

Lower Limb Muscle Mass Parameters Predict Short-Term Prognosis After Endovascular Intervention for Non-Thrombotic Iliac Vein Compression Syndrome With Varicose Veins

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Background: Lower limb muscle mass depletion has been associated with poor outcomes in various vascular diseases, yet its prognostic role in patients with non-thrombotic iliac vein compression syndrome (NIVCS) and varicose veins (VC) undergoing endovascular intervention remains unclear. This study aimed to investigate the predictive value of lower limb muscle mass parameters for short-term prognosis in this patient population.

Methods: A total of 241 patients with NIVCS and VC treated at our hospital from January 2022 to December 2024 were enrolled. Patients were stratified into poor prognosis ($n = 57$) and good prognosis ($n = 184$) groups based on one-year outcomes. Univariate and binary logistic regression analyses identified independent prognostic factors. Receiver operating characteristic (ROC) curve analysis evaluated the predictive performance of muscle mass parameters.

Results: There were statistically significant differences in comparisons of rectus femoris (RF) thickness, RF area, vastus intermedius (VI) thickness, classification, and Hb between the two groups ($p < 0.05$). Binary logistic regression analysis showed that RF thickness, RF area, and VI thickness were independent factors ($p < 0.05$). The ROC analysis demonstrated that the combined index of RF thickness, RF area, and VI thickness had an area under the curve of 0.894, with a standard error of 0.021 (95% CI: 0.853–0.936), a Youden index of 0.62, a sensitivity of 86.00%, and a specificity of 76.19%.

Conclusion: Lower limb muscle mass parameters, particularly the combined assessment of RF thickness, RF area, and VI thickness, serve as valuable predictors of short-term prognosis following endovascular intervention for NIVCS with VC and may have potential value for preoperative risk stratification and require external validation.

Keywords: lower limb muscle mass parameters; non-thrombotic iliac vein compression syndrome; varicose; prognosis; venous return

Introduction

Non-thrombotic iliac vein compression syndrome (NIVCS), as a significant secondary factor of lower limb venous insufficiency, often leads to venous reflux disorders and chronic venous insufficiency (CVI), significantly impacting patients' quality of life. Studies have shown that the prevalence of NIVCS in Western adult populations ranges from 7%–38% in males and 14%–51% [1] in females. In traditional diagnosis and treatment, imaging examinations, including computed tomography venography (CTV) and intravascular ultrasound (IVUS), focus on evaluating the degree of iliac vein stenosis and collateral venous circulation. However, individual differences in the short-term prognosis of intervention treatment for lower limb venous insufficiency

still exist [2,3,4]. In recent years, research in critical care has revealed that muscle mass depletion is closely associated with disease severity, functional recovery, and long-term prognosis. Muscle ultrasonography has emerged as a core bedside tool for muscle mass assessment due to its non-invasive nature and high reproducibility [5]. Nevertheless, the prognostic value of lower limb muscle mass parameters in the intervention treatment of NIVCS complicated with varicose veins (VC) remains unclear. Existing studies indicate that reduced lower limb muscle mass is associated with metabolic disorders, restricted activity, and inflammatory responses caused by venous hypertension. This may indirectly compromise the short-term efficacy of endovascular intervention by altering venous hemodynamics, exacerbating limb swelling, and delaying functional recovery.

ery. However, there is currently a lack of data on the dynamic monitoring of muscle mass in NIVCS patients. This study aims to investigate the predictive value of lower limb muscle mass parameters for the short-term prognosis in patients with NIVCS and VC undergoing endovascular intervention. The findings may provide a theoretical basis for optimizing treatment strategies and improving patient outcomes.

