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RESEARCH ARTICLE

Combination of Neutrophil Count and Gensini Score as a Prognostic Marker in Patients with ACS and Uncontrolled T2DM Undergoing PCI

Yanyan Xu[1–3,a], Zhen Qin[1–3,a], Jiamin Gao[1–3], Yu Yang[1–3], Yongzheng Lu[1–3], Fengyi Yu[1–3], Yan Lv[1–3], Zhaowei Sun[1–3], Jinying Zhang[1–3] and Junnan Tang[1–3]

[1]*Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China*
[2]*Henan Province Key Laboratory of Cardiac Injury and Repair, Zhengzhou, Henan, China*
[3]*Henan Province Clinical Research Center for Cardiovascular Diseases, Zhengzhou, Henan 450018, China*

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Abstract

Background: Several biomarkers have been studied as prognostic indicators among people with diabetes and coronary artery disease (CAD). The purpose of this study was to determine the prognostic value of neutrophil counts and the Gensini score in patients with diabetes and ACS undergoing percutaneous coronary intervention (PCI).

Methods: A total of 694 people with ACS and T2DM who simultaneously had elevated HBA1c received PCI. Spearman rank correlation estimates were used for correlation evaluation. Multivariate Cox regression and Kaplan-Meier analysis were used to identify characteristics associated with major adverse cardiovascular and cerebrovascular events (MACCEs) and patient survival. The effects of single- and multi-factor indices on MACCEs were evaluated through receiver operating characteristic curve analysis.

Results: The Gensini score and neutrophil count significantly differed between the MACCE and non-MACCE groups among patients receiving PCI who had concomitant ACS and T2DM with elevated HBA1c ($P < 0.001$). The Gensini score and neutrophil count were strongly associated with MACCEs (log-rank, $P < 0.001$). The Gensini score and neutrophil count, alone or in combination, were predictors of MACCEs, according to multivariate Cox regression analysis (adjusted hazard ratio [HR], 1.005; 95% confidence interval [CI], 1.002–1.008; $P = 0.002$; adjusted HR, 1.512; 95% CI, 1.005–2.274; $P = 0.047$, respectively). The Gensini score was strongly associated with neutrophil count (variance inflation factor ≥ 5). Area under the curve analysis revealed that the combination of multivariate factors predicted the occurrence of MACCEs better than any single variable.

Conclusion: In patients with T2DM and ACS with elevated HBA1c who underwent PCI, both the Gensini score and neutrophil count were independent predictors of outcomes. The combination of both predictors has a higher predictability.

Keywords: Gensini score; Neutrophil count; HBA_{1c}; Acute coronary syndrome; Type 2 diabetes mellitus; Percutaneous coronary intervention

[a]Yanyan Xu and Zhen Qin contributed equally.

Correspondence: **Junnan Tang**, Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China, E-mail: fcctangjn@zzu.edu.cn

Introduction

ACS includes non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, and unstable angina [1]. Diabetes mellitus (DM) can

accelerate the progression of cardiovascular disease (CVD). The coronary artery lesions in patients with ACS and DM are complex. In addition, patients with concomitant ACS and diabetes have not only a higher all-cause mortality rate, but also a higher risk of stroke and myocardial infarction (MI) than ACS patients without diabetes.

Several biomarkers have been investigated as prognostic indicators for patients with CHD and T2DM [2, 3]. The triglyceride-glucose index has been associated with CVD morbidity and mortality [4, 5]. To date, few biomarkers with high predictive value, such as natriuretic peptide (NP) for heart failure diagnosis and prognosis, and cardiac troponin (cTn) for diagnosing acute MI, have been identified [6]. Therefore, additional biomarkers with predictive ability are needed for patients with CHD and T2DM.

Neutrophils are specialist innate immune response effector cells with crucial roles in the inflammatory response, particularly in vascular inflammation and healing [7]. In ACS, neutrophils are involved in thrombus formation and contribute to ischemia-reperfusion injury. The massive recruitment of neutrophils in the infarct zone expands the infarct size, and the altered phenotype of neutrophils is associated with ACS [8]. Because of its role as a distinct prognostic marker for CAD, the neutrophil-lymphocyte ratio has recently attracted substantial attention. Moreover, neutrophil extracellular traps have been associated with both venous and arterial thrombosis. Neutrophils are linked to the pathophysiology of CVDs. Therefore, we speculated that the number of neutrophils would be strongly associated with CVD prognosis. Moreover, compared with other prognostic factors for CVDs, neutrophil counts are simple and easy to obtain.

The Gensini score [9] is the only metric used to assess the severity of coronary stenosis. It is simple, based on valid evidence, and suitable for most patients with CAD, particularly those with ACS who are undergoing emergency PCI.

In this investigation, we examined the relevant data from patients with diabetes with ACS who underwent PCI, to determine whether the Gensini score and neutrophil count might be associated with patient prognosis.

Methods

Study Design and Participants

From December 2017 to December 2020, we studied patients with ACS and T2DM with high HBA1c who underwent PCI at Zhengzhou University's First Affiliated Hospital (Henan, China).

ACS is currently recognized as an extremely severe clinical state induced by coronary atherosclerotic plaques, and is associated with non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, and unstable angina [1]. ACS is diagnosed in patients who have had prolonged resting angina for more than 20 minutes, fresh angina, chronic angina with recent worsening, or post-MI angina. ACS is characterized by electrocardiogram (ECG) alterations, including ST depression, transitory ST elevation, and T-wave variations, as well as changes in cardiac enzymes [10].

ST-segment ECG changes involve an ST elevation of 1 mm in all leads other than leads V2–V3 where the changes for men above 40 years of age, 2.5 mm for men below 40 years of age, and 1.5 mm for women of various ages. When the size of the J-point elevation in leads V2 and V3 is consistent with the prior ECG, a new J-point elevation of 1 mm relative to the previous ECG is considered to indicate an ischemia response. The ECG reveals a horizontal or downsloping ST-depression of 0.5 mm in two consecutive leads with a pronounced R wave or R/S ratio >1, with or without T inversion exceeding 1 mm, thus indicating myocardial ischemia [11]. Arrhythmia is a condition in which the origin, frequency, rhythm, conduction velocity, or sequence of cardiac impulses is aberrant.

