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ORIGINAL RESEARCH

Value of Glycemic Dispersion Index in Predicting Major Adverse Cardiovascular Events in Diabetic Patients with Concomitant Acute Coronary Syndrome

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Aim: This investigation aims to assess the predictive value of the glycemic dispersion index (GDI), calculated by incorporating glycated hemoglobin, fasting plasma glucose, and 2-hour postprandial plasma glucose, in predicting major adverse cardiovascular events (MACE) within a 12-month timeframe for diabetic patients with concomitant acute coronary syndrome (ACS).

Methods: A retrospective study was conducted on 3261 diabetic patients with ACS who were hospitalized in the Department of Cardiology, the Sixth Affiliated Hospital of Kunming Medical University, from January 2016 to July 2022. Based on the inclusion and exclusion criteria, 512 patients were ultimately enrolled in the study. Their general information and laboratory test indicators were collected, and the occurrence of MACE within 12 months after admission was followed up and recorded for the enrolled patients, With the last follow-up having been concluded on July 31, 2023. The enrolled patients were stratified into four groups (Q1, Q2, Q3, Q4) based on their GDI values, from the lowest to the highest. Cox proportional hazards regression analysis and Kaplan-Meier survival analysis were employed to investigate the risk factors associated with MACE occurrence across these groups and to assess the cumulative risk of MACE over time within each group.

Results: The percentages of enrolled patients experiencing MACE in groups Q1 to Q4 were 10.16%, 12.50%, 15.63%, and 16.41%, respectively. GDI independently predicted the hazards for MACE in enrolled patients. The cumulative risk of MACE over time was considerably more significant in those with a GDI>4.21 than those with a GDI≤4.21.

Conclusion: The elevated GDI is correlated with an augmented risk of MACE in diabetic patients with concomitant ACS, thereby serving as an early indicator for assessing the unfavorable clinical prognosis of patients. This study offers novel insights into glycemic variability monitoring, enhancing prevention and treatment strategies for cardiovascular disease in people with diabetes.

Keywords: diabetes, acute coronary syndrome, major adverse cardiovascular events, glycemic dispersion index, glycemic variability

Introduction

On December 6, 2021, the International Diabetes Federation released the "2021 IDF Global Diabetes Atlas (10th edition)", stating that approximately 537 million people with diabetes aged 20–79 globally. It is estimated that about 6.7 million adults die from diabetes or its complications.[1] Cardiovascular disease is the most common cause of death among individuals with diabetes, accounting for 52% of deaths in individuals with type 2 diabetes and 44% in those with type 1 diabetes.[2] Meanwhile, ACS represents a highly critical acute clinical subtype among them. ACS exhibits significant clinical variations, and even among

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patients discharged from the hospital after excluding ACS based solely on cardiac biomarkers and electrocardiography, there is still a 3% to 5% occurrence of myocardial infarction. The mortality rate for ACS patients within one month of discharge is 8.6%, which increases to 13.3% within one year.[3] Therefore, it is crucial to predict the risk of MACE in diabetic patients with concomitant ACS at an early stage and to promptly and accurately screen high-risk patients. Despite the incomplete understanding of the pathogenesis of ACS, research findings suggest that high concentrations of glucose in diabetic patients can participate in the pathological process of coronary endothelial injury through multiple signaling pathways, including protein kinase C, protein kinase B, NF-κB, and mitogen-activated protein kinase signaling pathways. Oxidative stress and pro-inflammatory mediators can serve as inducers to activate these pathways.[4] High concentrations of glucose can intensify oxidative stress by enhancing metabolic pathways that involve diacylglycerol, protein kinase C, NADPH oxidase, and reactive oxygen species.[5] This enhancement triggers a prothrombotic state and an increase in inflammatory mediators, which in turn accelerates the formation and rupture of coronary atherosclerotic plaques.[6] The currently clinically commonly used coronary artery lesion complexity scoring system, SYNTAX, is an essential tool for selecting revascularization strategies and performing risk stratification for patients with coronary heart disease. The SYNTAX score calculates a patient's score based on anatomical characteristics of coronary artery lesions, including location, severity, bifurcation, calcification, and so on. A higher score indicates a more complex coronary artery lesion, with a corresponding increase in surgical difficulty and risk.[7] Furthermore, epidemiological investigations have revealed that the SYNTAX score is independently and positively correlated with elevated glycemic variability. High-frequency and high amplitude glycemic variability are related to the severity of coronary artery disease.[8] The foundational experiments have also confirmed that high-frequency and high-amplitude glycemic variability have a more detrimental effect on coronary arteries than chronic persistent hyperglycemia.[9] NADPH oxidase is activated to a greater extent by high-amplitude glycemic variability than by sustained hyperglycemia, leading to increased ROS production,[5] and is also closely associated with plaque burden, thus promoting endothelial injury and plaque rupture in coronary arteries.[10] High-frequency and high-amplitude glycemic variability are some of the important risk factors leading to the occurrence of MACE in diabetic patients with concomitant ACS. Therefore, besides monitoring traditional risk factors such as blood pressure, blood glucose, and lipid levels, monitoring glycemic variability in diabetic patients with concomitant ACS is an essential approach to improve screening efficiency and early prevention of MACE occurrences.