Methods

Research Objects

241 patients with NIVCS and VC admitted to The First Affiliated Hospital of Anhui Medical University from January 2022 to December 2024 were selected. Patients were categorized into a poor prognosis group ($n = 57$) and a good prognosis group ($n = 184$) based on short-term prognosis criteria. According to predefined outcome criteria [6], the specific criteria were as follows: (1) Symptom improvement: At the 1-year follow-up, pain was assessed using the Visual Analogue Scale (VAS), and edema was evaluated using a lower extremity edema-specific rating scale. Significant symptom improvement was defined as a $\geq 50\%$ reduction in VAS score compared with baseline and a reduction of at least 2 grades in edema score (edema grading: grade 0 = no edema, grade 1 = mild pitting edema at the ankle and dorsum of the foot, grade 2 = obvious edema below the knee, grade 3 = severe edema above the knee). (2) Ulcer healing: For patients with pre-existing ulcers, no ulcer recurrence within 1 year postoperatively. (3) Imaging patency: At 1-year follow-up, color Doppler ultrasound or CTV was performed; patency of the stented or iliac vein segment was defined as continuous blood flow signal within the lumen with a peak systolic velocity ratio ≤ 2.5 on ultrasound, or lumen patency without $>50\%$ in-stent restenosis on CTV. (4) No complications: None of the following complications occurred within 1 year postoperatively: in-stent restenosis ($>50\%$), stent migration, stent fracture, new-onset deep vein thrombosis, pulmonary embolism, puncture-site hematoma requiring intervention, infection, or vascular injury. Patients who met all four criteria were assigned to the good prognosis group; those who failed to meet any one of the above criteria were assigned to the poor prognosis group.

Inclusion criteria were as follows: (1) All met the diagnostic criteria for NIVCS complicated with VC [7,8]; (2) treatment with endovascular intervention at our hospital; (3) availability of complete clinical data; (4) age >18 years; and (5) unilateral onset in all cases. Exclusion criteria were as follows: (1) Patients with cognitive, visual, or auditory impairments; (2) patients with organ dysfunctions such as cardiac or pulmonary impairments; (3) patients with other comorbid conditions (e.g., asthma) that could impact muscle mass function.

All clinical data, ultrasound measurements, and functional evaluation data of patients were sourced from

our standardized clinical follow-up database for vascular surgery. This database prospectively records the routine evaluation results of patients before surgery.

Research Methods

Muscle Mass Parameter Measurement Method

Using the Mindray M9 ultrasound machine and a linear array probe with a frequency range of 7–12 MHz, experienced ultrasound physicians measured the thickness and area of the rectus femoris (RF) and the thickness of the vastus intermedius (VI) in the affected limb before rehabilitation. During assessment, patients were placed in the supine position with the affected limb fully relaxed, and the linear array probe was positioned perpendicular to the femoral shaft at the lower 1/3 between the anterior superior iliac spine and the upper margin of the patella to clearly visualize the RF and VI. The thickness and area of the RF and the thickness of the VI in the affected limb were measured. Three measurements were obtained at each site and averaged for analysis.

General Data Collection

The general information and clinical indicators of patients were extracted through the hospital's electronic medical record system. The attending physician completed the evaluation according to standardized procedures and entered it into the system. The researcher did not make any additional phone or face-to-face inquiries to the patients.

Classification Criteria

The Clinical Etiology Anatomy Pathophysiology (CEAP) classification [1] system was utilized for categorization.

Grouping Criteria for Muscle Mass Parameters

Subgroup analysis using the Youden index receiver operating characteristic (ROC) curve analysis to determine the optimal critical value of muscle mass parameters.

Rehabilitation Therapy Protocol

All patients received a standardized rehabilitation therapy program for 6 weeks postoperatively, supervised by trained physical therapists. The specific components included: (1) Ankle pump exercise: In the supine position, patients performed maximal ankle dorsiflexion and plantarflexion, 20 repetitions per set, 3 sets daily. (2) Straight leg raise exercise: In the supine position, patients raised the affected lower limb straight to 30° – 45° and held for 5 seconds before slowly lowering, 15 repetitions per set, 3 sets daily. (3) Isometric quadriceps contraction training: In the supine position with the affected knee extended, patients contracted the quadriceps maximally for 5–10 seconds followed by relaxation, 20 repetitions per set, 3 sets daily. (4) Progressive walking training: Bedside ambulation was initiated on postoperative day 1; from day 3 on-

ward, daily walking distance was progressively increased, starting from 200 m/day and incrementing by 100–200 m per week, reaching 1000–1500 m/day by the end of week 6. Exercise intensity was guided by the Borg Rating of Perceived Exertion (target score 11–13). Training was paused or adjusted in case of aggravated pain or discomfort. Treatment adherence was recorded daily by therapists to ensure compliance.

