

PREOPERATIVE SERUM VON WILLEBRAND FACTOR, E-SELECTIN, AND TUMOR NECROSIS FACTOR-ALPHA PREDICT EARLY VENOUS OUTFLOW DYSFUNCTION AFTER FINGER REPLANTATION

PREOPERATIVNI SERUMSKI FON VILEBRANDOV FAKTOR, E-SELEKTIN I FAKTOR NEKROZE TUMORA ALFA PREDVIĐAJU RANU DISFUNKCIJU VENSKOG ODLIVA NAKON REPLANTACIJE PRSTA

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Summary

Background: Early venous outflow dysfunction is a leading cause of early failure after finger replantation. This study evaluated whether preoperative serum markers of endothelial activation and inflammation can predict early venous outflow dysfunction and developed a serum-based risk model.

Methods: This retrospective cohort included 150 patients who underwent finger replantation between January 2022 and October 2025. Peripheral venous blood was collected 2 h before surgery. Serum von Willebrand factor (vWF), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) were measured. Early venous outflow dysfunction was defined as venous congestion requiring intervention within 72 h postoperatively. Independent markers were identified using multivariable logistic regression. Model performance was assessed by receiver operating characteristic analysis (AUC with 95% confidence intervals by the DeLong method and between-model comparison by the DeLong test), calibration by the Hosmer-Lemeshow test, and internal validation using bootstrap resampling (200 iterations).

Results: All seven biomarkers were higher in cases (n=74) than controls (n=76) ($P<0.05$) and were positively

Kratak sadržaj

Uvod: Disfunkcija venskog odliva jedan je od vodećih uzroka ranog neuspeha nakon replantacije prsta. Ova studija ispitala je da li preoperativni serumski markeri endotelne aktivacije i inflamacije mogu predvideti ranu disfunkciju venskog odliva, kao i mogućnost razvoja serumski zasnovanog modela rizika.

Metode: Ova retrospektivna kohortna studija je obuhvatila 150 pacijenata koji su podvrgnuti replantaciji prsta u periodu od januara 2022. do oktobra 2025. godine. Periferna venska krv prikupljena je 2 sata pre operacije. Merene su serumske koncentracije von Willebrandovog faktora (vWF), intercelularnog adhezionog molekula-1 (ICAM-1), vaskularnog ćelijskog adhezionog molekula-1 (VCAM-1), E-selektina, C-reaktivnog proteina (CRP), interleukina-6 (IL-6) i faktora nekroze tumora alfa (TNF- α). Rana disfunkcija venskog odliva definisana je kao venska kongestija koja zahteva intervenciju u roku od 72 sata nakon operacije. Nezavisni markeri identifikovani su multivarijantnom logističkom regresijom. Performanse modela procenjene su analizom ROC krive (AUC sa 95% intervalima pouzdanosti dobijenim DeLongovom metodom i poređenjem modela DeLongovim testom), procenom kalibracije Hosmer-Lemeshow testom, kao i internom validacijom primenom *bootstrap* resampliranja (200 iteracija).

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correlated with crisis duration (all $P < 0.01$). vWF, E-selectin, and TNF- α remained independently associated with early venous outflow dysfunction. The resulting panel achieved an AUC of 0.811 (95% CI, 0.738–0.883), with 72.97% sensitivity and 84.21% specificity. Calibration was acceptable (Hosmer-Lemeshow $P = 0.093$), and the optimism-corrected AUC was 0.802. A clinical-variable model showed poorer discrimination (AUC 0.618; 95% CI, 0.527–0.709), and the biomarker panel improved discrimination significantly (DeLong $P = 0.001$).

Conclusion: A preoperative serum panel combining vWF, E-selectin, and TNF- α showed good discrimination for early venous outflow dysfunction after finger replantation. External validation is needed before routine clinical use.

Keywords: finger replantation, endothelial activation, inflammation, venous outflow dysfunction, predictive model

Introduction

Replantation of severed fingers is a key technique to restore hand function, and surgical success depends on the timely establishment and maintenance of microvascular patency (1). However, early venous outflow dysfunction (ERVD), manifested as postoperative venous congestion requiring additional intervention, occurs in approximately 10%–30% of cases (2). Delayed recognition and management may lead to replantation failure and tissue necrosis, compromising patient outcomes and increasing resource utilization (3). Current bedside assessments rely on physical findings (e.g., capillary refill, skin temperature, tissue turgor) and adjunctive imaging (e.g., Doppler ultrasound), which can be subjective and may lag behind early microcirculatory deterioration (4, 5). Accordingly, objective serum biomarkers that capture endothelial activation and inflammation have attracted interest for earlier risk stratification (6). Endothelial dysfunction, a core mechanism of ERVD, promotes release of markers such as von Willebrand factor (vWF) and intercellular adhesion molecule-1 (ICAM-1), reflecting endothelial injury and prothrombotic activation (7). In parallel, ischemia-reperfusion injury can amplify inflammatory signaling and microvascular plugging, further impairing venous outflow (8). However, existing research has largely focused on individual markers (9), with limited integrated evaluation of multidimensional serum biomarkers and a lack of validated multivariable prediction models for early ERVD risk stratification.

