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ORIGINAL RESEARCH

Relationship Between Serum HMGB1 and RAGE Levels and Restenosis in Type 2 Diabetes Mellitus Patients Complicated With Lower Extremity Vascular Disease: A Retrospective Study

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Purpose: To investigate the potential association between the serum concentrations of high mobility group protein B1 (HMGB1) and the receptor for advanced glycation end-products (RAGE) in relation to the occurrence of restenosis following interventional therapy for lower extremity vascular disease in patients diagnosed with type 2 diabetes mellitus (T2DM).

Patients and Methods: From March 2023 to January 2024, 96 T2DM patients with lower extremity vascular disease who underwent interventional therapy and 6-month follow-up in our hospital were studied. Patients were divided into in-stent restenosis (ISR) (n=38) and none-in-stent restenosis (NISR) (n=58) groups based on the occurrence of ISR. Pre-surgery demographics and serum levels of HMGB1, RAGE, glycated hemoglobin (HbA1c), and high-sensitivity C-reactive protein (hs-CRP) were analyzed. A Pearson correlation and multivariate Logistic regression were used to identify factors influencing restenosis. A predictive nomogram was built based on the identified factors. The receiver operating characteristic (ROC) curve analysis evaluated the predictive value of serum RAGE and HMGB1 for restenosis post-intervention.

Results: The ISR group exhibited statistically significant elevations in HbA1c, hs-CRP, HMGB1, and RAGE levels compared to the NISR group ($P<0.05$). Multivariate logistic regression analysis revealed that HMGB1 and RAGE were independent risk factors for restenosis in T2DM patients with lower extremity vascular disease undergoing interventional therapy. The predictive nomogram model developed specifically for this patient population demonstrated high accuracy. ROC curve analysis further emphasized the superior combined predictive value of HMGB1 and RAGE over individual biomarkers for restenosis after interventional therapy in this cohort.

Conclusion: Elevated preoperative serum levels of HMGB1 and RAGE in T2DM patients with lower extremity vascular disease are linked to restenosis following interventional therapy.

Keywords: type 2 diabetes mellitus, lower extremity vascular disease, interventional therapy, high mobility group protein B1, receptor of advanced glycosylation end-products

Introduction

Lower extremity vascular disease is one of the common macrovascular complications in type 2 diabetes mellitus (T2DM), primarily manifesting as gangrene, rest pain, and intermittent claudication. The lesions are predominantly characterized by infragenicular arterial occlusion or stenosis. The high incidence and disability rates associated with this condition significantly reduce patients' quality of life, increase the risk of amputation, and contribute to increased cardiovascular disease and mortality rates.[1–3] Currently, the armamentarium for managing lower extremity vascular disease encompasses diverse therapeutic modalities, with interventional therapy, synonymous with percutaneous transluminal angioplasty (PTA), emerging as a frontline treatment option. This approach, which encompasses techniques such

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as stent placement and balloon angioplasty, is favored for its minimal invasiveness, efficacy, and reproducibility, as evidenced in prior studies.[4,5] In-stent restenosis (ISR) refers to the phenomenon where the local vascular lumen narrows again due to the "healing" response following successful interventional therapy, which is a common issue in lower extremity vascular diseases.[6] Patients with T2DM and lower extremity vascular disease, influenced by hyperglycemia, experience increased inflammatory responses and endothelial damage, making them more susceptible to ISR post-surgery.[7] Additionally, studies have shown that high levels of fibrinogen and small dense Low-Density Lipoprotein (sdLDL) in serum are risk factors for ISR following vascular interventions, indicating that these laboratory markers can predict the occurrence of restenosis in patients with T2DM and lower extremity vascular disease.[8] Identifying the factors that significantly influence the occurrence of restenosis following interventional therapy in patients with T2DM and lower extremity vascular disease, as well as discovering reliable biomarkers, is of great importance for the clinical implementation of early interventions and the improvement of prognosis.