After a qualitative and quantitative study of coronary atherosclerosis in all patients by coronary angiography, we conducted PCI according to established procedures. All surgical choices were made by experienced interventional cardiologists on the basis of patient status, according to the targeted 2007 update of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions 2005 guidelines for PCI.

Patients can be diagnosed with diabetes if they have typical or critical hyperglycemia symptoms,

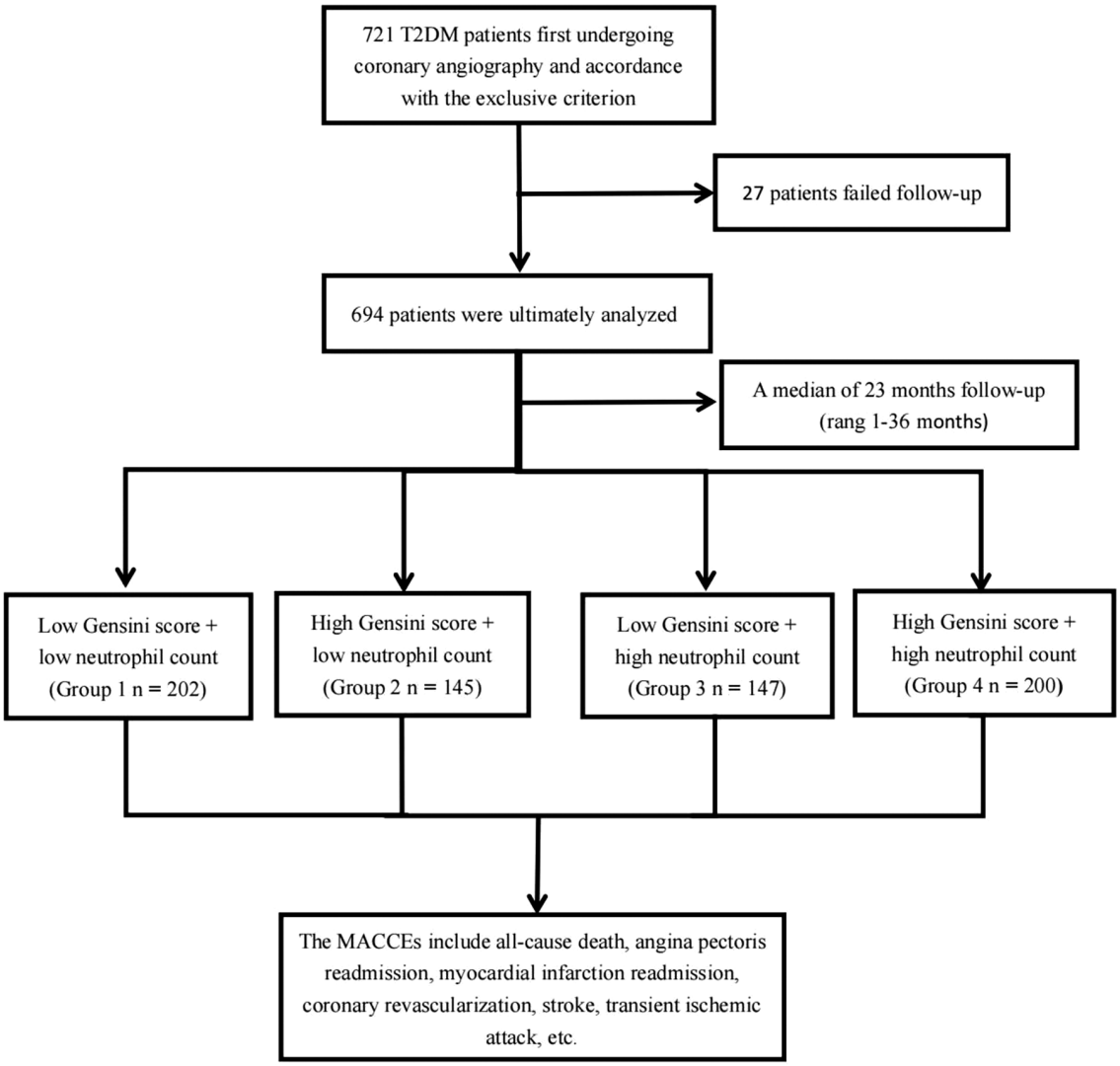

Figure 1 Research Flowchart.

and their fasting plasma glucose exceeds 126 mg/dL (7.0 mmol/L), their oral glucose tolerance test (OGTT) 2-hPG exceeds 200 mg/dL (11.1 mmol/L), their HbA1c exceeds 6.5%, or their random blood glucose exceeds 200 mg/dL (11.1 mmol/L). The World Health Organization has recommended using a dose of 75 g of anhydrous glucose dissolved in water in OGTTs [9].

The inclusion and exclusion criteria for this study were based on previous research [12]. This research included participants older than 18 years who were free from any other high-output cardiac diseases or other conditions, such as hypertrophic cardiomyopathy, pulmonary heart disease, congenital heart disease, etc., and who had complete clinical documentation.

After exclusion of 27 patients who were lost to follow-up, 694 participants participated in the trial. The Helsinki Declaration was strictly followed in this study, which received ethical approval from the Ethical Committee of Zhengzhou University's First Affiliated Hospital. We also obtained written informed consent from each participant. The study design can be found at http://www.chictr.org.cn (identifier: ChiCTR-2200055450). To gather follow-up information, we used medical records and/or telephone interviews. Figure 1 depicts the flowchart of our research.