Given this, the study evaluated whether a combined panel of preoperative serum biomarkers reflecting endothelial activation (vWF, ICAM-1, VCAM-1, and E-selectin) and systemic inflamma-

Rezultati: Svih sedam biomarkera bili su značajno viši kod bolesnika sa disfunkcijom venskog odliva ($n = 74$) u poređenju sa kontrolnom grupom ($n = 76$) ($P < 0,05$) i pokazali su pozitivnu korelaciju sa trajanjem krize (svi $P < 0,01$). vWF, E-selektin i TNF- α ostali su nezavisno povezani sa disfunkcijom ranog venskog odliva. Dobijeni biomarkerni panel ostvario je AUC od 0,811 (95% CI, 0,738–0,883), uz osetljivost od 72,97% i specifičnost od 84,21%. Kalibracija modela bila je prihvatljiva (Hosmer-Lemeshow $P = 0,093$), dok je optimistički korigovani AUC iznosio 0,802. Model zasnovan isključivo na kliničkim varijablama pokazao je slabiju diskriminativnu sposobnost (AUC 0,618; 95% CI, 0,527–0,709), dok je biomarkerni panel značajno unapredio diskriminaciju (DeLong $P = 0,001$).

Zaključak: Preoperativni serumski panel koji kombinuje vWF, E-selektin i TNF- α pokazao je dobru diskriminativnu sposobnost za predviđanje disfunkcije ranog venskog odliva nakon replantacije prsta. Pre rutinske kliničke primene neophodna je eksterna validacija modela.

Ključne reči: replantacija prsta, endotelna aktivacija, inflamacija, disfunkcija venskog odliva, prediktivni model

tion (CRP, IL-6, and TNF- α) could improve early risk stratification for ERVD. Specifically, the study: (i) quantified the discriminative performance of each candidate marker; (ii) identified independent predictors using multivariable regression with adjustment for key surgical and clinical confounders; and (iii) constructed a parsimonious preoperative serum-based model for early warning of ERVD after finger replantation. Importantly, to our knowledge, this is the first study to integrate endothelial activation and inflammatory biomarkers for ERVD risk stratification, thereby overcoming limitations of prior work focused on single markers or lacking rigorous model validation, and offering a clinically practical tool to support perioperative decision-making.

Materials and Methods

Ethics statement

This retrospective cohort study was approved by the Ethics Committee of Yongkang First People's Hospital (Approval No. 2022-6125) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before finger replantation surgery. For patients who were unable to provide consent due to acute injury, deferred informed consent was obtained from their legal representatives within 48 h postoperatively.

Sample size estimation

A retrospective cohort study design was adopted. The sample size was estimated based on the expected effect size and the statistical power. We assumed a 15%–25% incidence of ERVD post-fin-

ger replantation, based on previous literature (10), a two-tailed α of 0.05, and a power ($1-\beta$) of 0.8. Using G-Power software, it was calculated that each group needed 70 cases, and a total of 154 cases were included, considering a 10% dropout rate.

Research participants

The study population comprised patients who underwent replantation of severed fingers in the orthopedics department of our hospital from January 2022 to October 2025. All cases had complete perioperative serum samples, clinical follow-up records, and imaging data. Inclusion applied to cases meeting all of the following criteria: ① aged 18–65 with the first replantation of unilateral severed finger (single finger); ② successful operation (unobstructed blood flow shown by Doppler immediately after vascular anastomosis); ③ preoperative peripheral venous blood collection at 2 h before surgery, with valid serum samples for biomarker detection; ④ intact clinical data (including the cause of injury, ischemic time, vascular anastomosis technique, etc.). Fulfillment of any of the following means exclusion: ① serious basic diseases (e.g., HbA1c > 7% in diabetic patients, INR > 1.5 in those with coagulation dysfunction); ② multilevel segmental amputation, destructive injury, or inability to rebuild the blood supply of the replanted finger; (3) reoperation within 72 hours after surgery (e.g., vascular exploration); ④ hemolysis of the serum sample, insufficient volume, or failed detection.