Although clinical studies have confirmed that the standard deviation of blood glucose levels and the average amplitude of glycemic variability are strong independent predictors of the risk of MACE in diabetic patients,[11,12] However, it remains challenging for diabetic patients to lower the occurrence of MACE through monitoring glycemic variability, the main reason is that the current mainstream methods of monitoring glycemic variability are continuous glucose monitoring devices and self-blood glucose monitoring, which are both complex to operate, expensive, and involve complex evaluation indicators,[13,14] these factors have led to low clinical utilization rates of continuous glucose monitoring devices among diabetic patients. Poor compliance with self-blood glucose monitoring methods among elderly diabetic patients.[15] Furthermore, a significant portion of diabetic patients have not received effective monitoring of their glycemic variability. Therefore, in our previous research, our research group calculated a clinically applicable screening index for abnormal glycemic variability called the glycemic dispersion index (GDI) by combining glycated hemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (2hPG). Previous research conducted by our research group has confirmed the high screening efficiency of this index for abnormal glycemic variability.[16] Moreover, compared to traditional methods for monitoring glycemic variability, this index is more accessible to operate and more suitable for regular monitoring of glycemic variability in diabetic patients. Although this index can be a simplified alternative to traditional glycemic variability evaluation indicators, it remains unclear whether it can act as an independent predictor for the risk of MACE in diabetic patients with concomitant ACS. Therefore, this study conducted a 12-month follow-up on 512 diabetic patients with concomitant ACS to evaluate whether the GDI has predictive value for the risk of MACE occurrence in this patient population.

Research Design and Methods

Study Subjects

Study population: 3261 diabetic patients with concomitant ACS who were hospitalized in the Department of Cardiology of the Sixth Affiliated Hospital of Kunming Medical University from January 2016 to July 2022 were selected as study

participants. All patients met the diagnostic criteria for ACS recommended in the 2016 ACC/AHA guidelines[17] and the diagnostic and classification criteria for diabetes released by the American Diabetes Association in 2018.[18] A total of 2749 patients were excluded based on the exclusion criteria (Figure 1): (1) 2579 patients with missing data on HbA1c, FPG, or 2hPG; (2) 25 patients diagnosed with severe valve diseases or myocardial diseases; (3) 34 patients with concomitant malignant tumors; (4) 68 patients with CKD stages G3a-G5; and (5) 43 patients lost to follow-up during the study. The final follow-up was completed on July 31, 2023, through telephone interviews, clinical visits, and hospital records for all enrolled patients.

Clinical Data and Laboratory Indicators

The patient's gender, age, smoking history, history of hypertension, history of myocardial infarction/stroke, history of percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG), body mass index (BMI) measured on admission, systolic blood pressure (SBP), diastolic blood pressure, heart rate (HR), and any clinical symptoms of acute coronary syndrome occurring 24 hours before admission, including ST-elevation myocardial infarction (STEMI), non-ST -segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), were collected through the patient's medical records on admission.

The FPG, HbA1c, 2hPG, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CREA), total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatine kinase-MB (CK-MB), high-sensitivity troponin T (hs-cTnT), homocysteine (HCY), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), hemoglobin (HGB), white blood cells (WBC), and red blood cells (RBC) detected after the patient's admission was recorded.

GDI Formula and Study Subject Grouping

In our preliminary study, we have validated the area under the curve (AUC) of GDI for screening abnormal glycemic variability using ROC curve analysis and Pearson correlation analysis. The AUC was found to be 0.901 (95% CI: 0.856–0.945), with a sensitivity of 0.781 and a specificity of 0.905. Based on the sensitivity and specificity of each point on the ROC curve graph, we

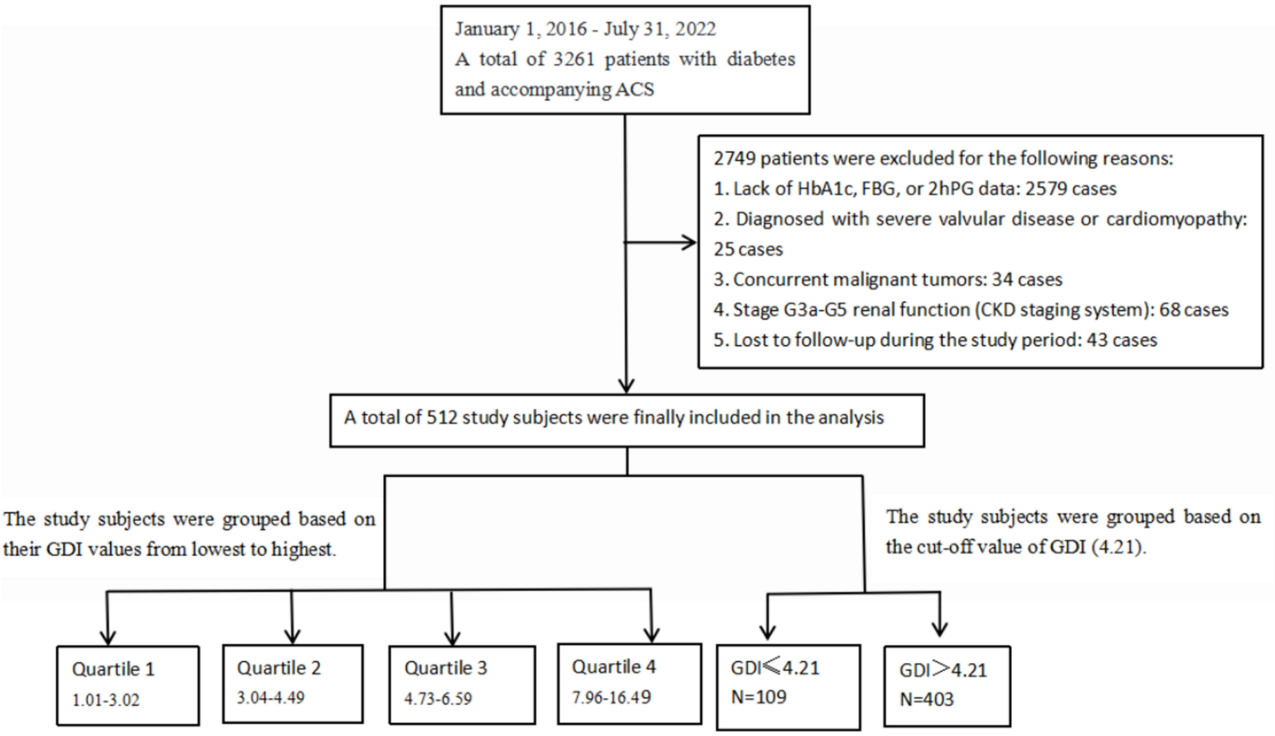

Figure 1 Flowchart of the study population.

calculated Youden's index (sensitivity + specificity - 1) for each point. The cut-off value was determined by selecting the point with the highest Youden's index, resulting in a final cut-off value of 4.21.[16] This calculation was performed using SPSS Statistical Software version 24.0.