High mobility group protein B1 (HMGB1) is a widespread DNA-binding factor that performs various functions in the cell nucleus, such as stabilizing nucleosome formation, aiding DNA bending, replication, promoting DNA transcription, and repair. When cells are damaged or stressed, HMGB1 can be released from the nucleus into the extracellular space, functioning as an important late inflammatory factor.[9] In recent years, the role of HMGB1 in T2DM and its complications has gradually been uncovered. Studies have demonstrated that HMGB1 can participate in the advancement of obesity and T2DM by exerting pro-inflammatory effects.[10] Additionally, research has demonstrated that HMGB1 expression increases in the serum of T2DM patients, and an elevated serum HMGB1 level correlates with an augmented risk of diabetic nephropathy progression in the T2DM individuals, suggesting that increased serum HMGB1 is an individual risk factor for diabetic nephropathy progression.[11] Previous in vitro research demonstrated that HMGB1 can influence the function of vascular smooth muscle cells (VSMCs) and the inflammatory response, potentially implicating its role in the repair process following vascular injury and the progression of cardiovascular restenosis.[12] However, the specific impact of HMGB1 on lower extremity vascular disease in T2DM patients remains unclear.

The receptor of advanced glycosylation end-products (RAGE), a component of the immunoglobulin superfamily on the cell surface, is widely present on various cell surfaces and is involved in intracellular signal transduction. RAGE is also a crucial receptor for HMGB1, as HMGB1 can bind to RAGE to promote the release of inflammatory factors and participate in various biological behaviors.[13,14] RAGE has also been proven to exert a significant influence in T2DM-related vascular complications, with elevated levels of RAGE and its ligands mediating the occurrence of microvascular and macrovascular complications in T2DM patients.[15] This study aims to investigate whether HMGB1 and RAGE can serve as predictive factors for restenosis after interventional surgery for lower extremity vascular disease in T2DM patients, providing a reference for early clinical intervention.

Materials and Methods

Research Population

For this retrospective study, clinical data were collected from 149 patients with T2DM complicated by lower extremity vascular disease who were treated at our hospital between March 2023 and January 2024. Following the application of stringent inclusion and exclusion criteria, along with comprehensive follow-up evaluations, a cohort of 96 patients was ultimately included in the definitive analysis. This group consisted of 52 males and 44 females, with an age distribution spanning from 50 to 82 years. Inclusion criteria: (1) meeting the diagnostic criteria for T2DM;[16] (2) meeting the diagnostic criteria for lower extremity vascular lesions in the "Clinical Guidelines for the Prevention and Treatment of Type 2 Diabetes in the Elderly in China (2020 Edition)";[17] (3) The patient has unilateral lower extremity vascular disease. Exclusion criteria: (1) Patients who cannot tolerate surgery; (2) having severe organ damage in the heart, brain, kidneys; (3) having autoimmune diseases; (4) having malignant tumors; (5) having severe lower extremity infections, trauma, or surgical history; (6) having severe coagulation disorders. Patients were allocated into the in-stent restenosis (ISR) group and the non-in-stent restenosis (NISR) group based on the results of CT angiography at the end of the 6th month of follow-up. Figure 1 illustrates the flow diagram of the participants.

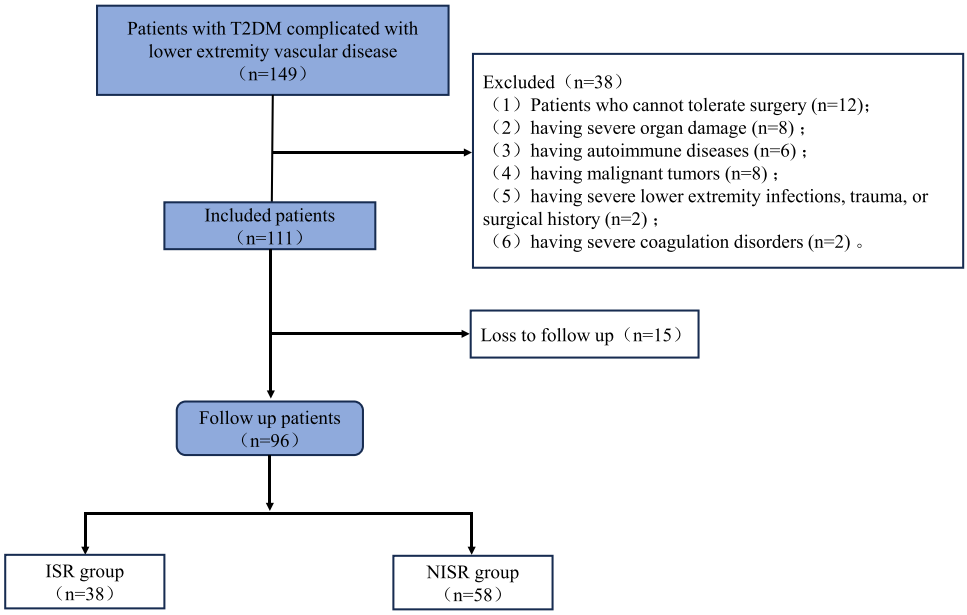

Figure 1 Flowchart of participant inclusion in this study.
Abbreviations: T2DM, type 2 diabetes mellitus; ISR, in-stent restenosis; NISR, non in-stent restenosis.