Grouping

Patients were dichotomized according to whether ERVD occurred within 72 hours postoperatively. ERVD was defined as the presence of at least two of the following objective criteria within 72 h postoperatively, confirmed by two independent senior hand surgeons, and requiring targeted intervention: ① Persistent purplish-blue discoloration of the replanted finger lasting > 1 h; ② Capillary refill time > 5 s or absent capillary refill; ③ Doppler ultrasound showing absent or reversed venous flow signals; ④ Tissue turgor increased with blister formation within 4 h. Non-ERVD group was defined as absence of the above criteria and no need for venous intervention within 72 h. There were 74 cases in the ERVD group and 76 in the Non-ERVD group. For ERVD cases, crisis duration (hours) was defined as the interval from the first documentation of objective ERVD criteria to the complete resolution of venous congestion (restoration of normal skin color, capillary refill time 2–3 s, and positive venous Doppler signals). All patients received standardized perioperative management, including continuous warm dressing (32–34 °C), heparin anticoagulation

(50 U/kg per day), and papaverine vasodilation (30 mg every 8 h) to minimize treatment-dependent variability in crisis duration. Clinicians responsible for ERVD assessment were blinded to the preoperative serum biomarker results to avoid assessment bias.

Data collection

Demographic and perioperative variables (age, sex, injury mechanism, amputation level, affected side, anastomosis type) and ischemia time were extracted from the electronic medical record system. Ischemia time (min) was defined as the interval from injury to arterial reperfusion, where arterial reperfusion was recorded at completion of arterial anastomosis with restoration of pulsation and/or visible arterial bleeding. For ERVD cases, crisis duration was recorded in hours.

Blood sample testing

Peripheral venous blood was collected 2 hours preoperatively. 2 mL of venous blood was drawn into an anticoagulant-free test tube, left standing at room temperature for 30 minutes, and then centrifuged (3000×g for 10 minutes) within 1 h of collection. The supernatant serum was separated and stored at -80 °C within 2 h of centrifugation for subsequent testing. No freeze-thaw cycles were allowed before detection. Serum samples were assessed for hemolysis (hemoglobin concentration < 0.5 g/L) and lipemia (triglyceride concentration < 5.6 mmol/L) using an automatic biochemical analyzer; samples with hemolysis or lipemia were excluded.

CRP measurement by immunoturbidimetry: The sample was mixed with a latex reagent at a 1:200 ratio and incubated at 37 °C for 5 minutes. An automatic biochemical analyzer measured absorbance changes, and the concentration was calculated based on the standard curve. Quality control: For each batch, high- and low-quality control samples were added simultaneously. (Bio-Rad Lyphochek Immunoassay Plus Controls). The instrument was calibrated daily (e.g., wavelength calibration for the microplate reader and magnetic bead count calibration for the chemiluminescence instrument), and the linear range was verified weekly using standards.

Von Willebrand factor (vWF): Enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, USA; Lot No. DY781-05), detection limit 0.5 IU/dL, intra-assay CV < 5%, inter-assay CV < 8%.

Intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin: ELISA kits (BD Biosciences, San Jose, USA; Lot Nos. 555248, 555297, 555127), detection lim-

its 2.0 ng/mL, 3.0 ng/mL, 1.5 ng/mL respectively, intra-assay CV <6%, inter-assay CV <9%.

Interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α): Chemiluminescent immunoassay kits (Siemens Healthcare, Erlangen, Germany; Lot Nos. 12345, 67890), detection limits 0.1 pg/mL, 0.2 pg/mL, respectively, intra-assay CV <4%, inter-assay CV <7%.

All assays were performed according to the manufacturers' instructions. Calibration curves were generated using standard solutions provided in each kit, and quality control samples were run in duplicate for each batch.

Statistical analyses

Statistical analyses were performed using SPSS 26.0 (IBM, USA), with additional procedures applied to evaluate model performance. Categorical variables are presented as n (%) and were compared using the chi-square test. Continuous variables (biomarker concentrations and crisis duration) were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were compared between groups using the independent-samples t test, whereas non-normally distributed variables were compared using the Mann-Whitney U test. Based on normality results, Pearson correlation was used for vWF and E-selectin, and Spearman rank correlation was used for ICAM-1, VCAM-1, CRP, IL-6, TNF- α , and crisis duration. For analyses involving the seven biomarkers (group comparisons, correlation analyses, and single-marker ROC analyses), a Bonferroni correction was applied, with an adjusted significance threshold of $\alpha=0.05/7\approx0.007$.

Multicollinearity among the seven candidate biomarkers was assessed using variance inflation factors (VIFs). VIF values ranged from 1.12 to 1.89 (all <5), indicating no meaningful multicollinearity. Logistic regression was used to identify independent biomarkers associated with ERVD, and a preoperative early-warning model was constructed based on the regression coefficients. Restricted cubic spline (RCS) analysis with three knots (10th, 50th, and 90th percentiles) was used to examine the linearity of continuous predictors (vWF, E-selectin, and TNF- α) on the logit scale; no evidence of non-linearity or threshold effects was observed (all P for non-linearity >0.05).