Clinical and Demographic Characteristics

Blood samples were collected before PCI within 24 hours of patient hospitalization. We collected

the patients' personal information, such as sex, age, and illness history, as well as certain laboratory test results, such as HbA1c and LDL-c. We calculated the Gensini score according to coronary angiography results.

Patient Groupings

We used the median as an indicator for grouping. The median neutrophil count was 4.545×10^9/L, and the median Gensini score was 72. On the basis of the median Gensini score (groups 1 and 2, Gensini score < 72; groups 3 and 4, Gensini score ≥ 72) and neutrophil count (groups 1 and 3, neutrophil count < 4.545×10^9/L; groups 2 and 4, neutrophil count ≥ 4.545×10^9/L), the patients were divided into four groups. Among all participants, 202 were assigned to group 1 (low Gensini score + low neutrophil count), 145 were assigned to group 2 (high Gensini score + low neutrophil count), 147 were assigned to group 3 (low Gensini score + high neutrophil count), and 200 were assigned to group 4 (high Gensini score + high neutrophil count). The patients were divided into two groups according to the presence (n = 194) or absence (n = 500) of MACCEs.

Clinical Endpoints and Follow-up

MACCEs included readmission for angina pectoris, readmission for MI, coronary revascularization, stroke, all-cause death, and transient ischemic attack. We followed patients via phone calls, emails, or outpatient visits. The study's follow-up time varied from 1 to 36 months, with a median of 23 months. Patients were followed until the trial ended if they had MACCEs; otherwise, they were followed until the study ended.

Statistical Analysis

SPSS version 26.0 and R software version 4.0.2 were both used for all analyses. We used the Kolmogorov-Smirnov test and Mann-Whitney U test as non-parametric methods. To ascertain whether quantitative variables had a normal distribution, we performed the Kolmogorov-Smirnov test. To examine differences between variables with non-normal distributions, we used the Mann-Whitney U test. The mean and standard deviation are used to express continuous data. We used the Student t-test to discriminate between two groups of normally distributed data and analysis of variance to distinguish between more than two groups. The percentages represent categorical variables that were compared with the chi-square test. Using Pearson's correlation coefficient analysis, we investigated the link between neutrophil count and Gensini score. Multivariate Cox regression analysis was used to investigate the prognostic predictive value of the neutrophil count and Gensini score. Before developing the Cox model, we developed a univariate model for each predictor. Variance inflation factor ≥ 5 and significant factors ($P < 0.05$) were eliminated to analyze variables that were significantly associated with MACCEs. These parameters were investigated through multivariate Cox model analysis. The 95% confidence intervals (CIs) and hazard ratios (HRs) were calculated. The log-rank test was used to compare groups, and the Kaplan-Meier approach was used to assess the cumulative incidence of long-term outcomes. $P < 0.05$ was considered to indicate statistical significance. For examining the prognostic values of risk factors, we constructed a receiver operating characteristic (ROC) curve. To assess the diagnostic efficacy of risk factors, we compared areas under the curves (AUC).

Results

Patients' Baseline Clinical Features

This study enrolled 694 patients who were characterized as having undergone PCI, and having both ACS and T2DM. We recorded the baseline data for the patients (Table 1). All patients were taking clopidogrel or ticagrelor. The four groups' age, illness duration, medication use, and other test results did not statistically significantly differ. In comparison to the other groups, group 4 had higher neutrophil count, LDL-C level, fasting blood glucose (FBG), cardiac enzyme level, use of oral antidiabetic medications (OADs) + insulin, and frequency of ECG ST segment alteration. The cardiac function of these patients was classified primarily as NYHA class I in groups 1 and 2, and class II in groups 3 and 4.

Table 1 Clinical Baseline Characteristics of Enrolled Patients According to the Neutrophil Count and Gensini Score.