Treatment Methods

Under local anesthesia, femoral artery punctures were performed in an antegrade or retrograde manner, followed by digital subtraction angiography (DSA) of the lower extremity arteries to observe the extent, degree, number, and flow rate of contrast agent in the iliac artery, popliteal artery, femoral artery, anterior tibial artery, tibiofibular trunk, and dorsalis pedis artery. If the stenosis was >50%, a suitable balloon was selected for balloon angioplasty. If the residual stenosis exceeded 30% after balloon angioplasty, endovascular stent placement was performed (the stent used was the VIABAHN heparin-coated endovascular peritoneal stent system from GORE, USA). Successful surgery was defined as a residual stenosis of <10% in the vessel lumen after stent implantation, with no significant dissection or surgery-related complications. All patients were administered antiplatelet therapy, which included a daily dose of 75 mg clopidogrel and 100 mg aspirin for one year after the surgery. After one year, antiplatelet therapy was continued with aspirin 100 mg once daily. Blood pressure, blood glucose, and blood lipids were controlled according to the standards of the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus' (2020 Edition)".[17]

All patients underwent a 6-month follow-up after surgery to observe the condition of their lower extremity arteries and symptoms, and to adjust the treatment plan based on blood glucose, blood pressure, and blood lipid levels. At the conclusion of the sixth month, CT angiography of the lower extremity arteries was performed to ascertain the presence or absence of ISR among the patients. Criteria for ISR:[18] (1) The primary criterion is a luminal diameter stenosis of ≥70% within the stent or within 5 mm of both ends of the stent within 6 months after stent placement; (2) The secondary criteria include ischemic ulcers that are difficult to heal, unavoidable amputations, and revascularization of the diseased vessel during the follow-up period.

Measurement of Plasma HMGB1, RAGE and Clinical Data Collection

Clinical data from patients were gathered, encompassing gender, age, BMI, duration of disease, smoking history, systolic blood pressure (SBP), ankle brachial index (ABI), and diastolic blood pressure (DBP).

In the morning, a 4 milliliter venous blood specimen was procured from patients. Subsequently, the fasting plasma glucose (FPG) level was quantified employing the glucose oxidase (GOD) method, while glycated hemoglobin (HbA1c) was evaluated through high-performance liquid chromatography. Additionally, the Abbott

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Alinity -c automated biochemistry analyzer was utilized to analyze various biochemical markers, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hs-CRP), and triglycerides (TG). On the day of surgery, a separate 4 milliliter venous blood sample was collected from patients in a fasted state, allowed to stand at room temperature for 30 minutes, then the supernatant was collected after centrifugation at 3000 g for 20 minutes and then stored at −20°C for subsequent use.

Serum levels of HMGB1 and RAGE were measured according to the instructions of the ELISA kits (HM10235, HM10778, Bioswamp, China). The patency and restenosis of lower extremity vessels were recorded after 6 months of follow-up.

Statistical Analysis

For statistical analysis, we employed SPSS 25.0, where normally distributed continuous variables were reported as mean values accompanied by standard deviations ($\bar{x} \pm s$), and group comparisons were facilitated through the application of the Student's *t*-test. Non-normally distributed continuous variables, on the other hand, were characterized using the median and interquartile range, with statistical differences between two groups being evaluated through the Mann-Whitney U test. Categorical variables were analyzed using Chi-square (χ^2) tests. Furthermore, we conducted Pearson correlation analysis to establish the relationship between serum levels of RAGE, HMGB1, HbA1c, and hs-CRP. To identify risk factors that could influence restenosis following interventional procedures in T2DM patients with lower extremity vascular disease, logistic regression analysis was performed. Additionally, we utilized R software to devise a nomogram prediction model. The predictive value of serum HMGB1 and RAGE for restenosis post-interventional procedures in T2DM patients with lower extremity vascular disease was evaluated using ROC curves. Throughout our analysis, a significance level of $P<0.05$ was deemed statistically significant.