The GDI calculation formula is as follows:

$$\mathrm{GDI} = \sqrt{(FPG - eAG)^2 + (2hPG - eAG)^2}$$

$$\mathrm{eAG}_{\mathrm{mmol/l}} = 1.59 \times \ \mathrm{HAb1c\%} - 2.59$$

The patients' FPG, 2hPG, and HbA1c values are inputted into the following formula to calculate the GDI value for each patient. Based on the GDI levels from low to high, the patients are grouped into quartiles, namely Q1, Q2, Q3, and Q4 groups. According to the GDI cut-off value of 4.21, they are further divided into GDI ≤ 4.21 group and GDI > 4.21 group.

Follow-Up of Study Subjects

Following discharge, the enrolled patients were followed up, and the occurrence of MACE within 12 months was recorded. MACE includes all-cause mortality (cardiac and non-cardiac), non-fatal myocardial infarction, non-fatal stroke (ischemic and hemorrhagic), cardiogenic shock, heart failure, and coronary revascularization.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median [Q1, Q3], while categorical variables are presented as n%. Essential demographic characteristics among groups were compared using ANOVA, Kruskal–Wallis test, and Pearson chi-square test. COX proportional hazards regression analysis was employed to identify risk factors for the occurrence of MACE, and Kaplan-Meier survival analysis was used to analyze the cumulative risk of MACE among different GDI groups. A p-value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS Statistical Software 24.0.

Result

Comparison of Patient Clinical Data and Laboratory Indices

The number of individuals in the MACE and non-MACE groups is 70 and 442, respectively. The GDI values of patients in the MACE group were higher than those in the non-MACE group (Figure 2). The median values of GDI for the MACE and non-MACE groups were 5.43 (3.39–7.89) and 4.49 (2.96–6.51), respectively. The study subjects were divided into four groups (Q1, Q2, Q3, Q4) based on ascending GDI values. The proportions of MACE occurrence in Q1 to Q4 groups are 10.16%, 12.50%, 15.63%, and 16.41%, respectively. The differences in GDI, SBP, DBP, WBC, hs-CRP, and FPG among the four groups were statistically significant (P<0.05). The hs-CRP and FPG values of patients in the Q4 group were significantly higher than those in the Q1 to Q3 groups, while there was no significant trend in SBP, DBP, and WBC levels among the groups. The between-group differences in other clinical data were not statistically significant (P>0.05) (Table 1).

Risk Factor Analysis for the Occurrence of MACE Within 12 Months in Diabetic Patients with Concomitant ACS

A univariate analysis using COX proportional hazards regression revealed that risks associated with MACE included Hs-CRP, admission clinical symptoms of STEMI, and UA (P<0.05). After adjusting for confounding factors, the multivariate Cox proportional hazards regression analysis showed that GDI, STEMI, TC, TG, LDL, and Hs-CRP independently predicted the risk of MACE occurrence in diabetic patients with concomitant ACS (P<0.05) (Table 2). Kaplan-Meier survival analysis was utilized to compare the occurrence of endpoint events during the follow-up period among patients in the Q1 to Q4 groups. The analysis results indicated that, as time progressively extended, the cumulative risk of MACE in the Q3 and Q4 groups steadily surpassed that of the Q1 and Q2 groups (Figure 3A). Based on previous studies, the cut-

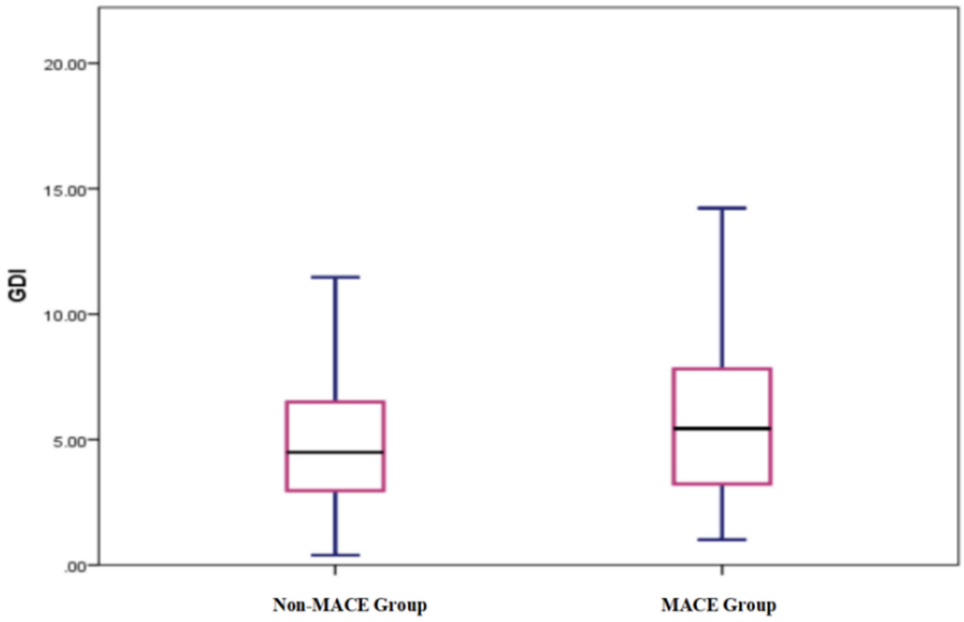

Figure 2 Comparison of GDI Values between Non-MACE Group and MACE Group.

off value of the GDI for screening abnormal glycemic variability was determined to be 4.21. The study subjects were divided into two groups: a GDI≤4.21 group and a GDI>4.21 group. Kaplan-Meier survival analysis revealed that the cumulative risk of MACE was significantly higher in the GDI>4.21 group compared to the GDI≤4.21 group (Log-rank $\chi 2=4.406$, P=0.036) (Figure 3B).