Characteristic	Low Gensini score + low neutrophil count (group 1, n = 202)	High Gensini score + low neutrophil count (group 2, n = 145)	Low Gensini score + high neutrophil count (group 3, n = 147)	High Gensini score + high neutrophil count (group 4, n = 200)	Statistics	P
Age (years)	59 (53–66)	62 (54–68)	60 (52–66)	61 (53–68)	5.461	0.141
Duration of diabetes (years)	5 (2–10)	6 (2–12)	6 (2–10)	7 (4–10)	3.846	0.279
Sex						
Male, n (%)	111 (54.95)	94 (64.83)	98 (66.67)	136 (68.00)	8.821	0.032
Laboratory parameters						
WBC (10^9/L)	5.80 (5.10–6.58)	6.12 (5.30–6.84)	8.50 (7.47–10.50)	8.37 (7.20–10.16)	365.803	<0.001
Neutrophil count (10^9/L)	3.44 (2.75–3.87)	3.66 (2.99–4.11)	5.69 (5.10–7.99)	5.98 (5.14–8.54)	521.761	<0.001
Plt (10^9/L)	206.00 (179.00–245.00)	207.00 (171.00–238.00)	230.00 (187.00–287.00)	219.00 (176.00–265.00)	18.012	<0.001
Hb (g/L)	131.40 (121.00–142.00)	132.00 (122.00–142.00)	134.00 (122.00–143.00)	134.70 (122.00–146.00)	2.679	0.444
ALB (g/L)	42.10 (39.40–44.30)	42.20 (40.10–44.40)	41.30 (38.80–43.60)	41.30 (38.20–43.70)	8.466	0.037
FIB (g/L)	2.90 (2.54–3.35)	2.96 (2.57–3.37)	3.10 (2.70–3.60)	3.31 (2.77–3.92)	28.129	<0.001
LDL-C (mmol/L)	1.91 (1.37–2.57)	1.89 (1.44–2.40)	2.05 (1.50–2.80)	2.15 (1.67–2.85)	13.183	0.004
HDL-C (mmol/L)	0.98 (0.80–1.13)	0.94 (0.80–1.13)	0.96 (0.85–1.17)	0.97 (0.85–1.11)	1.647	0.649
TG (mmol/L)	1.40 (1.01–1.89)	1.53 (1.09–2.06)	1.58 (1.10–2.05)	1.54 (1.19–1.99)	5.592	0.133
TC (mmol/L)	3.38 (2.84–4.19)	3.50 (2.87–4.30)	3.63 (2.99–4.47)	3.75 (3.05–4.44)	6.671	0.083
eGFR (ml/min)	98.08 (89.89–105.00)	95.10 (82.98–102.66)	94.51 (83.17–102.97)	94.37 (77.75–103.54)	11.688	0.009
sCr (μmol/L)	64.00 (57.00–74.00)	66.00 (58.80–80.00)	67.20 (60.00–80.90)	69.60 (60.40–86.00)	14.034	0.003
FBG (mmol/L)	7.56 (6.26–9.27)	8.04 (6.34–10.55)	7.79 (6.48–10.39)	8.63 (7.30–10.70)	16.765	<0.001
HbA_{1c} (%)	7.80 (7.10–8.70)	7.90 (7.20–8.90)	7.79 (7.00–9.00)	8.10 (7.10–9.20)	3.559	0.313
NT-pro BNP (ng/L)	141.400 (56.00–311.00)	217.00 (72.38–614.94)	208.00 (105.00–993.50)	613.00 (166.00–1816.00)	74.912	<0.001
Elevated cardiac enzymes, n (%)	42 (20.79)	50 (34.48)	62 (42.18)	121 (60.50)	68.380	<0.001
Medication						
Aspirin, n (%)	193 (95.55)	138 (95.17)	137 (93.20)	190 (95.00)	1.052	0.789
Clopidogrel or ticagrello, n (%)	100 (49.51)	63 (43.45)	75 (51.02)	99 (49.50)	2.016	0.569
Statins, n (%)	196 (97.03)	138 (95.17)	141 (95.92)	193 (96.50)	0.887	0.829
β-receptor blocker, n (%)	145 (71.78)	116 (80.00)	117 (79.59)	157 (78.50)	4.664	0.198
SGLT2 inhibitor, n (%)	63 (31.19)	39 (26.90)	31 (21.09)	54 (27.00)	4.409	0.221
CCBs, n (%)	69 (34.16)	49 (33.80)	39 (26.53)	64 (32.00)	2.667	0.446
OADs, n (%)	139 (68.81)	103 (71.03)	104 (70.75)	145 (72.50)	0.668	1.881

Table 1 (continued)

Characteristic	Low Gensini score + low neutrophil count (group 1, n = 202)	High Gensini score + low neutrophil count (group 2, n = 145)	Low Gensini score + high neutrophil count (group 3, n = 147)	High Gensini score + high neutrophil count (group 4, n = 200)	Statistics	P
Gliclazide, n (%)	29 (14.36)	21 (14.48)	24 (16.33)	43 (21.50)	4.590	0.204
Acarbose, n (%)	61 (30.20)	51 (35.17)	39 (26.53)	63 (31.50)	2.636	0.451
Metformin, n (%)	96 (47.53)	80 (55.17)	81 (55.10)	98 (49.00)	3.290	0.349
Insulin, n (%)	38 (18.81)	39 (26.90)	30 (20.41)	58 (29.00)	7.458	0.059
OADs + insulin, n (%)	20 (9.90)	19 (13.10)	15 (10.20)	41 (20.50)	11.859	0.008
NYNA, n (%)						
I	89 (44.06)	62 (42.76)	61 (41.50)	58 (29.00)	25.277	0.003
II	88 (43.56)	50 (34.48)	63 (42.86)	86 (43.00)		
III	19 (9.41)	29 (20.00)	18 (12.25)	47 (23.50)		
IV	6 (2.97)	4 (2.76)	5 (3.40)	9 (4.50)		
ECG ST segment changes, n (%)	129 (63.86)	104 (71.72)	110 (74.83)	172 (86.00)	26.325	<0.001
Arrhythmia, n (%)	13 (6.44)	3 (2.07)	12 (8.16)	9 (4.50)	6.155	0.104
Stroke, n (%)	30 (14.85)	28 (19.31)	26 (17.69)	33 (16.50)	1.293	0.731
Daily smokers, n (%)	79 (39.11)	67 (46.21)	57 (38.78)	85 (42.50)	2.331	0.507
Daily drinkers, n (%)	75 (37.13)	62 (42.76)	51 (34.69)	74 (37.00)	2.213	0.529
Gensini score	47.00 (33.00–59.00)	98.00 (83.00–129.00)	50.50 (37.50–63.00)	97.00 (85.50–121.00)	520.774	<0.001

Abbreviations: WBC, white blood cell count; Plt, platelet; Hb, hemoglobin; ALB, serum albumin; sCr, serum creatinine; FIB, fibrinogen; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; eGFR: estimated glomerular filtration rate; FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; NT-proBNP, B-type natriuretic peptide; SGLT2, sodium glucose cotransporter 2; CCBs: calcium channel blockers; OADs, oral antidiabetic drugs; NYHA: New York Heart Association; ECG: echocardiography.

Clinical Characteristics of Patients With and Without MACCEs

A total of 694 patients were enrolled, of whom 194 experienced MACCEs and 500 did not. Patients with MACCEs had diabetes for longer periods of time than patients who did not. The MACCE group, compared with the non-MACCE group, showed substantially higher blood levels of WBC, neutrophils, BNP, and myocardial enzymes, and used much more insulin and antiplatelet medications, such as clopidogrel or ticagrelor (Table 2).

Risk Factors for MACCEs

Cox proportional hazards analysis was used to determine the risk variables for MACCEs in patients with diabetes with poor long-term glycemic control and ACS who underwent PCI (Table 3). Univariate analysis was used to analyze the data in Table 2 and identify the independent risk factors. Multivariate analysis was used to further analyze these variables and identify the predictors.

