed as independent risk factors. The prediction model can provide a quantitative reference for clinicians to identify high-risk patients and formulate individualized anticoagulation strategies during the perioperative period.

The relationship between iron metabolism disorders and thrombosis has been a research hotspot in recent years. The present study revealed that preoperative ferritin levels were significantly higher in the DVT group than in the non-DVT group, and ferritin was an independent risk factor for postoperative DVT, suggesting that hyperferritinemia may reflect the inflammatory burden in RA patients and then promote thrombosis. As an acute-phase protein, the synthesis and release of ferritin are regulated by inflammatory factors. In the chronic inflammatory state of RA, IL-6 continues to increase. On the one hand, it induces the increase of hepcidin synthesis in the liver and leads to the retention of iron in the reticuloendothelial system, which is manifested as decreased serum iron levels and increased ferritin [18,20]. On the other hand, IL-6 can directly activate the coagulation system, upregulate the expression of tissue factor, inhibit the protein C system, promote platelet activation, thereby jointly creating a prothrombotic environment [21]. However, it is noteworthy that ferritin is a well-known acute-phase reactant, and the observed association between ferritin levels and DVT risk may partially reflect the underlying inflammatory burden rather than directly representing iron metabolism. Chronic inflammation is a key driver of both hyperferritinemia and thrombosis, making it challenging to distinguish the independent contribution of iron metabolism [22]. Nevertheless, ferritin remains a clinically useful marker that reflects both inflammatory status and iron storage, and its predictive value for DVT was supported by the findings of this study. Future studies incorporating specific markers of inflammation (e.g., IL-6, hepcidin) and iron metabolism may help further elucidate the underlying mechanisms. This study further demonstrated that the DAS28 score in the DVT group was significantly higher than that in the non-DVT group, and was an independent risk factor for postoperative DVT, which supported the central role of inflammatory burden in thrombosis [23]. Hyperferritin, as a marker of inflammation, may indirectly reflect the overall inflammatory state of RA patients, associated with an increased risk of DVT.

Notably, no statistically significant differences in serum iron and TIBC were observed between the DVT and non-DVT groups in this study. This result is consistent with some previous studies on iron deficiency and the risk

of thrombosis. A large retrospective study showed a significantly increased risk of DVT in patients with iron deficiency anemia [12]. However, the subject of this study was the general population, in whom iron deficiency is primarily caused by nutritional deficiency or chronic blood loss; therefore, the underlying mechanism differs from that of inflammatory anemia in RA patients. In RA patients, hepcidin-mediated iron "retention" leads to reduced circulating iron levels, but this reduction represents functional iron deficiency rather than a real reduction of the body's total iron stores. Khalaf *et al*. [24] confirmed that hepcidin in RA patients was significantly negatively correlated with serum iron and TIBC, while ferritin was positively associated with hepcidin, reflecting the characteristics of inflammatory anemia. In this study, although serum iron levels were lower in the DVT group, the difference did not reach statistical significance, which may reflect the modest sample size or variations in disease activity across the study population. Future prospective studies with larger cohorts are needed to validate the predictive role of serum iron for thrombosis in RA patients.

D-dimer, a marker of coagulation activation and fibrinolysis, is valuable for diagnosing and predicting DVT risk. Linnemann *et al*. [25] noted that combining clinical probability assessment with D-dimer testing is a key component of the standardized DVT diagnostic and treatment protocol. In this study, D-dimer levels were significantly higher in the DVT group than in the non-DVT group, and multivariate regression identified it as an independent risk factor for postoperative DVT, consistent with previous studies. Incorporating D-dimer into the prediction model significantly enhances its discriminative ability.

The model constructed in this study integrates ferritin, D-dimer, and DAS28 score to realize the individualized prediction of DVT risk in RA patients after joint replacement. The model has good discrimination and calibration (the calibration curve basically coincided with the ideal line), suggesting that it has high accuracy and reliability in clinical utility. Compared with the traditional risk assessment tools, this model includes RA disease-specific indicators (ferritin and DAS28 score), which can better reflect the pathophysiological characteristics of RA patients and are expected to provide more targeted guidance for the prevention of thrombosis in RA patients during the perioperative period.

The present study has several novel aspects. To our knowledge, this is the first study to systematically evaluate the predictive value of preoperative iron metabolism markers—particularly ferritin—for DVT after joint replacement in RA patients. Unlike previous studies that focused primarily on traditional coagulation parameters or general DVT risk assessment tools, we incorporated RA-specific indicators (ferritin and DAS28) into a model. This approach captures the unique interplay between chronic inflammation and iron dysregulation that underlies RA-related thrombosis, offering a more tailored risk stratification tool. A key distinctive feature of this study is that our findings revealed that ferritin, rather than serum iron or TIBC, emerged as an independent risk factor for postoperative DVT. This distinction is clinically meaningful, suggesting that in RA patients, it is the inflammatory component of iron dysregulation—reflected by hyperferritinemia—rather than circulating iron availability per se that drives thrombotic risk.

This study has the following limitations. First, the sample size (n = 180, with only 45 DVT events) is relatively small, and the limited events per variable (EPV) may compromise model stability and generalizability. Continuous variables were used in univariate analysis, while quartile-categorized versions were included in the multivariate model. This discrepancy, required due to the nonlinearity identified by the Box-Tidwell test, may affect the interpretation of effect sizes across the two analytical stages. Therefore, readers should interpret the results with this distinction in mind. Second, although ferritin and D-dimer were categorized into quartiles to address nonlinearity, quartile classification inevitably leads to information loss and reduced statistical efficiency, and may amplify effect estimates. Nonetheless, this approach was necessary to satisfy the linearity assumption and enhance clinical interpretability. Third, external validation was not performed due to the lack of available external datasets; therefore, the generalizability of the model needs to be further confirmed in future multicenter prospective studies. Fourth, key perioperative factors such as antithrombotic regimens, postoperative mobility, and surgical duration were not included in the analysis due to the retrospective data, and these variables may act as potential confounders. Additionally, only preoperative baseline values of iron metabolism markers were analyzed due to the lack of serial perioperative measurements. Future prospective studies with longitudinal sampling are needed to clarify the time-dependent predictive value of these indicators. Sixth, subgroup analyses stratified by joint replacement site, RA disease duration, and anticoagulation regimens were not performed due to limited sample size and data availability. Future large-scale studies are warranted to verify the model's stability across different subgroups.

Conclusions

In conclusion, preoperative ferritin, D-dimer levels and DAS28 score were identified as independent risk factors for postoperative DVT. The logistic regression prediction model combining these indicators showed favorable predictive performance upon internal validation, offering a useful reference for individualized thromboprophylaxis. Future multi-center prospective studies should validate this model and explore the molecular mechanisms by which iron metabolism and inflammation drive RA-associated thrombosis.

Availability of Data and Materials

The datasets that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

MGD designed the research study. MGD and SHZ conducted the research and acquisition of data. MGD and CMW analyzed the data. MGD drafted the article. All authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Hangzhou Geriatric Hospital (approval number: ZN-2024317-01), and all procedures followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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