Results

Univariate Analysis of ISR After Interventional Procedures for Lower Extremity Vascular Disease in T2MD Patients

Based on whether patients developed ISR during postoperative follow-up, they were divided into the ISR group (38 patients) and the NISR group (58 patients). The univariate analysis results indicated significant differences in HbA1c, hs-CRP, HMGB1, and RAGE levels between the two groups. Compared with the NISR group, HbA1c, hs-CRP, HMGB1, and RAGE levels in the ISR group were significantly increased (all $P<0.05$). No statistically significant differences were observed in other indicators between the two groups ($P>0.05$) (Table 1).

The Correlation Between Serum RAGE, HMGB1, HbA1c, and Hs-CRP Levels in the ISR Group

The serum levels of HMGB1 in the ISR group were positively correlated with HbA1c ($r=0.321$, $P=0.049$) and hs-CRP ($r=0.390$, $P=0.015$), while serum RAGE levels were also positively correlated with HbA1c ($r=0.326$, $P=0.046$) and hs-CRP ($r=0.435$, $P=0.006$), suggesting that serum HMGB1 and RAGE are associated with the inflammatory status and metabolic level of the patients (Figure 2A–D).

Multivariate Logistic Regression Analysis of Risk Factors Influencing ISR After Interventional Surgery Among Patients With T2DM and Lower Extremity Vascular Disease

A multivariate logistic regression analysis was conducted using the occurrence of ISR as the dependent variable and HbA1c, hs-CRP, RAGE, and HMGB1 as independent variables. The results showed that the levels of HMGB1 and RAGE were significant independent risk factors for the development of ISR following interventional surgery in T2DM patients with lower extremity vascular disease ($P<0.05$) (Tables 2 and 3).

Table 1 Univariate Analysis Results of ISR After Interventional Procedures for Lower Extremity Vascular Disease in T2MD Patients

Item	ISR (n=38)	NISR (n=58)	χ^2/t/U	*P*
Age (years, $\bar{x}$±s)	64.00 (53.00, 69.25)	62.50 (55.75, 68.25)	1101.000*	0.994
Gender			3.422#	0.064
Male	25	27		
Female	13	31		
Course of diabetes (years, $\bar{x}$±s)	9.31±3.21	9.16±2.21	0.271^	0.787
Smoking history (years, $\bar{x}$±s)			1.171#	0.279
Yes	20	24		
No	18	34		
SBP (mmHg)	132.87±16.06	134.86+18.36	−0.546^	0.586
DBP (mmHg)	88.26±10.36	86.84±10.02	0.669^	0.505
ABI	0.600 (0.500, 0.700)	0.600 (0.575, 0.700)	1009.500*	0.468
BMI (kg/m^2, $\bar{x}$±s)	24.73±3.03	24.79±3.14	−0.094^	0.925
FPG (mmol/L)	9.28±0.99	8.87±1.76	1.304^	0.196
HbA1c (%)	9.31±1.29	8.72±1.62	1.991^	0.049
TC (mmol/L)	4.92±1.06	4.88±1.17	0.167^	0.868
TG (mmol/L)	1.82±0.56	1.68±0.72	0.996^	0.322
HDL-C (mmol/L)	0.99±0.19	1.05±0.37	−0.922^	0.359
LDL-C (mmol/L)	3.34±0.82	3.04±0.77	1.816^	0.073
Hs-CRP (mg/L)	2.59±0.79	1.76±0.85	4.885^	<0.0001
HMGB1 (ng/ml)	103.86 (91.64, 130.01)	74.52 (60.20, 89.09)	285.500*	<0.0001
RAGE (ng/ml)	583.33 (552.59, 928.98)	454.52 (415.58, 486.31)	177.000*	<0.0001

Notes: * Mann-Whitney U test results. # Chi-square (χ^2) test results. ^ Student's *t*-test results.
Abbreviations: ISR, in-stent restenosis; NISR, non in-stent restenosis; T2DM, type 2 diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABI, ankle brachial index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, hypersensitive C-reactive protein; HMGB1, high mobility group protein; RAGE, receptor of advanced glycation end-products.