Statistical Analysis

The experimental data collected were analyzed using SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed continuous variables were presented as $\bar{x} \pm S$ and compared using the independent-samples t -test for inter-group comparisons or the F test for comparisons among multiple groups. Categorical variables were presented as n (%), and were compared using the χ^2 test or Fisher's exact test, as appropriate. Factors associated with prognosis were analyzed using univariate and binary logistic regression analyses. To construct a parsimonious prediction model, CEAP classification and hemoglobin, which were not statistically significant in the initial multivariable model, were removed, and the logistic regression model was refitted using RF thickness, RF area, and VI thickness. Both models were based on the same patient cohort and used the same variable definitions and original measurement units. The predicted probabilities generated from the refitted three-variable model presented in Table 3 were used for the combined ROC analysis. The predictive value of lower limb muscle mass parameters for the short-term prognosis of patients with NIVCS and VC undergoing endovascular intervention was evaluated using ROC curves. Research the application of Bootstrap method for internal validation of models. A two-sided $p < 0.05$ was considered statistically significant.

Calculation Method of the Combined Index

Based on the binary logistic regression analysis results, the three independent predictors—RF thickness, RF area, and VI thickness—were incorporated into the model to calculate the predicted probability for each patient. The specific formula was: $\text{Logit}(p) = \beta_0 + \beta_1 \times (\text{RF thickness}) + \beta_2 \times (\text{RF area}) + \beta_3 \times (\text{VI thickness})$, where β_0 is the constant term, and β_1 , β_2 , and β_3 are the regression coefficients of the respective variables (see Table 3). The combined index was defined as this predicted probability value, ranging from 0 to 1, with higher values indicating higher risk of poor prognosis. ROC curve analysis was performed using this predicted probability as the test variable and the actual prognosis grouping as the state variable to evaluate its predictive performance. This approach integrates the weighted contributions of the three indicators, with weights determined by their respective regression coefficients, eliminating the need for additional arbitrary weighting.

Results

Univariate Analysis of Factors Affecting Short-Term Prognosis of Patients With NIVCS and VC Undergoing Intervention

Among the baseline variables, no statistically significant differences were observed between the two groups in age, gender, body mass index (BMI), hypertension, diabetes, affected limb side, disease duration, platelet count (PLT), albumin (ALB), prothrombin time (PT), fibrinogen (Fib), white blood cell (WBC), or 25-hydroxyvitamin D3 (25-OH-D₃) levels (all $p > 0.05$). Statistical analysis revealed significant differences ($p < 0.05$) in the comparison of RF thickness, RF area, VI thickness, classification, and Hb between the two groups, as shown in Table 1.

Binary Logistic Regression Analysis of Factors Affecting Short-Term Prognosis of Patients With NIVCS and VC Undergoing Intervention

Using the significant variables identified in the univariate analysis as independent variables, values were assigned accordingly (original values for metric data, classification $\leq C_2 = 0$, $>C_2 = 1$). The prognosis was considered the dependent variable (poor prognosis = 1, good prognosis = 0) for analysis. The binary logistic regression analysis indicated that RF thickness, RF area, and VI thickness were independent factors ($p < 0.05$). The binary logistic regression analysis was performed on the independent influencing factors, and the resulting β values were used in the formula for the subsequent joint model, as shown in Table 2, 3 and Fig. 1.

ROC Curve Analysis of Predictive Value of Indicators

The ROC analysis demonstrated that the combined index of RF thickness, RF area, and VI thickness had an area under the curve (AUC) of 0.894 with a standard error of 0.021 (95% CI: 0.853–0.936) and a Youden index of 0.62. At this point, the sensitivity is 86.00%, and the specificity is 76.19% (Table 4 and Fig. 2). To assess the internal validity of the combined predictive model, bootstrap resampling with 1000 iterations was performed. The optimism-corrected AUC after bootstrap validation was 0.820 (95% CI: 0.750–0.900). The calibration curve for the combined index demonstrated good agreement between predicted probabilities and observed outcomes, with a calibration slope close to the ideal value of 1.0 (See Fig. 3).