The univariate analysis indicated that serum creatinine (sCR; HR, 1.003; 95% CI, 1.002–1.004; $P < 0.001$), FIB (HR, 1.289; 95% CI, 1.105–1.502; $P = 0.001$), FBG (HR, 1.109; 95% CI, 1.077–1.141; $P < 0.001$), serum albumin (ALB; HR, 0.928; 95% CI, 0.900–0.957; $P < 0.001$), TG (HR, 1.138; 95% CI, 1.002–1.293; $P = 0.046$), WBC (HR, 1.14; 95% CI, 1.079–1.204; $P < 0.001$), estimated glomerular filtration rate (eGFR; HR, 0.982; 95% CI, 0.976–0.988; $P < 0.001$), neutrophil count (HR, 1.139; 95% CI, 1.089–1.191; $P < 0.001$), and the Gensini score (HR, 1.007; 95% CI, 1.004–1.009; $P < 0.001$) were positively correlated with MACCEs. High neutrophil counts plus high Gensini scores were found to be independent risk variables for MACCEs (HR, 2.136; 95% CI, 1.609–2.835; $P < 0.001$).

The Gensini score plus neutrophil count demonstrated collinearity (variance inflation factor ≥ 5), whereas other risk variables did not.

After adjusting the covariates of Model 1 the following factors were significant associations with MACCEs: FBG (HR, 1.065; 95% CI, 1.032–1.098; $P < 0.001$), ALB (HR, 0.944; 95% CI, 0.915–0.975; $P < 0.001$), TG (HR, 1.171; 95% CI, 1.018–1.347; $P = 0.028$), eGFR (HR, 0.990; 95% CI, 0.983–0.997; $P = 0.007$), neutrophil count (HR, 1.123; 95% CI, 1.021–1.236; $P = 0.017$), and Gensini score (HR, 1.005; 95% CI, 1.002–1.008; $P = 0.002$).

The following variables were significantly associated with MACCEs in the multivariate Cox analysis of model 2: sCr (HR, 1.002; 95% CI, 1.000–1.004; $P = 0.037$), FBG (HR, 1.059; 95% CI, 1.022–1.098; $P = 0.001$), ALB (HR, 0.948; 95% CI, 0.918–0.978; $P = 0.001$), and eGFR (HR, 0.991; 95% CI, 0.984–0.998; $P = 0.008$). A higher risk of MACCEs was indicated by both a high Gensini score and a high neutrophil count (HR, 1.512; 95% CI, 1.005–2.274; $P = 0.047$).

To analyze patients' long-term survival, we performed Kaplan-Meier survival analysis. The 3-year MACCEs differed significantly among the four groups (Figure 2). Patients with a high Gensini score combined with a high neutrophil count had the poorest survival (log-rank, $P < 0.001$).

Effects of Gensini Score and Neutrophil Count on MACCE

We performed ROC curve analysis to determine whether the Gensini score and neutrophil count could be predicted in diabetic individuals with ACS and elevated HBA1c who underwent PCI. The Gensini score's AUC was 0.646 (95% CI, 0.603–0.689; $P < 0.001$), whereas the neutrophil count's AUC was 0.652 (95% CI, 0.605–0.698; $P < 0.001$), and the combined AUC of the both predictors was 0.699 (95% CI, 0.657–0.741; $P < 0.001$; Figure 3).

Discussion

In early 2018, the prevalence of diabetes reached 11% in China, not including people with undiagnosed diabetes [13]. Individuals with diabetes and ACS are currently considered distinct from ACS patients without diabetes because of their elevated risk of cardiovascular mortality [14, 15]. DM not only contributes to the occurrence of CVD, particularly CAD, but also hastens progression of these diseases. Diabetes can exacerbate the magnitude of CAD and affect prognosis in people with ACS. In addition, patients with ACS with, rather than without, diabetes have a greater risk of recurrent revascularization, stroke, and myocardial infarction.

Table 2 Comparison of Clinical and Laboratory Characteristics of Enrolled Patients According to the Occurrence of MACCEs.

Characteristic	Non-MACCE (n = 500)	MACCE (n = 194)	Statistics	P
Age (years)	61 (54–66)	61(52–68)	−0.323	0.747
Duration of diabetes (years)	6 (2–10)	7 (4–10)	−1.970	0.048
Sex				
Male, n (%)	308 (61.60)	131 (67.53)	2.112	0.146
Laboratory parameters				
WBC (10^9/L)	6.80 (5.74–8.10)	7.30 (6.20–9.90)	−4.532	<0.001
Neutrophil count (10^9/L)	4.320 (3.41–5.44)	5.33 (3.89–8.54)	−6.203	<0.001
Plt (10^9/L)	215.00 (179.00–254.00)	209.00 (173.00–256.00)	0.592	0.554
Hb (g/L)	133.00 (124.00–143.20)	134.00 (117.20–143.00)	1.107	0.268
ALB (g/L)	42.20 (39.60–44.30)	40.60 (37.60–43.30)	4.646	<0.001
FIB (g/L)	3.00 (2.62–3.46)	3.20 (2.73–3.82)	−2.832	0.005
LDL-C (mmol/L)	2.01 (1.44–2.67)	2.03 (1.64–2.72)	−1.330	0.184
HDL-C (mmol/L)	0.96 (0.83–1.13)	0.96 (0.83–1.15)	−0.453	0.650
TG (mmol/L)	1.51 (1.05–1.93)	1.55 (1.18–2.08)	−2.216	0.027
TC (mmol/L)	3.53 (2.86–4.40)	3.44 (3.05–4.33)	−0.555	0.579
eGFR (ml/min)	93.63±16.99	85.53±23.25	4.395	<0.001
sCr (μmol/L)	65.80 (58.00–78.00)	69.00 (58.00–94.20)	−2.773	0.006
FBG (mmol/L)	7.56 (6.26–9.37)	9.38 (7.62–12.18)	−7.230	<0.001
HbA_{1c} (%)	7.90 (7.10–9.00)	7.70 (7.10–8.90)	1.114	0.265
NT-pro BNP (ng/L)	188.00 (74.00–574.69)	420.57 (144.00–2034.00)	−5.878	<0.001
Elevated cardiac enzymes, n (%)	109 (21.80)	166 (85.57)	237.562	<0.001
Medication				
Aspirin, n (%)	478 (95.60)	180 (92.78)	2.254	0.133
Clopidogrel or ticagrello, n (%)	225 (45.00)	112 (57.73)	9.070	0.003
Statins, n (%)	481 (96.20)	187 (96.39)	0.014	0.905
β-receptor blocker, n (%)	382 (76.40)	153 (78.87)	0.481	0.488
SGLT2 inhibitor, n (%)	134 (26.80)	53 (27.32)	0.019	0.890
CCBs, n (%)	161 (32.20)	60 (30.93)	0.104	0.747
OADs, n (%)	354 (70.80)	137 (70.62)	0.002	0.962
Gliclazide, n (%)	83 (16.60)	34 (17.53)	0.085	0.770
Acarbose, n (%)	158 (31.60)	56 (28.87)	0.490	0.484
Metformin, n (%)	253 (50.60)	102 (52.58)	0.219	0.640
Insulin, n (%)	102 (20.40)	63 (32.47)	11.244	<0.001
OADs + insulin, n (%)	59 (11.80)	36 (18.56)	5.401	0.020