Constructing a Nomogram Prediction Model for ISR After Interventional Surgery Among Patients With T2DM and Lower Extremity Vascular Disease

According to the Logistic regression analysis, two independent risk factors for ISR following interventional surgery among T2DM patients with lower extremity vascular disease were identified, a nomogram prediction model was constructed. The results demonstrated that the model score gradually increased with the elevation of HMGB1 and RAGE levels. For instance, a T2DM patient with lower extremity vascular disease who has a RAGE level of 26 ng/ml would receive a score of 55 points, and a HMGB1 level of 16 ng/ml would contribute an additional 25 points, resulting in a total score of 80 points. This predicts a probability of over 90% for ISR to occur after interventional surgery (Figure 3). The calibration curve indicated a strong agreement between the predicted and actual probabilities of ISR after interventional surgery among T2DM patients with lower extremity vascular disease using the nomogram model (Figure 4).

The Value of HMGB1 and RAGE in Predicting ISR After Interventional Surgery Among Patients With T2DM and Lower Extremity Vascular Disease

The analysis of the ROC curve revealed that the AUC of HMGB1 and RAGE levels in T2DM patients with lower extremity vascular disease before surgery predicting the occurrence of ISR after interventional surgery were 0.871 and 0.920, with 95% CI of 0.801–0.940 and 0.850–0.990, respectively. The combined predictive AUC was 0.934 with a 95% CI of 0.876–0.993 (Figure 5).

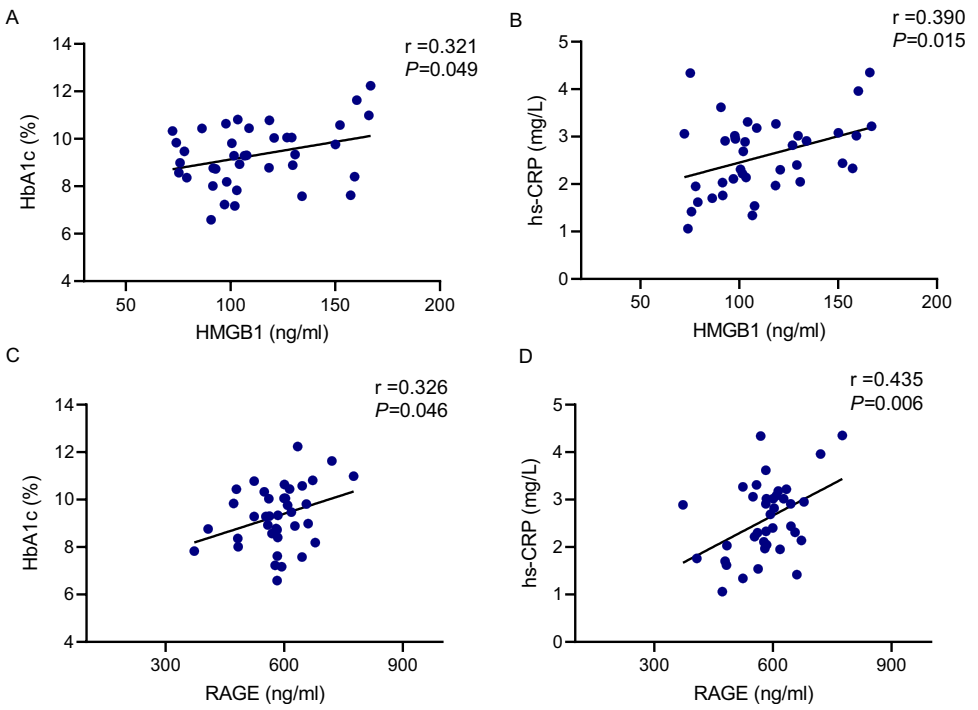

Figure 2 Correlation analysis of serum HMGB1 and RAGE levels with HbA1c and hs-CRP in ISR group patients. A: Correlation analysis between serum HMGB1 levels and HbA1c levels; B: Correlation analysis between serum HMGB1 levels and hs-CRP levels; C: Correlation analysis between serum RAGE levels and HbA1c levels; D: Correlation analysis between serum RAGE levels and hs-CRP levels.

Abbreviations: HbA1c, hemoglobin A1c; HMGB1, high mobility group protein; hs-CRP, hypersensitive C-reactive protein; RAGE, receptor of advanced glycation end-products.

Discussion

Lower extremity vascular disease is one of the leading causes of disability and mortality among diabetic patients, with atherosclerosis being its primary pathological change. Currently, the main treatments for diabetic lower extremity

Table 2 Assignment Table for Logistic Regression Analysis Indicators

Variable	Assignment
HbA1c	Continuous variable
hs-CRP	Continuous variable
RAGE	Continuous variable
HMGB1	Continuous variable
ISR occurrence situation	No stenosis = 0, stenosis = 1

Abbreviations: HbA1c, hemoglobin A1c; hs-CRP, hypersensitive C-reactive protein; RAGE, receptor of advanced glycation end-products; HMGB1, high mobility group protein; ISR, in-stent restenosis.