Discussion

The China Cardiovascular Disease Care Collaborative (CCC) project has shown that the prevalence of diabetes and prediabetes among patients with ACS is as high as 37.6%. Furthermore, ACS patients with comorbid diabetes or prediabetes have a 1.5-fold increased risk of MACE and a 2-fold increased risk of all-cause mortality.[19] The 2017 European Society of Cardiology (ESC) Guidelines for the management of ST-elevation myocardial infarction (STEMI)[20] and the 2020 ESC Guidelines for the management of non-ST-elevation acute coronary syndromes (NSTE-ACS)[21] both recommend risk stratification of patients with Acute Myocardial Infarction (AMI). Early risk stratification is of significant importance for selecting optimal secondary prevention medications. Currently, the primary risk model for predicting MACE in patients with ACS is the Global Registry of Acute Coronary Events (GRACE) score.[22] However, there is currently no risk assessment model designed explicitly for predicting MACE in ACS patients with comorbid diabetes. Additionally, when the GRACE score is used in the diabetic population, it lacks laboratory markers that reflect inflammation, oxidative stress, and other pathophysiological aspects related to metabolic diseases,[22] and its predictive accuracy is insufficient to provide timely and accurate clinical evidence for drug intervention. Therefore, it is of great significance to identify objective indicators that reflect the prognosis of diabetic patients with concomitant ACS and utilize them to screen the risk of MACE occurrence, and this will provide meaningful guidance for clinical treatment and improve patient outcomes.

Research shows that in the diabetic population, high-frequency and high-amplitude glycemic variability enhances oxidative stress, triggering an intensified inflammatory response that exacerbates endothelial damage within blood vessels. This damage to the coronary endothelium may even be more severe than the damage caused by persistent hyperglycemia.[5,8–10] The results of the study conducted by Lim S[23] suggest that higher glycemic variability is a significant risk factor for MACE in diabetic patients. Sungha Park[24] found that higher glycemic variability during hospitalization was associated with all-cause mortality within one year in diabetic patients with comorbid cardiovascular disease.

Table 1 Comparison of Patient Clinical Data and Laboratory Indices

Variable	Total Population	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
	n=512	n=128	n=128	n=128	n=128	
GDI (range)	4.49 (2.97–6.59)	2.05 (1.52–2.64)	3.81 (3.45–4.20)	5.38 (4.96–5.83)	8.56 (7.47–9.96)	0.000
Age (years)	62.19±10.78	61.75±10.44	61.82±11.48	61.78±10.23	63.85±10.56	0.443
Physical examination						
BMI (kg/m^2)	24.78±9.29	24.88±2.67	26.34±18.16	24.05±2.82	23.83±2.92	0.132
HR (bpm)	81.22±15.42	81.87±16.18	79.91±14.57	80.03±14.13	82.11±16.10	0.386
SBP (mmHg)	131.58±22.70	132.45±22.19	129.21±23.48	127.91±22.47	136.16±21.49	0.026
DBP (mmHg)	80.76±14.41	82.06±14.54	77.87±13.22	79.56±14.31	83.08±15.29	0.017
Laboratory data						
TC (mmol/L)	4.27±1.18	4.32±1.09	4.11±1.14	4.34±1.16	4.36±1.31	0.383
TG (mmol/L)	1.68 (1.12–2.67)	1.79 (1.26–2.96)	1.71 (1.12–2.69)	1.63 (1.12–2.55)	1.62 (1.02–2.84)	0.790
HDL (mmol/L)	1.06±0.28	1.04±0.26	1.04±0.28	1.07±0.27	1.07±0.32	0.728
LDL (mmol/L)	2.48±0.94	2.51±0.90	2.32±0.96	2.54±0.91	2.60±1.00	0.222
CK-MB (U/L)	2.46 (1.54–4.32)	2.51 (1.48–4.37)	2.20 (1.48–3.63)	2.34 (1.54–4.27)	3.00 (1.68–5.03)	0.787
NT-proBNP (pg/mL)	666.80 (202.40–1718.50)	579.70 (187.60–1447.75)	562.20 (151.95–1480.00)	700.95 (223.33–1469.50)	1011.00 (310.43–2882.00)	0.115
WBC (×10^9)	8.70±3.17	8.66±3.16	8.81±3.21	8.30±3.00	8.86±3.06	0.000
RBC (×10^{12})	4.59±0.61	4.62±0.64	4.57±0.61	4.62±0.56	4.61±0.58	0.253
HGB (g/L)	126.38±44.16	131.60±38.81	124.28±47.63	126.32±45.66	124.42±45.18	0.953
Hs-CRP (mg/L)	4.47 (1.57–19.05)	4.21 (1.50–13.33)	3.20 (1.07–27.71)	4.17 (1.52–14.31)	8.02 (2.27–29.47)	0.013
ALT (u/L)	30.00 (19.00–48.00)	32.00 (21.00–48.00)	28.50 (19.00–45.75)	26.50 (18.00–47.00)	28.00 (16.75–51.00)	0.557
AST (u/L)	42.00 (22.00–133.00)	43.50 (24.00–128.75)	37.00 (20.00–115.00)	43.50 (21.00–132.25)	44.00 (24.00–171.00)	0.384
CREA (umol/L)	77.00 (62.00–99.00)	74.50 (59.75–99.00)	77.00 (62.25–95.00)	76.00 (64.00–90.75)	79.50 (63.50–114.25)	0.266
hs-cTnT (ng/L)	0.71 (0.04–2.44)	0.71 (0.02–2.63)	0.48 (0.15–2.41)	0.96 (0.17–2.25)	0.79 (0.07–2.76)	0.326
HCY (umol/L)	14.80 (12.40–17.90)	14.80 (12.10–18.33)	14.80 (12.53–16.60)	14.45 (12.25–18.38)	14.8 (12.55–18.40)	0.603
FPG (mmol/L)	10.38±4.34	9.19±2.90	9.62±3.41	10.37±3.87	12.11±5.59	0.000