Discussion

This study focuses on patients with NIVCS and VC and comprehensively investigates the predictive value of lower limb muscle mass parameters for short-term prognosis following endovascular intervention. The results indicate that RF thickness, RF area, and VI thickness are independent factors influencing short-term prognosis of patients

Table 1. Univariate analysis of factors affecting short-term prognosis of patients with NIVCS and VC Undergoing intervention.

Indicator		Poor prognosis group (n = 57)	Good prognosis group (n = 184)	t/χ^2 value	p value
Age (years)		67.46 ± 4.68	67.69 ± 5.48	0.286	0.775
Gender	Male	36 (63.16)	97 (52.72)	1.918	0.166
	Female	21 (36.84)	87 (47.28)		
BMI (kg/m ²)		21.84 ± 1.06	22.04 ± 1.21	1.121	0.263
Hypertension	Yes	17 (29.82)	50 (27.17)	0.152	0.696
	No	40 (70.18)	134 (72.83)		
Diabetes	Yes	14 (24.56)	41 (22.28)	0.128	0.720
	No	43 (75.44)	143 (77.72)		
Affected limb	Left	24 (42.11)	99 (53.80)	2.384	0.123
	Right	33 (57.89)	85 (46.20)		
Disease duration (years)		6.48 ± 2.14	6.54 ± 2.08	0.189	0.850
Classification	≤C ₂	19 (33.33)	103 (55.98)	8.928	0.003
	>C ₂	38 (66.67)	81 (44.02)		
PLT (×10 ⁹ /L)		131.54 ± 16.58	133.84 ± 17.54	0.876	0.382
ALB (g/L)		35.84 ± 5.48	35.61 ± 5.33	0.283	0.778
PT (s)		14.52 ± 3.15	14.42 ± 3.48	0.194	0.847
Hb (g/L)		120.84 ± 29.54	129.84 ± 24.56	2.300	0.022
Fib (g/L)		1.72 ± 0.22	1.71 ± 0.31	0.226	0.821
WBC (×10 ⁹ /L)		4.19 ± 0.85	4.24 ± 0.76	0.422	0.674
25-OH-D ₃ (ng/mL)		19.46 ± 2.94	19.64 ± 2.82	0.417	0.677
RF thickness (cm)		2.09 ± 0.34	2.29 ± 0.39	3.482	0.001
RF area (cm ²)		3.13 ± 0.37	3.24 ± 0.28	2.391	0.018
VI thickness (cm)		1.59 ± 0.22	1.84 ± 0.31	5.659	<0.001

Note: BMI, body mass index; RF, rectus femoris; VI, vastus intermedius; 25-OH-D₃, 25-hydroxyvitamin D₃; PLT, platelet count; WBC, white blood cell; ALB, albumin; PT, prothrombin time; Fib, fibrinogen; Hb, hemoglobin; NIVCS, non-thrombotic iliac vein compression syndrome; VC, varicose veins.

Table 2. Binary logistic regression analysis of factors affecting short-term prognosis of patients with NIVCS and VC undergoing intervention.

Factor	β	SE	Wald	p	Exp(β)	95% CI	VIF
RF thickness	-0.603	0.215	7.874	0.005	0.547	0.359~0.834	1.222
RF Area	-0.759	0.314	5.847	0.016	0.468	0.253~0.866	1.295
VI thickness	-1.194	0.419	8.121	0.004	0.303	0.133~0.689	1.633
Classification	0.114	0.163	0.491	0.483	1.121	0.814~1.543	--
Hb	-0.048	0.047	1.050	0.306	0.953	0.868~1.045	1.083

Note: SE, standard error.

Table 3. Binary logistic regression analysis results of three variable models selected.