Table 2 (continued)

Characteristic	Non-MACCE (n = 500)	MACCE (n = 194)	Statistics	P
NYHA stage, n (%)				
I	194 (38.80)	76 (39.18)	4.390	0.222
II	215 (43.00)	72 (37.11)		
III	73 (14.60)	40 (20.62)		
IV	18 (3.60)	6 (3.09)		
ECG ST segment changes, n (%)	339(67.800)	176(90.722)	38.367	<0.001
Arrhythmia, n (%)	32(6.400)	5(2.577)	4.047	0.044
Stroke, n (%)	89 (17.80)	28 (14.43)	1.130	0.288
Daily smokers, n (%)	209 (41.80)	79 (40.72)	0.067	0.796
Daily drinkers, n (%)	193 (38.60)	69 (35.57)	0.547	0.459
Gensini score	66.50 (42.50–92.00)	85.00 (64.50–107.00)	−5.989	<0.001

Abbreviations: WBC, white blood cell count; Plt, platelet; Hb, hemoglobin; ALB, serum albumin; sCr, serum creatinine; FIB, fibrinogen; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; eGFR: estimated glomerular filtration rate; FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; NT-proBNP, B-type natriuretic peptide; SGLT2, sodium glucose cotransporter 2; CCBs: calcium channel blockers; OADs, oral antidiabetic drugs; NYHA: New York Heart Association; ECG: echocardiography.

Table 3 Univariate and Multivariate Cox Regression Analysis Results for MACCEs.

Variables	Univariate analysis		Multivariate analysis			
	Crude HR (95% CI)	Crude P	Model 1		Model 2	
			Adjusted HR (95% CI)	Adjusted P	Adjusted HR (95% CI)	Adjusted P
sCr (μmol/L)	1.003 (1.002–1.004)	<0.001	1.002 (1.000–1.004)	0.067	1.002 (1.000–1.004)	0.037
WBC (10^9/L)	1.140 (1.079–1.204)	<0.001	0.949 (0.849–1.06)	0.351	1.050 (0.990–1.114)	0.106
FIB (g/L)	1.289 (1.105–1.502)	0.001	1.123 (0.957–1.319)	0.155	1.144 (0.972–1.345)	0.105
FBG (mmol/L)	1.109 (1.077–1.141)	<0.001	1.065 (1.032–1.098)	<0.001	1.059 (1.022–1.098)	0.001
ALB (g/L)	0.928 (0.9–0.957)	<0.001	0.944 (0.915–0.975)	<0.001	0.948 (0.918–0.978)	0.001
TG (mmol/L)	1.138 (1.002–1.293)	0.046	1.171 (1.018–1.347)	0.028	1.061 (0.889–1.268)	0.510
eGFR (ml/min)	0.982 (0.976–0.988)	<0.001	0.990 (0.983–0.997)	0.007	0.991 (0.984–0.998)	0.008
Neutrophil count (10^9/L)	1.139 (1.089–1.191)	<0.001	1.123 (1.021–1.236)	0.017	—	—
Gensini score	1.007 (1.004–1.009)	<0.001	1.005 (1.002–1.008)	0.002	—	—
High Gensini score + high neutrophil count	2.136 (1.609–2.835)	<0.001	—	—	1.512 (1.005–2.274)	0.047

Abbreviations: HR, hazard ratio; CI, confidence interval; sCr, serum creatinine; WBC, white blood cell count; FIB, fibrinogen; FBG, fasting blood glucose; ALB, serum albumin; TG, triglyceride; eGFR: estimated glomerular filtration rate.