Table 3 Logistic Regression Analysis Results of Factors Influencing ISR After Interventional Surgery Among Patients With T2DM and Lower Extremity Vascular Disease

Influence Factor	*B*	*S.E*	*Wald*	*P*	*OR*	*95%CI*
RAGE	0.027	0.007	12.948	<0.0001	1.027	1.012–1.042
HMGB1	0.058	0.022	6.906	0.009	1.060	1.015–1.106
hs-CRP	0.513	0.435	1.393	0.238	1.671	0.712–3.919
HbA1c	0.039	0.269	0.021	0.885	1.040	0.613–1.763

Abbreviations: ISR, in-stent restenosis; T2DM, type 2 diabetes mellitus; RAGE, receptor of advanced glycation end-products; HMGB1, high mobility group protein; hs-CRP, hypersensitive C-reactive protein; HbA1c, hemoglobin A1c.

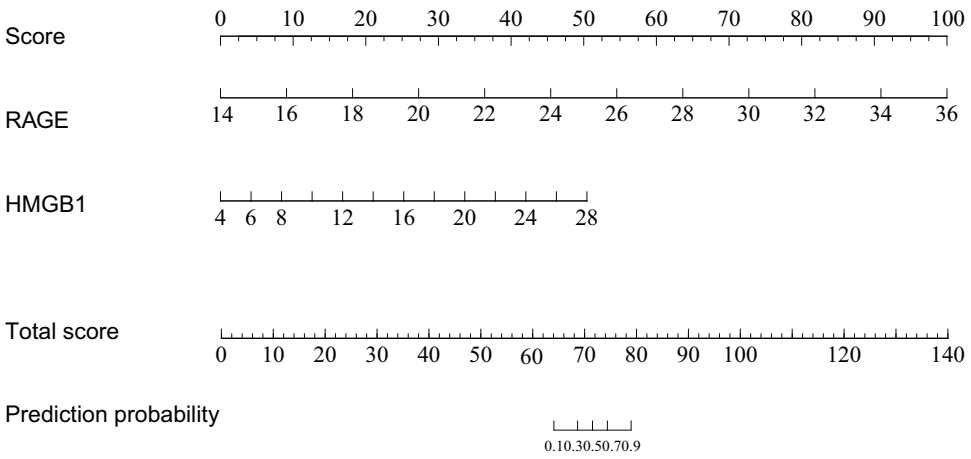

Figure 3 Nomogram model for predicting ISR in patients with T2MD and lower extremity vascular disease after endovascular intervention.
Abbreviations: RAGE, receptor of advanced glycation end-products; HMGB1, high mobility group protein.

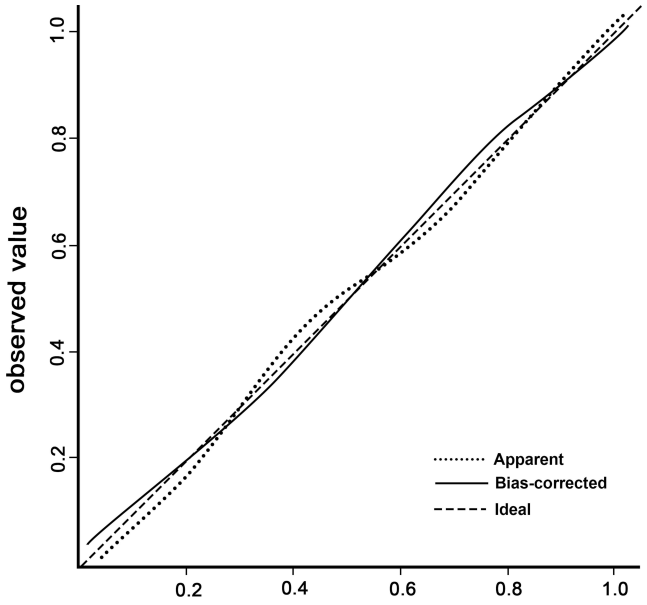

Figure 4 Calibration curve of the nomogram model.