Clinical presentation						
STEMI (n%)	51.37	53.91	47.66	56.25	47.66	0.397
NSTEMI (n%)	19.73	21.09	26.56	14.84	16.41	0.080
UA (n%)	28.90	25.00	25.78	28.91	35.94	0.200
Medical history						
Previous Stroke, (n%)	53.71	56.25	53.13	55.47	50.00	0.704
Hypertension (n%)	32.42	31.25	28.91	39.06	30.47	0.308
PCI/CABG (n%)	87.11	82.03	87.50	90.63	88.28	0.210
Previous MI/Stroke (n%)	79.49	74.22	78.91	84.38	80.47	0.245

Notes: Parameter are presented as mean ± standard deviation (SD), median [Q1, Q3], or percentage.

Abbreviations: GDI, glycemic dispersion index; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CK-MB, creatine kinase-MB; NT-proBNP: N-terminal pro-B-type natriuretic peptide; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREA, creatinine; hs-cTnT, high-sensitivity cardiac troponin T; HCY, homocysteine; FPG, fasting plasma glucose; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

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Table 2 Independent Predictors of MACE

Variable	Univariate HR (95% CI)	p-value	Multivariate Adjusted HR (95% CI)	p-value
GDI (range)	1.059 (0.992–1.131)	0.087	1.133 (1.055–1.216)	0.001
Age (years)	0.996 (0.975–1.018)	0.741		
Physical examination				
BMI (kg/m2)	0.999 (0.972–1.027)	0.929		
HR (bpm)	0.993 (0.977–1.008)	0.338		
SBP (mmHg)	1.005 (0.995–1.015)	0.316		
DBP (mmHg)	1.011 (0.996–1.027)	0.660		
Laboratory data				
TC (mmol/L)	0.978 (0.797–1.199)	0.827	2.064 (1.283–3.321)	0.003
TG (mmol/L)	1.005 (0.936–1.080)	0.883	0.838 (0.728–0.965)	0.014
HDL (mmol/L)	1.333 (0.590–3.010)	0.480		
LDL (mmol/L)	0.811 (0.624–1.055)	0.119	0.364 (0.205–0.648)	0.001
CK-MB (U/L)	1.001 (0.995–1.007)	0.693		
NT-proBNP (pg/mL)	1.000 (1.000–1.000)	0.353		
WBC ($\times 10^9$)	0.972 (0.899–1.051)	0.476		
RBC ($\times 10^{12}$)	1.101 (0.749–1.619)	0.624		
HGB (g/L)	0.996 (0.992–1.001)	0.113		
ALT (u/L)	0.991 (0.981–1.002)	0.104		
AST (u/L)	0.999 (0.997–1.001)	0.273		
CREA (umol/L)	0.999 (0.996–1.002)	0.497		
hs-cTnT (ng/L)	1.000 (1.000–1.000)	0.965		
HCY (umol/L)	0.986 (0.956–1.018)	0.392		
FPG (mmol/L)	0.961 (0.906–1.020)	0.191	0.943 (0.885–1.005)	0.069
Clinical presentation				
STEMI (n%)	1.643 (1.011–2.667)	0.045	2.166 (1.038–3.587)	0.003
NSTEMI (n%)	1.035 (0.576–1.859)	0.908		
UA (n%)	0.487 (0.262–0.907)	0.023		
Medical history				
Previous Stroke (n%)	0.953 (0.595–1.525)	0.840		
Hypertension (n%)	1.172 (0.719–1.910)	0.525		
Past PCI/CABG (n%)	0.874 (0.478–1.596)	0.661		
Previous MI/Stroke (n%)	0.858 (0.411–1.791)	0.683		

Abbreviations: GDI, glycemic dispersion index; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CK-MB, creatine kinase-MB; NT-proBNP: N-terminal pro-B-type natriuretic peptide; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREA, creatinine; hs-cTnT, high-sensitivity cardiac troponin T; HCY, homocysteine; FPG, fasting plasma glucose; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