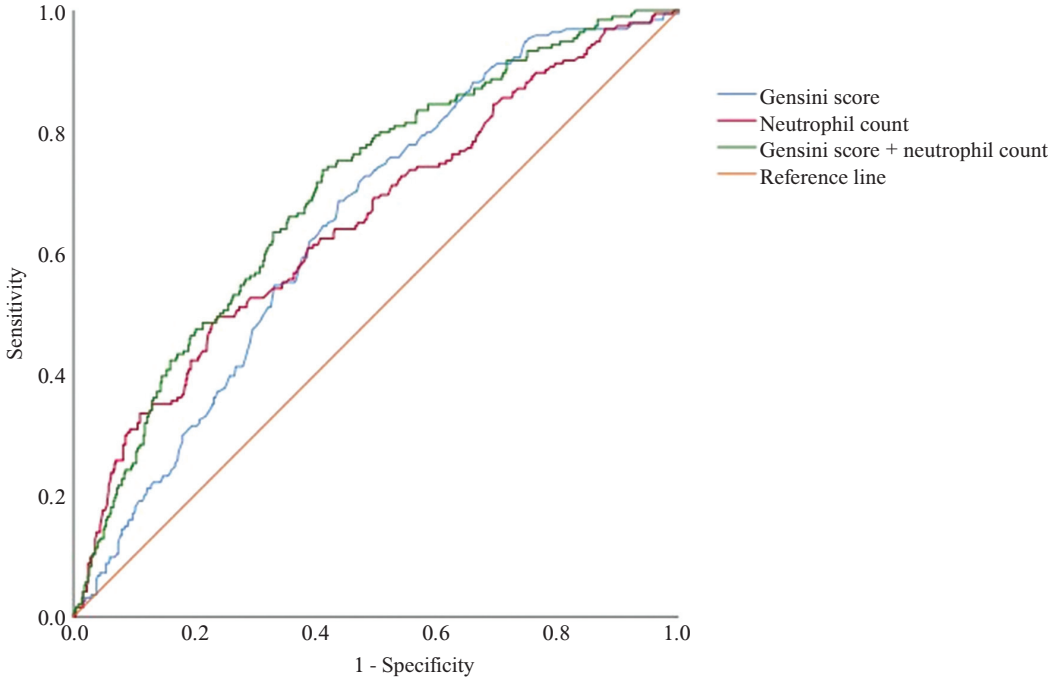

Figure 2 Kaplan-Meier Survial Analysis.

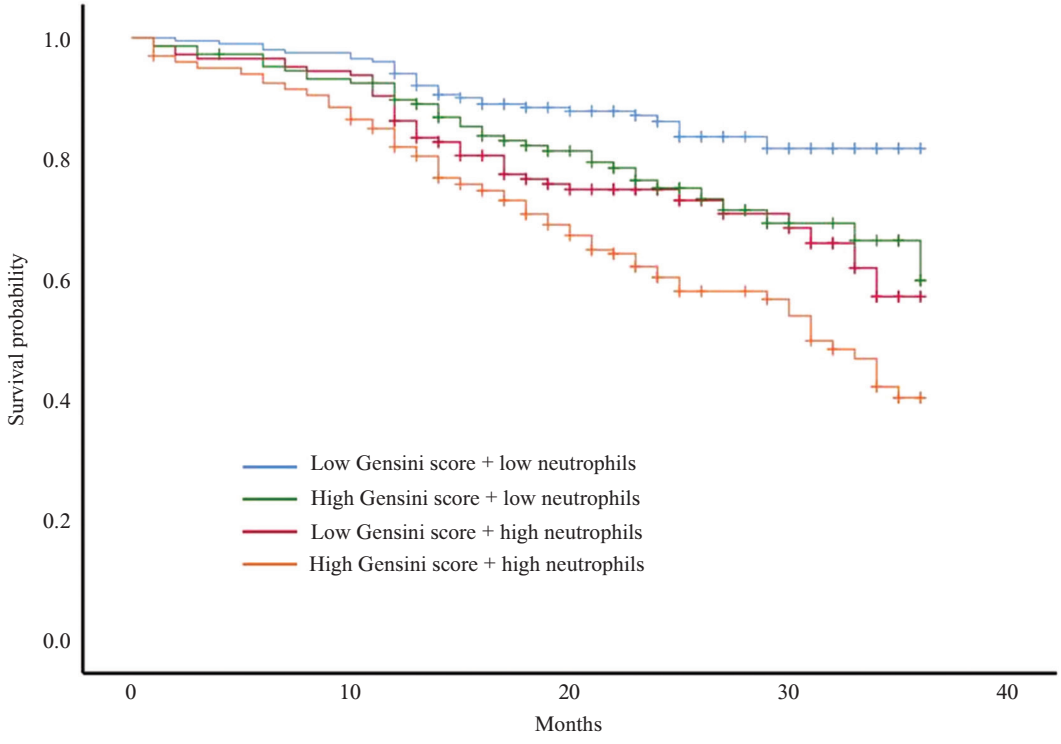

Figure 3 ROC Curve Analysis.

A lack of glucose control in people with diabetes and ACS leads to poorer prognosis. People with ACS who have uncontrolled glucose have a greater risk of ischemic stroke and vascular mortality than those with regulated glucose [16]. Moreover, patients who exhibit inadequate control of blood glucose, particularly those with poor long-term control who have been diagnosed with ACS, have

been found to have a notably elevated rate of stenosis after PCI [17]. FBG, OGTT, and HbA1c are the currently used methods to diagnose diabetes, and are also prognostic indicators for patients with ACS and diabetes. FBG indicates immediate blood glucose readings at the time of testing but does not provide insight into overall glycemic control over an extended time period [18]. OGTT indicates the ability of a patient's pancreatic beta cells to secrete insulin [19]. HBA1c, which represents a patient's 3-month average glucose level, has a strong predictive value for diabetes complications and is therefore widely used in the clinical evaluation of glucose control. The current target for HBA1c is 7% for people with diabetes and CHD. [20]. However, HBA_{1c} is an indirect method for measuring average blood glucose and does not reflect fluctuations. Moreover, because its level is affected by certain diseases and drugs, it has inherent limitations as a biomarker. In patients with acute myocardial infarction, the stress-hyperglycemia ratio correctly captures the true acute hyperglycemia state, which is associated with poor short-term outcomes [21]. Most patients with ACS are in an acute stress state, in which HbA1c is not affected by stress-induced hyperglycemia, and FBG may show false positive results [22]. However, the chance of serious adverse cardiovascular events in patients with ACS within 6 months is not predicted by HbA1c [22].

In this investigation, in patients with elevated HBA1c undergoing PCI, the neutrophil count and Gensini score were both found to be independent predictors of ACS and T2DM. Moreover, the combination of the neutrophil count plus the Gensini score further increased the predictive value for MACCEs.