vascular disease include conservative medical treatment, surgical treatment, and interventional surgery. Compared to pharmacological therapy, lower extremity vascular interventional therapy can more effectively improve ischemia in patients with lower extremity vascular disease, reducing mortality and disability rates.[19,20] This method is particularly suitable for elderly patients with poor general conditions, those without suitable vessels for transplantation, and those with poor outflow tract conditions suffering from lower extremity atherosclerosis.[11] However, ISR occurring after vascular interventional surgery remains a significant clinical challenge, with a complex pathogenesis that involves multiple processes such as inflammation, excessive proliferation of vascular smooth muscle cells, and vascular remodeling.[21]

HMGB1 is a proinflammatory factor present in the body, which can be released extracellularly through active or passive means to initiate early immune responses and inflammatory reactions, participating in the pathogenesis of various inflammation-related diseases.[22] During the formation of atherosclerosis, HMGB1 acts as an inflammatory mediator extracellularly, inducing autophagy in vascular endothelial cells via monocyte chemoattractant protein 1, causing ischemia-reperfusion injury, and increasing the expression of interleukin in vascular smooth muscle cells through

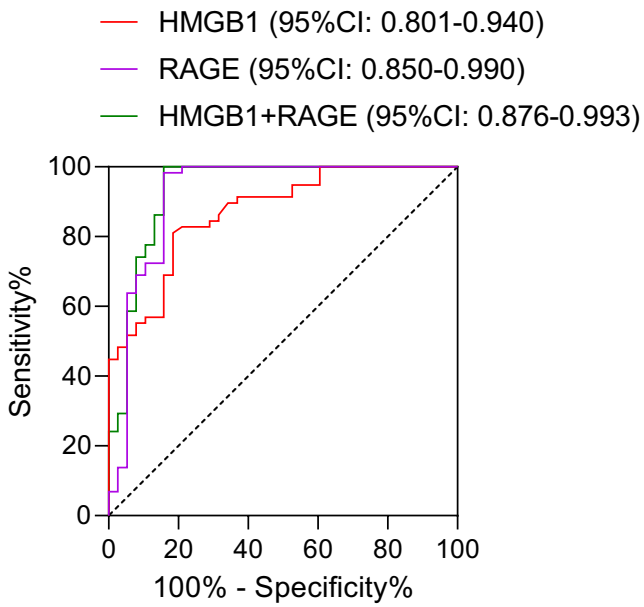

Figure 5 ROC curve results of HMGB1 and RAGE in predicting ISR in patients with T2MD and lower limb vascular disease after endovascular intervention.
Abbreviations: HMGB1, high mobility group protein; RAGE, receptor of advanced glycation end-products.

inflammasomes, thereby promoting the development of atherosclerosis.[23,24] Emerging evidence suggested that post-operative serum HMGB1 levels were independently linked to the risk of vascular restenosis in individuals with lower extremity arteriosclerosis obliterans (LEASO).[25] In elucidating the potential mechanisms underlying HMGB1's role in the promotion of ISR, prior research had established that HMGB1 significantly augmented the proliferation of VSMCs and elicited inflammatory responses, which are pivotal in the pathogenesis of ISR.[12] Our present study further confirms that patients with ISR exhibit significantly elevated levels of hs-CRP compared to those with NISR, indicating a substantial activation of inflammatory activity in ISR patients. Moreover, Pearson correlation analysis revealed a positive correlation between serum HMGB1 and both HbA1c and hs-CRP levels, suggesting that serum HMGB1 contributes to inflammation and metabolic dysregulation in T2DM patients with lower extremity vascular disease and is linked to an unfavorable prognosis following interventional surgery.

Diabetes-induced hyperglycemia triggers intricate metabolic and hemodynamic alterations within the body, culminating in the generation of advanced glycation end products (AGEs) via non-enzymatic glycosylation reactions. This process also stimulates the production of reactive oxygen species (ROS) and the subsequent activation of protein kinase C (PKC), resulting in characteristic changes in diabetic vascular diseases.[26] RAGE is a membrane protein present in various cell types and serves as a multi-ligand receptor belonging to the immunoglobulin superfamily, which can co-express with its ligands. RAGE is highly expressed in vascular endothelial cells, monocytes, and smooth muscle cells, with the majority located in smooth muscle cells.[27,28] The interaction between AGEs and RAGE on smooth muscle cells contributes to the production of various pro-inflammatory factors, increasing the occurrence of atherosclerosis. AGEs can directly stimulate the generation of intracellular ROS and induce smooth muscle cell migration. Additionally, they can trigger ROS production by activating targets upon binding to RAGE, promoting the proliferation of smooth muscle cells,[29] and accelerating intracellular calcium deposition to promote calcification of smooth muscle cells.[30] In this study, the significantly elevated RAGE levels in the ISR group indicate that RAGE is a risk factor for ISR after intervention in T2DM patients. The results of Pearson correlation analysis revealed a positive correlation between RAGE and HbA1c, hs-CRP levels, revealing the crucial role of RAGE in hyperglycemia and inflammatory-related pathological processes.