Discrimination was assessed using ROC analysis. AUCs with 95% confidence intervals were estimated using the DeLong method, and AUCs were compared using the DeLong test. Calibration was evaluated using the Hosmer-Lemeshow test. Internal validation was performed via bootstrap resampling (200 iterations) to obtain an optimism-cor-

rected AUC. For each bootstrap resample, the full model-building process (forward stepwise selection and model fitting) was repeated to reduce optimism. The optimism-corrected AUC was derived by subtracting the mean overfitting bias across bootstrap samples from the apparent AUC. A clinical-variable model including age, sex, injury mechanism, amputation level, affected side, anastomosis type, and ischemia time served as the comparator. All tests were two-sided, and $P<0.05$ was considered statistically significant unless otherwise specified by Bonferroni adjustment.

Results

Baseline data of research participants

Baseline clinical characteristics of the ERVD group and the non-ERVD group are presented in Table I. No statistically significant differences were observed in these characteristics ($P>0.05$).

Comparison of endothelial function markers

Compared with the non-ERVD group, vWF, ICAM-1, VCAM-1, and E-selectin were higher in the ERVD group ($P<0.05$) (Figure 1).

Differences in inflammatory cytokines

Similarly, the inflammatory cytokines, CRP, IL-6, and TNF- α , exhibited higher levels in ERVD cases than in their non-ERVD counterparts ($P<0.05$) (Figure 2).

Correlation of endothelial function markers and inflammatory cytokines with crisis duration

According to correlation analysis, both endothelial function markers and inflammatory cytokines were positively correlated with crisis duration ($P<0.05$). That is, the longer the crisis lasts, the higher the levels of vWF, ICAM-1, VCAM-1, E-selectin, CRP, IL-6, and TNF- α ($P<0.05$) (Figure 3 and Table II).

Prognostic risk stratification value of endothelial function markers and inflammatory cytokines for ERVD

As shown in ROC curves, both endothelial function markers and inflammatory cytokines demonstrated strong prognostic risk stratification for ERVD, with vWF (AUC=0.726) outperforming the others (AUC<0.7) (Figure 4 and Table III).

Table I Comparison of baseline clinical data between the ERVD group and the non-ERVD group.

Variables	Non-ERVD group (n=76)	ERVD group (n=74)	Statistics and P
Age	35.32±8.92	36.73±7.49	t=1.049, P=0.296
Male/female	58/18 (76.32%/23.68%)	60/14 (81.08%/18.92%)	$\chi^2=0.507$, P=0.476
Causes of injury			$\chi^2=0.957$, P=0.620
Crush injury	34 (44.74)	39 (52.70)	
Cutting wound	37 (48.68)	31 (41.89)	
Other	5 (6.58)	4 (5.41)	
Plane of discontinuity			$\chi^2=0.538$, P=0.463
Fingertip segment	47 (61.84)	50 (67.57)	
Middle finger segment	29 (38.16)	24 (32.43)	
Ischemic time (min)	129.12±37.72	124.45±32.53	t=0.812, P=0.418
Side of the disease			$\chi^2=0.910$, P=0.340
Left hand	26 (34.21)	20 (27.03)	
Right hand	50 (65.79)	54 (72.97)	
Vascular anastomosis			$\chi^2=0.672$, P=0.412
End-to-end anastomosis	62 (81.58)	64 (86.49)	
End-to-side anastomosis	14 (18.42)	10 (13.51)	
Crush severity			$\chi^2=0.568$, P=0.753
Grade 1	26 (34.21)	23 (31.08)	
Grade 2	46 (60.53)	45 (60.81)	
Grade 3	4 (5.26)	6 (8.11)	
Vessel caliber			$\chi^2=0.400$, P=0.527
<1.0 mm	27 (35.53)	30 (40.54)	
≥1.0 mm	49 (64.47)	44 (59.46)	
Smoking			$\chi^2=1.058$, P=0.304
Yes	34 (44.74)	27 (36.49)	
No	42 (55.26)	47 (63.51)	