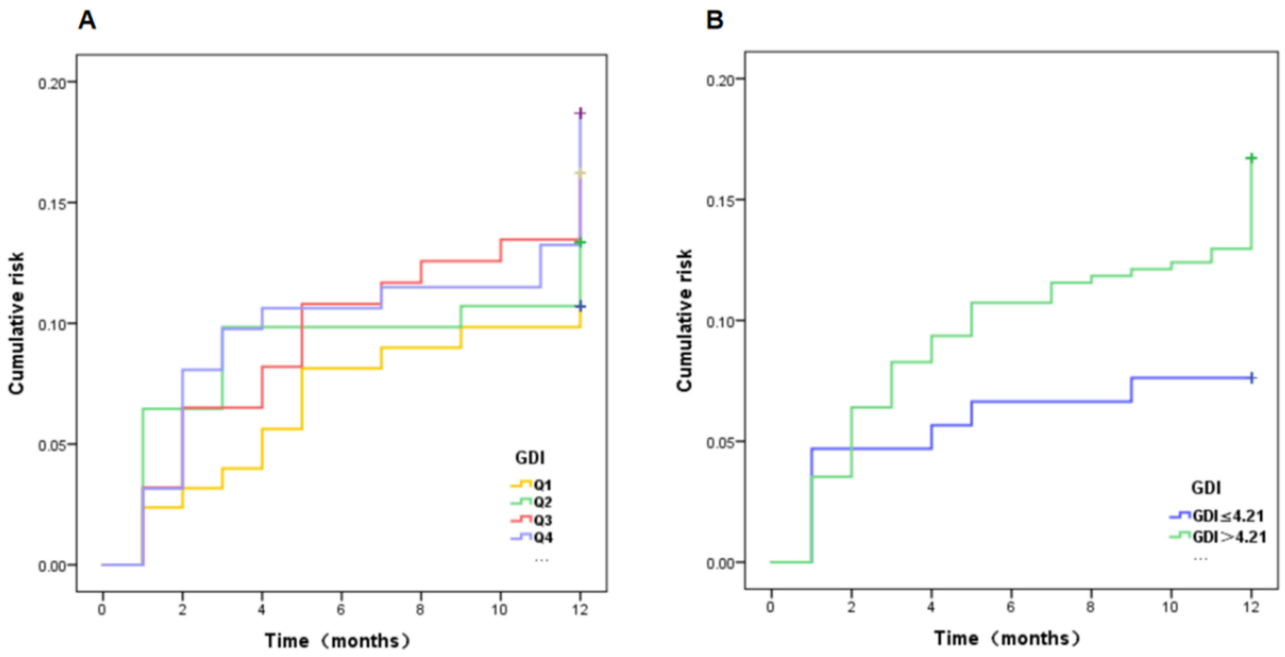

Figure 3 Kaplan-Meier survival analysis for MACE occurrence within 12 months in diabetic patients with concomitant ACS; (**A**) Divided into groups from low to high according to GDI level; (**B**) Divided into groups according to the cut-off value of GDI (4.21).

Therefore, based on previous literature reports and our preliminary validation results on the effectiveness of GDI in screening abnormal glycemic variability, we believe that GDI screening for abnormal glycemic variability has good efficacy and can be used as a predictive factor for the risk of MACE in diabetic patients with ACS.

In this study, the GDI values of patients in the MACE group were analyzed and compared to those in the non-MACE group. It was observed that the median, upper quartile, and lower quartile of the GDI values in the MACE group were higher than those in the non-MACE group. Subsequently, the study population was divided into four groups based on the ascending order of their GDI values, ranging from low to high. The incidence of MACE gradually increased from the first group to the fourth group, indicating a progressive rise in MACE occurrence with increasing GDI values. Multivariable COX proportional hazards regression was used to investigate whether GDI is a risk factor for MACE in diabetic patients with concomitant ACS. Results revealed that GDI, STEMI, TC, TG, LDL, and Hs-CRP could independently predict the risk of MACE occurrence in diabetic patients with concomitant ACS.

Moreover, GDI, STEMI, and TC are identified as risk factors for the occurrence of MACE. However, the study results showed that TG, LDL, and Hs-CRP are protective factors, which is inconsistent with conventional beliefs. In the studies conducted by Subin Lim[23] and Marjo Okkonen,[25] inverse relationships between plasma lipids and the risk of MACE occurrence were also observed. Some scholars believe that this may be related to higher cardiovascular disease prevention and treatment awareness among patients with elevated plasma lipid levels. Our research group believes that although the lipid infiltration theory has been recognized as an essential mechanism in the development of coronary artery disease, the widespread use of lipid-lowering drugs has made plasma lipid levels no longer reflect the actual lipid metabolism status of patients. Therefore, coronary heart disease risk assessment models such as China-PAR Project[26] and UK QRISK[27] do not include any plasma lipid-related laboratory parameters but only consider "the use of lipid-lowering drugs" as an assessment factor. These phenomena may be influenced by lipid substances such as small dense LDL[28] and remnant lipoprotein cholesterol,[29] which have been proposed in recent years. The specific mechanisms behind these effects require further in-depth research in the future.

Regarding the analysis of Hs-CRP as a protective factor for MACE in this study, our research group believes that although Hs-CRP is a recognized cardiovascular disease biomarker. Many clinical studies consider it as an independent risk factor for cardiovascular disease. Previous studies have focused on healthy individuals or sub-healthy individuals who have previously

experienced ACS but were asymptomatic at the time of inclusion in the study cohorts.[30] In contrast, the subjects of this study are diabetes patients admitted for ACS occurrence. Research reports have shown that Hs-CRP levels in ACS patients are significantly higher than those in stable angina patients and healthy individuals.[31] Hs-CRP peaks on the second day after the occurrence of ACS and is much higher than the reference value. Moreover, the relative variability of hs-CRP levels within one year after ACS occurrence can reach up to 206.1%.[32] Therefore, the Hs-CRP levels detected in this study may be considerably higher than those of patients in non-stressful states, resulting in a contradiction between the research findings of Hs-CRP in this study and traditional beliefs. It is worth noting that recent research has revealed the high variability of hs-CRP even in asymptomatic and clinically stable ACS patients,[32] factors such as obesity, short-term temperature fluctuations, genetic polymorphism of the angiotensinogen gene, as well as the expression levels of miR-27a and miR-329 in peripheral blood monocytes, can all influence hs-CRP levels,[33–36] therefore, taking individual differences into account, continuous periodic monitoring of hs-CRP values and evaluating them based on the mean level of hs-CRP may potentially yield more accurate assessment results in cardiovascular disease risk assessment.