Factor	β	SE	Wald	p	Exp(β)	95% CI
RF thickness	-5.775	1.066	29.342	<0.001	0.003	0.000~0.025
RF Area	-4.408	1.178	13.994	<0.001	0.012	0.001~0.123
VI thickness	-6.980	1.320	27.951	<0.001	0.001	0.000~0.012
Constant	37.540	5.833	41.413	<0.001	-	-

Note: This model was refitted using the same patient cohort and the original measurement units after CEAP classification and hemoglobin were removed from the initial model. The regression coefficients were newly estimated and were used to calculate the combined prediction index.

with NIVCS and VC undergoing endovascular intervention. The combined index of these three factors achieved an area under the curve of 0.894, demonstrating excellent

predictive performance. These findings suggest that lower limb muscle mass parameters may serve as valuable reference indicators for short-term prognosis assessment, assist-

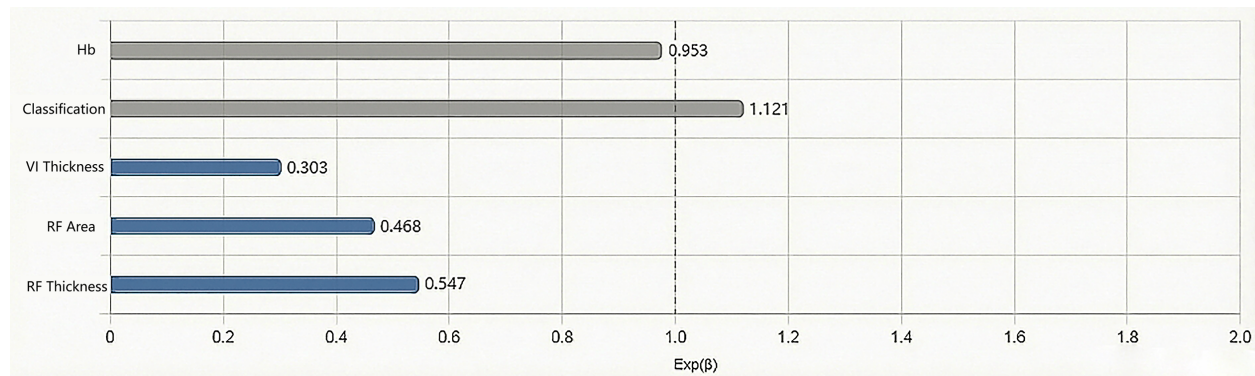


Fig. 1. Intuitive OR value diagram. OR, odds ratio.

Table 4. ROC analysis results.

Indicator	AUC	SE	<i>p</i>	95% CI	Youden	Sensitivity	Specificity	Optimal cut-off value
RF thickness	0.759	0.034	<0.001	0.691~0.826	0.38	98.19	40.21	2.18
RF area	0.672	0.043	<0.001	0.587~0.757	0.28	40.36	88.00	3.14
VI thickness	0.759	0.032	<0.001	0.696~0.821	0.47	98.11	48.86	1.82
Combined index	0.894	0.021	<0.001	0.853~0.936	0.62	86.00	76.19	0.22

ROC, receiver operating characteristic; AUC, area under the curve.

ing physicians in obtaining a more comprehensive understanding of patients' conditions preoperatively. This facilitates the development of personalized treatment plans, ultimately improving clinical outcomes and patients' quality of life.

The lower limb muscles play a crucial role in venous return, particularly the contraction and relaxation of the calf muscle pump and thigh muscles, facilitating blood flow from the lower limbs back to the heart. The thickness and area of the RF, as well as the thickness of the VI, as important muscle groups in the thigh, reflect muscle quality and strength. Greater values of these parameters indicate stronger muscle contraction, enabling more effective compression of veins, promoting blood flow, reducing venous pressure, thus lowering the risk of varicose vein recurrence and complications post-intervention, aiding in the recovery of patients [9]. Conversely, in patients with poor muscle quality, insufficient muscle contraction leads to diminished venous return, blood stasis, and increased venous pressure, compromising the efficacy of endovascular intervention and leading to poor prognosis [10]. This suggests that patients with higher lower limb muscle quality exhibit better physical function, enabling them to adapt more effectively to postoperative rehabilitation, actively engage in rehabilitation training, and achieve better treatment outcomes. On the other hand, patients with poor muscle quality experience impaired physical function and limited mobility, potentially compromising adherence to rehabilitation training and reducing their effectiveness, consequently affecting short-term prognosis [11,12]. From the perspective of pathophysiology and molecular mechanisms, the decline in lower limb muscle mass is not only a mechanical weaken-