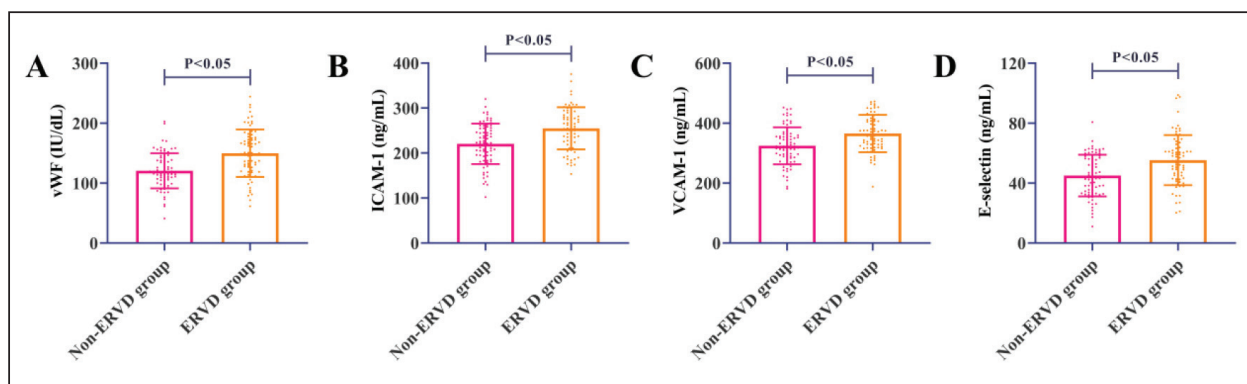


Figure 1 Comparison of endothelial function markers levels between the ERVD group and the non-ERVD group (A) vWF, (B) ICAM-1, (C) VCAM-1, (D) E-selectin. The independent-samples t-test showed significant differences between the two groups ($P < 0.05$).

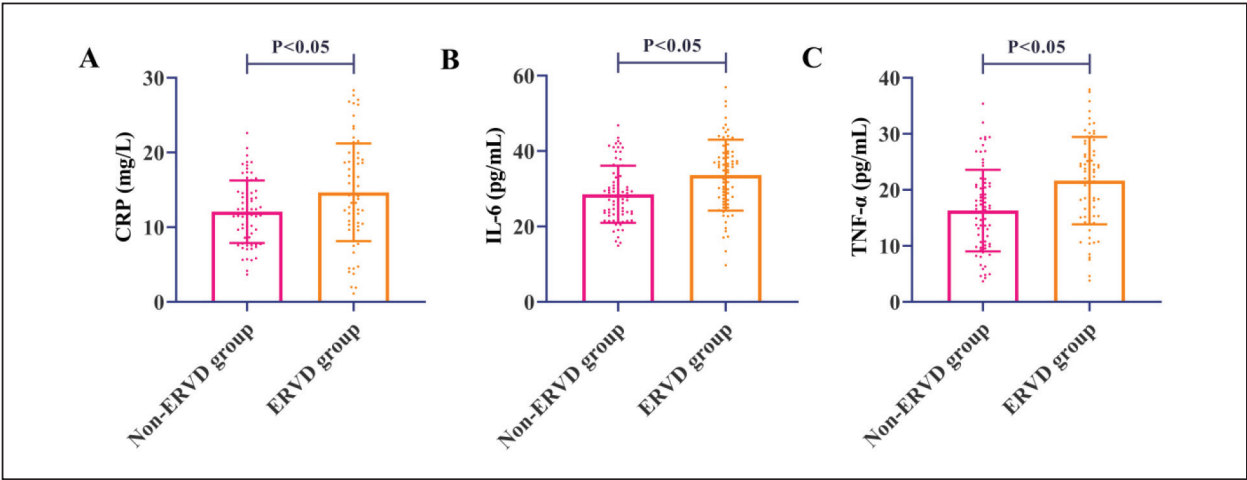


Figure 2 Comparison of the levels of inflammatory factors between the ERVD group and the non-ERVD group (A) CRP, (B) IL-6, (C) TNF- α . The results of t independent-samples t-test showed that there was a difference between the two groups ($P < 0.05$).