In the 694 included patients, we examined the connection between MACCE prevalence and Gensini score. Our findings indicated that the Gensini score accurately predicted the outcomes of patients undergoing PCI who had both ACS and T2DM, as well as elevated HBA1c. According to Wang [23], the Gensini score can predict unfavorable outcomes for patients with CHD after PCI, particularly for those who also have diabetes and CHD.

The pathophysiology of atherosclerosis is influenced by dyslipidemia, the immunological response, and inflammation [24]. Inflammation damages the vascular endothelium, thereby leading to the endothelial penetration of lipids. Subsequently, macrophages absorb plasma-derived lipoproteins and form foam cells, which in turn become atherosclerotic lesions. Insufficient clearance of apoptotic cells and foam cells leads to atherosclerosis progression [25]. Regulatory T cells have anti-inflammatory properties and have been found to protect against atherosclerosis in experimental conditions [26]. Therefore, abnormal lipid metabolism, abnormal function of immune cells, and inflammatory cytokine release are associated with CAD prognosis. Yang has demonstrated that MACCEs and MI in patients receiving PCI are independently predicted by the ratio of high-sensitivity C-reactive protein to albumin [27]. IL-1β is involved in pancreatic cell destruction and can be used to predict CVD risk in people with T2DM [28]. TNF-α has been implicated in insulin resistance, and found to contribute to atherosclerosis and heart failure [29]. Soluble tumorigenesis-2 suppression has been associated with unfavorable cardiovascular outcomes in individuals with diabetes and CHD, thus demonstrating tumorigenesis-2's potential to serve as a biomarker [6]. Interleukin-33, vascular cell adhesion molecule-1, oxidized LDL/LDL-C ratio [30], glycemic index, and glycemic load [31] can also be used to predict the prognosis of patients with diabetes with CVD. A complete blood count [32] can be used as a biomarker to predict adverse outcomes in patients with CVD. Wan has discovered that neutrophil infiltration hastens the evolution of CAD and CHD in people with diabetes and is independently linked to CAD severity and prognosis [33, 34]. The neutrophil-to-lymphocyte ratio may predict CAD [35]. NETs are associated with venous and arterial thrombosis [31]. In patients with T2DM and inadequate glycemic control, lipid profiles in conjunction with levels of inflammatory cytokines can predict the prognosis of CVD, according to cohort research from the United States [36].

We also found a significant association between the incidence of MACCEs and neutrophil counts. Neutrophil counts are easier to obtain as a prognostic factor than the aforementioned inflammatory factors. In patients with diabetes and ACS who received PCI, univariate analysis indicated that neutrophil count (HR, 1.139; 95% CI, 1.089–1.191; $P < 0.001$) was an independent risk factor for MACCEs. After adjustment of model 1 for covariates, neutrophil

count (HR, 1.123; 95% CI, 1.021–1.236; P = 0.017) remained a risk factor for MACCEs.

Only the Gensini score, among the other grading systems, can currently be used to evaluate the quantity, distribution, and size of coronary artery lesions. It separates the coronary artery into several sections with various weighting factors. Patients may be accurately categorized with the Gensini score according to the functional importance of CAD, and patients with comparable levels of CAD can be matched. This score supports ongoing research on interobserver and intraobserver variability with microprocessor assistance. The Gensini score is now often used in clinical research. The Gensini score was identified in univariate analysis as a risk factor for MACCEs (HR, 1.007; 95% CI, 1.004–1.009; P < 0.001) in patients with concomitant ACS and T2DM undergoing PCI. After adjustment of model 1 for covariates, the Gensini score (HR, 1.005; 95% CI, 1.002–1.008; P = 0.002) remained a risk factor for MACCEs.

In addition, we studied the association between MACCEs and the combination of the Gensini score and neutrophil count in patients receiving PCI who had both ACS and T2DM. A high Gensini score and a high neutrophil count combined (HR, 2.136; 95% CI, 1.609–2.835; P < 0.001) were found to be independent risk factors for MACCEs in univariate analysis. An elevated risk of MACCEs was associated with a high Gensini score and a high neutrophil count (HR, 1.512; 95% CI, 1.005–2.274; P = 0.047).

In conclusion, we were able to forecast the potential outcomes of patients who had PCI with concurrent ACS and uncontrolled T2DM by using the neutrophil count and Gensini score. Neutrophil count, the Gensini score, and their combination were independent risk factors for MACCEs (Table 3). The ROC curve indicated that patients with a high Gensini score and a high neutrophil count had the shortest survival (Figure 2). Therefore, the neutrophil count and Gensini score together can predict the outcomes of patients undergoing PCI who have concurrent ACS and uncontrolled T2DM.

Limitations

This study has several limitations. First, it had a single center design and a modest sample size. To support our findings, large-scale, multi-center cohort studies should be performed, ideally in patients from diverse ethnic groups.

Conclusion

According to our findings, the Gensini score and neutrophil count can be used to forecast the incidence of MACCEs in patients undergoing PCI who have concurrent ACS and uncontrolled T2DM. The number of neutrophils was associated with the Gensini score. The Gensini score and neutrophil count can be combined to improve their prognostic value for clinical outcomes.

Data Sharing Statement

In the absence of legal or ethical issues, the dataset will be provided by the corresponding authors upon reasonable request. For ethical reasons, the dataset has not been publicly shared.

Ethics Statement

This study underwent formal clinical trial registration. The study's design may be found on http://www.chictr.org.cn (identifier: ChiCTR-2200055450). The Helsinki Declaration was strictly followed in this study, which was given permission by the Ethical Committee of Zhengzhou University's First Affiliated Hospital.

Author Contributions

YX and ZQ did the literature search and wrote the original manuscript. JT conceived the idea and provided financial support. JT polished the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest

According to the authors, there are no apparent conflicts of interest with this study.

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