The nomogram model presents various clinical risk factors in the form of line segments, enabling specific scoring of risk factors and quantifying the probability of occurrence of disease events. In this research, we constructed a nomogram model based on the risk factors screened through Logistic regression analysis and subsequently validated the model, with

results showing good validity and discrimination. Further confirmation through ROC curve analysis indicated that the combined prediction of HMGB1 and RAGE had a higher value in predicting ISR after intervention in patients with T2DM lower extremity vascular disease than their individual predictive values.

In summary, serum HMGB1 and RAGE have been confirmed as important risk factors for ISR after intervention in patients with T2DM and lower extremity vascular disease. This finding suggests that we should closely monitor the levels of these two markers in clinical practice to timely detect and intervene potential risks, thereby improving patient outcomes. To further optimize treatment strategies and enhance patients' quality of life, future research can explore specific interventions targeting HMGB1 and RAGE, aiming to diminish the incidence of ISR after intervention in patients with T2DM and lower extremity vascular disease. While the present study has illuminated serum HMGB1 and RAGE as significant contributors to the risk of ISR following interventional procedures in patients with T2DM and lower extremity vascular disease, it is imperative to acknowledge the existence of certain limitations within the scope of this research. For instance, the relatively modest sample size employed in this investigation may have potentially impacted the robustness and applicability of the statistical findings. Furthermore, while the study primarily centered on elucidating the correlation between HMGB1, RAGE, and ISR, it did not delve into their specific molecular mechanisms. In the future, multi-center, large-sample studies will be further conducted, and research methods such as cell experiments and animal models will be employed to thoroughly investigate the specific molecular mechanisms of HMGB1 and RAGE in the onset and progression of ISR, providing a theoretical basis for the development of targeted interventions.

Strengths and Limitations of This Study

The primary strengths of this research endeavor reside in its meticulous exploration of the intricate interplay between serum levels of HMGB1 and RAGE, and their potential influence on the risk of restenosis subsequent to interventional therapeutic interventions for lower extremity vascular disease in individuals diagnosed with type 2 diabetes mellitus. By comprehensively analyzing these biomarkers, the study provides valuable insights into their potential as predictive factors for restenosis, thereby enhancing our understanding of the pathophysiological mechanisms involved and facilitating the development of targeted interventions. Furthermore, the creation of a nomogram prediction model based on these biomarkers demonstrates the study's practical application in clinical settings, aiding in the early identification of high-risk patients and subsequent management strategies.

However, several limitations merit consideration. Firstly, the relatively small sample size, while sufficient for statistical significance, may limit the generalizability of the study's findings to a broader patient population. Multi-center studies with larger cohorts would further strengthen the evidence base. Further, the study primarily focused on correlational analysis rather than mechanistic exploration, leaving open questions about the specific pathways and interactions through which HMGB1 and RAGE influence restenosis.

Conclusion

This study demonstrates that elevated preoperative serum levels of HMGB1 and RAGE in patients with T2DM complicated by lower extremity vascular disease are significantly associated with the occurrence of ISR following interventional therapy. The findings suggest that both HMGB1 and RAGE independently serve as risk factors for restenosis in this patient population. Furthermore, the combination of HMGB1 and RAGE exhibits a higher predictive value for restenosis after interventional therapy compared to a single predictor, highlighting the potential utility of these biomarkers in identifying patients at risk for restenosis and guiding post-interventional management strategies.

Data Sharing Statement

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Ethics Statement

This study was approved by the ethics committee of the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology [approval number WHZXKYL-2022-087]. This study only collected the clinical

medical records information of patients, without involving the collection of their personal information, and all data were anonymized; we obtained the approval of the ethics committee for the exemption of informed consent, given that the exemption of informed consent would not adversely affect the rights or welfare of the research subjects. The study was conducted following the ethical requirements of the Declaration of Helsinki.

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Disclosure

The author(s) report no conflicts of interest in this work.

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