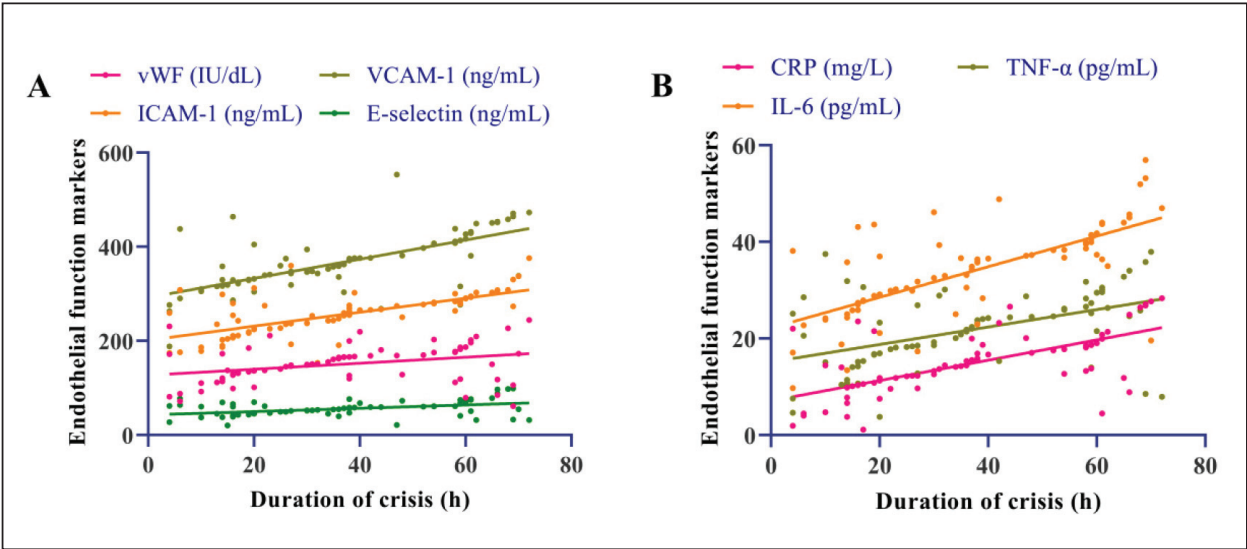


Figure 3 Scatter plot of correlation between markers of endothelial function and inflammatory factors and duration of crisis. (A) Relationship between crisis duration and endothelial function markers, (B) Relationship between crisis duration and inflammatory factors. The correlation was analyzed by the Pearson or Spearman correlation coefficient.

Table II Correlation analysis of endothelial function markers and inflammatory factors with the duration of crisis.

Indicator		r	95% CI	P
Endothelial function markers	vWF	0.327	0.107–0.517	0.005
	ICAM-1	0.645	0.488–0.761	$P < 0.001$
	VCAM-1	0.663	0.512–0.774	$P < 0.001$
	E-selectin	0.430	0.223–0.600	$P < 0.001$
Inflammatory cytokines	CRP	0.654	0.500–0.768	$P < 0.001$
	IL-6	0.684	0.540–0.789	$P < 0.001$
	TNF- α	0.471	0.272–0.631	$P < 0.001$

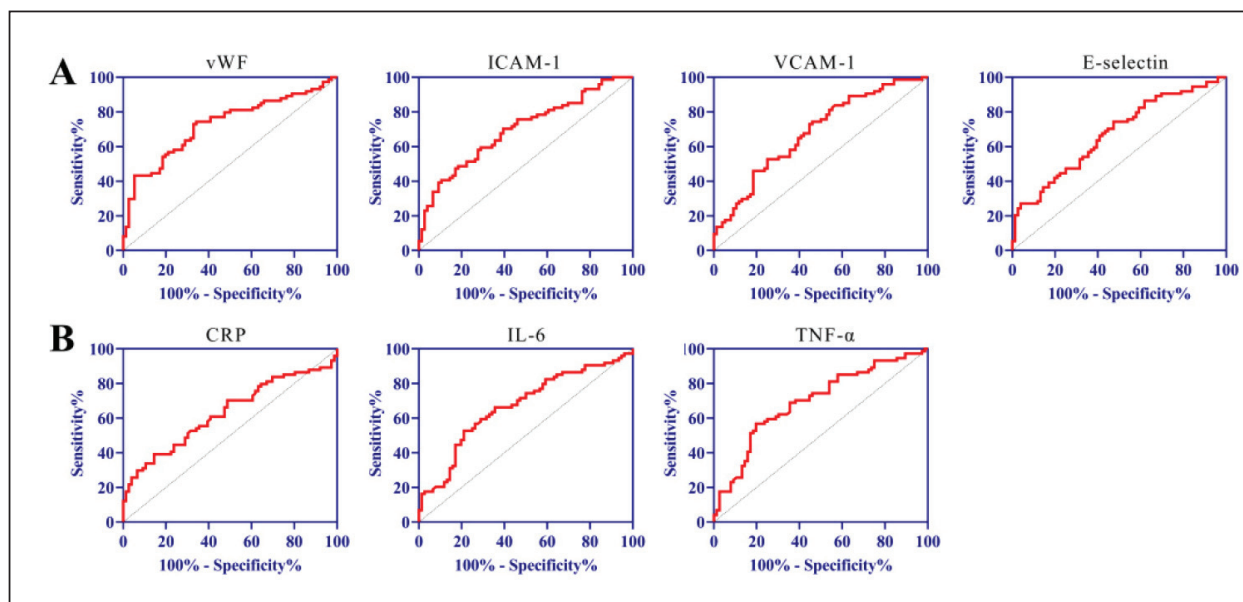


Figure 4 ROC curves of single endothelial function markers and inflammatory factors for prognostic risk stratification of ERVD.

(A) The prognostic risk stratification value of Endothelial function markers for ERVD, (B) The prognostic risk stratification value of inflammatory factors on ERVD.