ing of the muscle pump function. Muscle atrophy or muscle fat infiltration can induce a local chronic low-grade inflammatory state, promoting the release of inflammatory factors such as tumor necrosis factor- α and interleukin-6. These factors can directly damage venous endothelial cells, leading to endothelial dysfunction and increased permeability, exacerbating venous hypertension and reflux [13]. Meanwhile, skeletal muscle functions as an important endocrine organ, and the loss of skeletal muscle mass can reduce the secretion of vascular protective factors (such as insulin-like growth factor-1 and vascular endothelial growth factor), weaken vascular wall nutrition and repair, leading to atrophy of smooth muscle cells and abnormal remodeling of collagen fibers within the venous wall. In addition, muscle tissue hypoxia can activate the transforming growth factor- β -1/Smad signaling pathway, promoting extracellular matrix deposition and venous wall fibrosis, and decreasing vascular compliance [14]. Therefore, muscle mass parameters reflect the pathological processes of local microenvironment homeostasis, vasoactive factor secretion, and vascular wall remodeling, and serve as an intrinsic molecular bridge connecting muscle function and venous disease progression. This provides a deeper biological explanation for the impact of muscle mass on the prognosis of interventional therapy.

At present, there is relatively limited evidence on the prognosis of venous diseases in relation to lower limb muscle mass. Nevertheless, some studies have suggested an association between lower muscle mass and venous function. Previous research by Venco R et al. [15] has shown a correlation between lower muscle mass and adverse outcomes in critically ill patients. These findings are consistent with our