In this study, GDI was identified as a simple screening index for abnormal glycemic variability. It was considered the leading risk factor for the occurrence of MACE in diabetic patients with concomitant ACS in multivariate COX proportional hazards regression. In Kaplan-Meier survival analysis, within the follow-up period, the cumulative risk of MACE occurring within 12 months in the high GDI group gradually exceeds that of the low GDI group. Furthermore, the abnormal GDI group demonstrates a significantly faster increase in the cumulative risk of MACE occurrence within 12 months than the normal GDI group, further confirming the close association between GDI and the risk of MACE occurrence in diabetes patients with concomitant ACS.

In summary, when the GRACE score, Hs-CRP, and traditional lipid parameters are not suitable for evaluating the risk of MACE occurrence in diabetes patients, the level of glycemic variability serves as an important indicator reflecting the pathological levels of oxidative stress, inflammation, and other factors within the bodies of diabetes patients, close monitoring of this level can help improve the prognosis of diabetes patients with concomitant ACS. In this study, the GDI has been confirmed as an independent predictor for the occurrence of MACE within 12 months in diabetes patients with concomitant ACS. Additionally, monitoring GDI values is simple, cost-effective, and demonstrates high clinical applicability. Therefore, in clinical practice, paying attention to the GDI value of patients, along with their clinical symptoms and physiological and biochemical indicators, and conducting a comprehensive assessment of the risk of MACE occurrence in diabetes patients with concomitant ACS is crucial, early implementation of primary and secondary preventive treatments holds significant importance in improving patient prognosis.

Limitations of This Study Include

This single-center observational study is limited by the singularity of data sources and potential data missing issues, which may lead to selection bias and affect the reliability of the results. To validate and improve the quality of the research, plans include conducting multi-center studies covering different regions and populations and employing multi-source data validation strategies such as comparing Hospital Information Systems (HIS) and Electronic Medical Records (EMR) to identify and correct missing or erroneous data. This approach aims to externally validate the current research results and further explore the clinical value of GDI indicators in assessing the risk of diabetes-related complications, such as diabetic nephropathy and diabetic retinopathy, in future research. Additionally, the current study only focuses on the GDI indicators at the time of patient admission and lacks continuous dynamic monitoring throughout the treatment process, which is also an area that needs improvement in future studies.

Abbreviations

GDI, glycemic dispersion index; MACE, major adverse cardiovascular events; ACS, acute coronary syndrome; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CK-MB, creatine kinase-MB; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WBC, white blood cell count; RBC, red blood cell; HGB, hemoglobin; 2hPG, 2-hour postprandial plasma glucose; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREA, creatinine; hs-cTnT, high-sensitivity cardiac troponinT; HCY, homocysteine; FPG,

fasting plasma glucose; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Data Confidentiality and Anonymization Statement

This statement serves to clearly articulate that, throughout the data collection, processing, and analysis phases of this research project, we have adhered strictly to internationally recognized privacy protection principles. To ensure the privacy and information security of the patients participating in this study, we have implemented a series of rigorous measures to comprehensively and thoroughly anonymize the sensitive information in the raw data.

Specifically, all information that could potentially directly or indirectly reveal a patient's identity, including but not limited to their real names, medical record numbers, and other identifiers, has been thoroughly removed during the initial stages of data collection. Instead, each patient has been assigned a unique, non-traceable identification number that serves as the sole identifier within the research data. These numbers are used exclusively to ensure accurate data correlation and analysis within the scope of this study while completely severing any possibility of linking the research findings back to the patients' true identities.

We are acutely aware of the paramount importance of protecting patient privacy. Consequently, the research team commits to continually adopting all necessary measures throughout the entire research cycle and in subsequent data storage processes to maintain the anonymity and confidentiality of the data. Any unauthorized access, use, or disclosure of the data will be subject to strict accountability.

Data Sharing Statement

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

Ethics Approval

This study was approved by the ethics committee of the Sixth Affiliated Hospital of Kunming Medical University [approval number 2022kmykdx6f154]. 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 authors declare no competing interests.

References

1. Internationales diabetes federation. IDF diabetes atlas; 2021. Available from: https://diabetesatlas.org/. Accessed September 9, 2024.
2. Morrish NJ, Wang SL, Stevens LK, et al. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia*. 2001;44(2):S14–S21. doi:10.1007/PL00002934