Table III Results of ROC curve analysis of single endothelial function markers and inflammatory factors in the prognostic risk stratification value of ERVD.

Indicator		Cut-off	AUC	Std. Error	95% CI	Sensitivity (%)	Specificity (%)	p
Endothelial function markers	vWF	>126.1	0.726	0.042	0.644–0.808	74.32	65.79	P<0.001
	ICAM-1	>234.7	0.699	0.043	0.616–0.782	70.27	60.53	P<0.001
	VCAM-1	>323.9	0.681	0.044	0.597–0.766	74.32	53.95	P<0.001
	E-selectin	>44.82	0.673	0.044	0.587–0.758	74.32	52.63	P<0.001
Inflammatory cytokines	CRP	>16.68	0.630	0.046	0.540–0.721	39.19	85.53	0.006
	IL-6	>34.21	0.669	0.044	0.582–0.756	52.70	78.95	P<0.001
	TNF-α	>21.49	0.696	0.043	0.612–0.781	56.76	80.26	P<0.001

Establishment and effect verification of the joint model

The variable selection strategy for multivariable modeling was pre-specified based on biological plausibility and statistical significance: ① initially include all seven candidate biomarkers (vWF, ICAM-1, VCAM-1, E-selectin, CRP, IL-6, TNF-α) that were significantly associated with ERVD in univariate analysis ($P < 0.007$); ② perform forward stepwise logistic regression with entry criterion $P < 0.05$ and removal criterion $P > 0.10$ to select independent predictors. In multivariable logistic regression including seven candidate biomarkers, vWF, E-selectin, and TNF-α remained independent-

ly associated with ERVD (Table IV). Based on their regression coefficients, a serum biomarker panel model was constructed: $\text{logit}(P) = -6.584 + \text{vWF (IU/dL)} + 0.040 \times \text{E-selectin (ng/mL)} + 0.064 \times \text{TNF-}\alpha \text{ (pg/mL)}$. The model achieved an AUC of 0.811 (95% CI 0.738–0.883) with 72.97% sensitivity and 84.21% specificity (cut-off >0.5436, Table V; Figure 5). Compared with the clinical-variable model (AUC 0.618, 95% CI 0.527–0.709), discrimination was significantly improved (DeLong $P = 0.001$). Calibration was acceptable (Hosmer-Lemeshow $P = 0.093$); bootstrap internal validation (200 resamples) yielded an optimism-corrected AUC of 0.802. To evaluate the potential impact of temporal changes in surgical techniques or perioperative protocols, a sensitivity

Table IV Multivariable logistic regression analysis of candidate biomarkers associated with ERVD.

Indicators	B	SE	Wald	P	OR	95% CI (Upper)	
vWF	0.023	0.007	11.308	0.001	1.023	1.009	1.036
ICAM-1	0.008	0.005	2.993	0.084	1.008	0.999	1.018
VCAM-1	0.006	0.004	2.491	0.115	1.006	0.999	1.013
E-selectin	0.032	0.015	4.391	0.036	1.032	1.002	1.063
CRP	0.005	0.043	0.012	0.913	1.005	0.924	1.092
IL-6	0.024	0.027	0.757	0.384	1.024	0.971	1.08
TNF- α	0.058	0.027	4.685	0.030	1.060	1.006	1.118

Table V Logistic regression coefficients of the biomarker panel model (vWF+E-selectin+TNF- α) for ERVD prediction.

Indicators	B	SE	Wald	P	OR	95% CI (Upper)	
vWF	0.025	0.006	16.234	<0.001	1.025	1.013	1.038
E-selectin	0.040	0.014	8.386	0.004	1.041	1.013	1.069
TNF- α	0.064	0.026	6.167	0.013	1.066	1.014	1.121
Constant	-6.584	1.232	28.561	<0.001	-	-	-

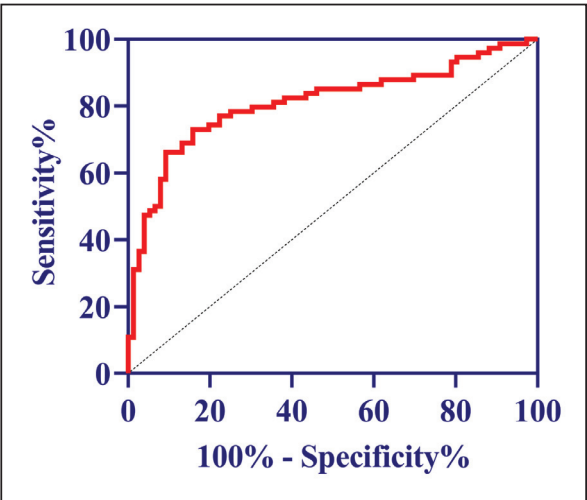


Figure 5 ROC curve of the combined warning model (vWF+E-selectin+TNF- α) for prognostic risk stratification value of ERVD.

analysis stratified the cohort into two time periods: 2022–2023 (n=72) and 2024–2025 (n=78). The biomarker panel model yielded AUCs of 0.798 (95% CI 0.692–0.885) in the 2022–2023 subgroup and 0.823 (95% CI 0.731–0.896) in the 2024–2025 subgroup, with no significant difference in AUCs between the two subgroups (DeLong P=0.682). This indicates that the model performance was not affected by calendar-time effects.