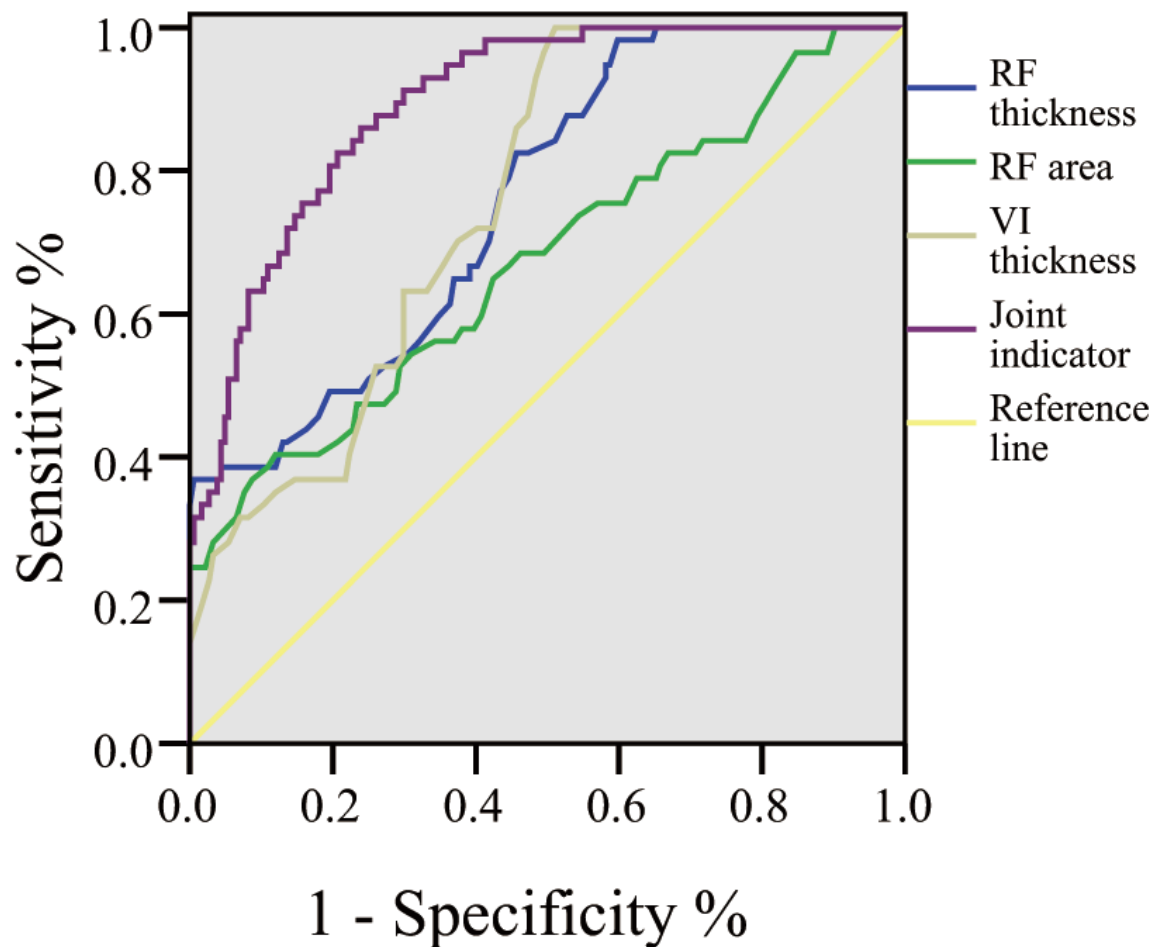


Fig. 2. ROC curve.

results, indicating that lower limb muscle mass parameters can serve as important indicators for assessing the prognosis of venous diseases. Collectively, this further validates the significant role of lower limb muscle mass in venous return and disease progression, providing more comprehensive evidence for clinical applications. However, there may be some differences among different studies. For example, differences in the muscle groups, assessment methods, and treatment strategies may lead to inconsistent results. Therefore, further in-depth studies are needed to validate these results in the future [16,17].

Lower limb muscle mass parameters can serve as important indicators for the pre-intervention assessment of patients with NIVCS and VC. By assessing parameters such as RF thickness, RF area, and VI thickness, doctors can predict the short-term prognosis of patients undergoing endovascular intervention, identifying high-risk patients with poor prognosis. For these patients, doctors can implement more proactive intervention planning, such as enhancing preoperative rehabilitation training, optimizing surgical plans, and closely monitoring postoperative recovery, to reduce the risk of complications and improve prognosis. Based on lower limb muscle mass parameters, doctors can tai-

lor personalized treatment plans for patients. Patients with higher muscle quality may be suitable for routine intervention methods, while those with poorer muscle quality may require comprehensive strategies, including rehabilitation therapy and nutritional support, to enhance muscle quality and strength, promote venous return, and improve treatment outcomes. Additionally, lower limb muscle mass parameters can guide patients' rehabilitation training. Specifically, tailored rehabilitation plans can be developed based on the patient's muscle quality, enhancing the specificity and effectiveness of rehabilitation training. Following endovascular intervention, lower limb muscle mass parameters can serve as important indicators for prognosis follow-up and evaluation of treatment efficacy. Regular assessment of changes in lower limb muscle mass can provide timely insights into patients' rehabilitation progress and treatment outcomes. Continuous improvement in muscle mass parameters indicates favorable rehabilitation progress; conversely, if there are no significant changes or further deterioration in muscle mass parameters, adjustments to treatment plans and intensified intervention strategies may be necessary.