3. Panduranga P, Sulaiman KJ, Al-Zakwani I, et al. Acute coronary syndrome in Indian subcontinent patients residing in the Middle East: results from gulf registry of acute coronary events II. *Angiology*. 2018;66(9):818–825. doi:10.1177/0003319714556812
4. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. *Int J Physiol Pathophysiol Pharm*. 2019;11 (3):45–63.
5. Zhang ZY, Miao LF, Qian LL, et al. Molecular mechanisms of glucose fluctuations on diabetic complications. *Front Endocrinol*. 2019;10:640. doi:10.3389/fendo.2019.00640
6. Huang D, Refaat M, Mohammedi K, et al. Macrovascular complications in patients with diabetes and prediabetes. *Biomed Res Int*. 2017;2017:7839101. doi:10.1155/2017/7839101
7. Mulari S, Eskin A, Lampinen M, et al. Ischemic heart disease selectively modifies the right atrial appendage transcriptome. *Front Cardiovasc Med*. 2021;8:728198. doi:10.3389/fcvm.2021.728198
8. Benalia M, Zeller M, Mouhat B, et al. Glycaemic variability is associated with severity of coronary artery disease in patients with poorly controlled type 2 diabetes and acute myocardial infarction. *Diabetes Metab*. 2019;45(5):446–452. doi:10.1016/j.diabet.2019.01.012
9. Wu N, Shen H, Liu H, et al. Acute blood glucose fluctuation enhances rat aorta endothelial cell apoptosis, oxidative stress and pro-inflammatory cytokine expression in vivo. *Cardiovasc Diabetol*. 2018;15(1):1–13 doi:10.1186/s12933-016-0427-0
10. Zhang T, Su G, Mi SH, et al. Association between blood glucose variability and the characteristics of vulnerable plaque in elderly non-ST segment elevation acute coronary syndrome patients. *Int Heart J*. 2019;60(3):569–576. doi:10.1536/ihj.18-503
11. Gerbaud E, Darier R, Montaudon M, et al. Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. *Diabetes Care*. 2019;42(4):674–681. doi:10.2337/dc18-2047
12. Takahashi H, Iwahashi N, Kirigaya J, et al. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. *Cardiovasc Diabetol*. 2018;17:116. doi:10.1186/s12933-018-0761-5
13. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631–1640. doi:10.2337/dc17-1600
14. Onisie O, Crocket H, de Bock M. The CGM grey market: a reflection of global access inequity. *Lancet Diabetes Endocrinol*. 2019;7(11):823–825. doi:10.1016/S2213-8587(19)30263-3
15. Li XL. Research progress on factors affecting blood glucose monitoring compliance and nursing in elderly patients with diabetes. *Elect J Practl Clin Nurs Sci*. 2018;3(7):16–21.
16. Shi R, Feng L, Liu YM, et al. Glycemic dispersion: a new index for screening high glycemic variability. *Diabetol Metab Syndr*. 2023;15(1):95. doi:10.1186/s13098-023-01077-y
17. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients With ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2016;133(11):1135–1147. doi:10.1161/CIR.0000000000000336
18. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41 (Suppl.1):S13–S27. doi:10.2337/dc18-S002
19. Metabolic Cardiovascular Disease Group of the Cardiovascular Disease Branch of the Chinese Medical Association. Editorial board of the Chinese journal of cardiovascular diseases. Chinese expert consensus on comprehensive management of cardiovascular risk in patients with cardiovascular diseases and abnormal glucose metabolism. *Chinese J Cardiol*. 2021;49(7):656–672. doi:10.3760/cma.j.cn112148-20210114-00050
20. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119–177. doi:10.1093/eurheartj/ehx393
21. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289–1367. doi:10.1093/eurheartj/ehaa575
22. Shuvy M, Beeri G, Klein E, et al. Accuracy of the global registry of acute coronary events (GRACE) risk score in contemporary treatment of patients with acute coronary syndrome. *Can J Cardiol*. 2018;34(12):1613–1617. doi:10.1016/j.cjca.2018.09.015
23. Lim S, Hwa Chung S, Hyeon Kim J, et al. Effects of metabolic parameters' variability on cardiovascular outcomes in diabetic patients. *Cardiovasc Diabetol*. 2023;22(1):114. doi:10.1186/s12933-023-01848-x
24. Park S, Jaewon O, Park S, et al. In-hospital glycemic variability and all-cause mortality among patients hospitalized for acute heart failure. *Cardiovasc Diabetol*. 2022;21(1):291. doi:10.1186/s12933-022-01720-4
25. Okkonen M, SHavulinna A, Ukkola O, et al. Risk factors for major adverse cardiovascular events after the first acute coronary syndrome. *Ann Med*. 2021;53(1):817–823. doi:10.1080/07853890.2021.1924395
26. Liu F, Jianxin L, Chen J, et al. Predicting lifetime risk for developing atherosclerotic cardiovascular disease in Chinese population: the China-PAR project. *Sci Bull*. 2018;63(12):779–787. doi:10.1016/j.scib.2018.05.020
27. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:j2099. doi:10.1136/bmj.j2099
28. Otrante A, Bounafaa A, Berrougui H, et al. Small Dense LDL Level and LDL/HDL distribution in acute coronary syndrome patients. *Biomedicines*. 2023;11(4):1198. doi:10.3390/biomedicines11041198
29. Chen YY, Lue ZB, Zhao X. Correlation of Discordance between Remnant Lipoprotein Cholesterol and Non-high-density Lipoprotein Cholesterol and Severity of Coronary Stenosis. *Chin Gen Pract*. 2023;26(24):3010–3015.
30. Denegri A, Boriani G. High Sensitivity C-reactive Protein (hs-CRP) and its implications in cardiovascular outcomes. *Curr Pharm Des*. 2021;27 (2):263–275. doi:10.2174/1381612826666200717090334
31. Yang Y, Li G, Zhang R. Correlation analysis of acute coronary syndrome with serum IL-18, MMP-9, hs-CRP, and Plasma FIB. *Biomed Res Int*. 2022;2022(1):1–9. doi:10.1155/2022/4319194
32. Victor J, van den Berg VU, Brankovic M, et al. Stabilization patterns and variability of hs-CRP, NT-proBNP and ST2 during 1 year after acute coronary syndrome admission: results of the BIOMArCS study. *Clin Chem Lab Med*. 2020;58(12):2099–2106. doi:10.1515/cclm-2019-1320

33. Xinyan B, Ting Loo Y, Ponnalagu S, et al. Obesity is an independent determinant of elevated C-reactive protein in healthy women but not men. *Biomarkers*. 2019;24(1):64–69. doi:10.1080/1354750X.2018.1501763
34. Kang Y, Tang H, Jiang L, et al. Air temperature variability and high-sensitivity C reactive protein in a general population of China. *Sci Total Environ*. 2020;749:141588. doi:10.1016/j.scitotenv.2020.141588
35. Zhu M, Lin J, Wang C, et al. The relationship among angiotensinogen genes polymorphisms and hs-CRP and coronary artery disease. *J Clin Lab Anal*. 2019;33(5):e22881. doi:10.1002/jcla.22881
36. Rafiei A, Ferns GA, Ahmadi R, et al. Expression levels of miR-27a, miR-329, ABCA1, and ABCG1 genes in peripheral blood mononuclear cells and their correlation with serum levels of oxidative stress and hs-CRP in the patients with coronary artery disease. *IUBMB Life*. 2021;73:223–237. doi:10.1002/iub.2421