Discussion

This study evaluated preoperative serum markers of endothelial activation and inflammation in patients undergoing finger replantation and developed a serum-based model for early ERVD risk stratification. The main findings were: (i) endothelial markers (vWF, ICAM-1, VCAM-1, and E-selectin) and inflammatory cytokines (CRP, IL-6, and TNF- α) were higher in ERVD cases; (ii) these markers were positively correlated with crisis duration; and (iii) a parsimonious panel combining vWF, E-selectin and TNF- α achieved good discrimination and acceptable calibration (11).

Among the endothelial markers, vWF showed the best individual discrimination. vWF is released from activated endothelial cells and platelets and serves as an index of endothelial perturbation and thromboinflammatory activation – processes that are pivotal for microvascular patency after revascularization (12–15). The observed odds ratio (OR) of 1.025 for vWF indicates a modest but statistically significant association with ERVD, suggesting that higher preoperative vWF levels may incrementally increase the risk of venous congestion. E-selectin is upregulated on activated endothelium and promotes leukocyte rolling and adhesion, thereby coupling endothelial activation to inflammatory cell recruitment and microvascular plugging (16). With an OR of 1.041, E-selectin showed a slightly stronger

association with ERVD than vWF, underscoring the contribution of leukocyte-endothelial interactions in this context. In the multivariable biomarker model, vWF and E-selectin remained independently associated with ERVD, supporting the premise that endothelial activation is detectable before clinically overt venous congestion.

Inflammatory activation is another key driver of post-reperfusion microvascular dysfunction. TNF- α can amplify endothelial permeability, promote leukocyte-endothelial interactions, and enhance local thrombogenicity, which may aggravate venous outflow impairment (17, 18). The OR of 1.066 for TNF- α is the highest among the three markers in the panel, indicating that preoperative TNF- α levels have the strongest prognostic value for ERVD. However, the 95% CI of 1.014–1.121 suggests some uncertainty in the magnitude of this effect, which warrants further validation in larger cohorts. Although IL-6 and CRP were higher in ERVD cases, they did not remain independently associated after adjustment for other biomarkers, suggesting that these markers may capture downstream systemic responses rather than proximal vascular events in this setting.

From a clinical standpoint, the serum biomarker panel (vWF + E-selectin + TNF- α) offers an actionable pathway for perioperative risk-based management. Based on ROC analysis, the optimal decision threshold was $\text{logit}(P)=0.5436$, corresponding to a predicted probability of 23.5%. Patients with a predicted probability $\geq 23.5\%$ can be classified as high risk for ERVD, for whom targeted measures may be considered, including: (1) intensified postoperative surveillance (every 15 minutes during the first 6 h, then every 30 minutes over the subsequent 18 h); (2) early consideration of venous exploration within 24 h if Doppler signals demonstrate evolving abnormalities; and (3) anticoagulation adjustment (e.g., increasing heparin to 75 U/kg/day, according to institutional protocols and bleeding risk). For patients below this threshold ($<23.5\%$), routine monitoring may be sufficient. This risk-stratified approach provides a pragmatic framework to support clinical translation of the model. Future work should prioritize prospective validation with prespecified sampling windows and standardized postoperative

management algorithms to determine whether biomarker-guided surveillance can shorten crisis duration and improve replant survival. In addition, the single-center, retrospective design may introduce selection bias, and residual confounding cannot be ruled out. External validation in independent cohorts is required before generalization. Third, only a single preoperative timepoint was analyzed; dynamic perioperative changes may provide additional prognostic information. The sample size constrained the complexity of multivariable modeling, and larger studies are needed to refine cut-offs and assess clinical utility. Finally, although the sensitivity analysis confirmed that calendar time did not affect model performance, the generalizability to centers with different surgical protocols needs further verification (19–22).

Conclusion

Endothelial activation and inflammatory responses appear to be closely linked to early ERVD after finger replantation. A preoperative serum panel combining von Willebrand factor, E-selectin, and TNF- α demonstrated good discrimination and acceptable calibration for identifying patients at higher risk of ERVD within 72 hours. External validation and prospective studies are needed to define clinically actionable cut-offs and to determine whether biomarker-guided surveillance can improve outcomes.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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