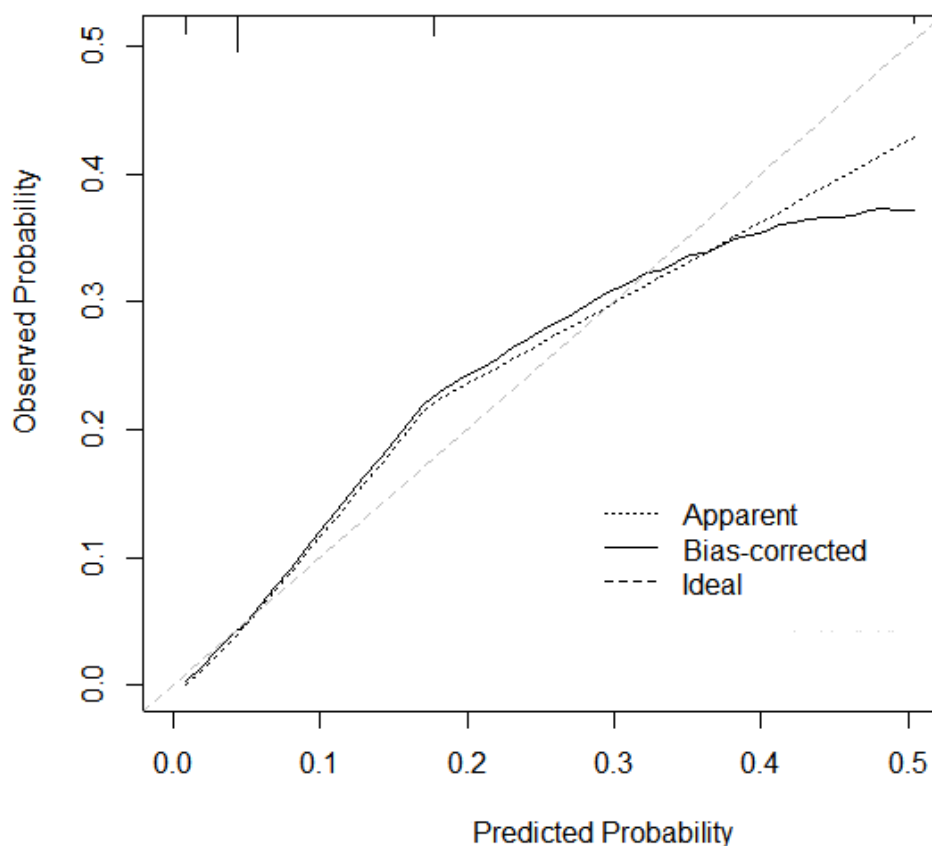


Fig. 3. Calibration curve of combined index.

This study has several limitations that should be acknowledged. First, as a single-center retrospective study with a relatively limited sample size ($n = 241$), selection bias may have been introduced, potentially limiting the generalizability and applicability of these findings. Second, the study focused exclusively on the effect of lower limb muscle mass parameters on short-term (one-year) prognosis following endovascular intervention. The absence of long-term follow-up precluded assessment of whether these parameters are also associated with sustained clinical benefit, stent durability, or late adverse events such as delayed restenosis. Third, regarding the prognostic grouping strategy, the use of a composite endpoint, while clinically meaningful, inevitably introduced heterogeneity within the poor prognosis group, as patients may fail to meet different individual endpoint components. This heterogeneity may have diluted the observed associations and limited the ability to identify component-specific predictors. Fourth, although variables such as hypertension, diabetes, and laboratory parameters were adjusted for, other potentially important confounders, including patients' psychological status, lifestyle factors, and socioeconomic status, were not captured in this retrospective analysis, despite their potential roles in disease progression and postoperative recovery.

To address these limitations, future studies should: (a) expand the sample size and adopt a multicenter design to en-

hance the robustness and external validity of the findings; (b) extend the follow-up period to evaluate whether lower limb muscle mass parameters predict long-term outcomes beyond the first year; (c) perform component-specific analyses of the composite endpoint in larger cohorts to clarify which outcomes are most closely associated with muscle mass; and (d) prospectively collect additional psychosocial, lifestyle, and functional data to better control for residual confounding and to explore potential mediating pathways.

Conclusion

In conclusion, lower limb muscle mass parameters demonstrate potential value in predicting the short-term prognosis of patients with NIVCS and VC undergoing endovascular intervention, suggesting their inclusion as evaluation indicators. Future research should delve deeper into their mechanisms of action, broaden the scope of study, and provide a more scientific and precise basis for clinical treatment and prognosis assessment.

Availability of Data and Materials

The data used or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

YQZ, WC, PQ, and JHZ contributed to the conception and design of the study. CSL and JW performed the research. TMW and ZGW contributed to data acquisition. YQZ, CSL, HJP, and HM contributed to data analysis and interpretation. YQZ and CSL drafted the original manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ-YX2026-035). As this was a retrospective study using anonymized data, the requirement for informed consent was waived by the ethics committee.

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Conflict of Interest

The authors declare no conflict of interest.

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