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Article

Correlation between Mean Platelet Volume and Gensini Score in Patients with Coronary Heart Disease in Different Diabetic States

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Abstract

Subject: To investigate the correlation between mean platelet volume (MPV) levels and Gensini scores in stable coronary heart disease (CHD) patients with or without diabetes. **Methods**: A retrospective analysis was conducted on 2525 patients with stable CHD in Zhongshan Hospital, Fudan University. There were 1274 in the low MPV group and 1251 in the high MPV group, divided by a median MPV level of 10.9 fL. In the total population, 1605 patients were non-diabetic and 920 were diabetic. The severity of coronary artery disease was quantified using the Gensini score. **Results**: The Gensini score was significantly higher in the high MPV group than in the low MPV group ($p < 0.001$). MPV levels increased significantly with the number of stenotic (>50%) coronary vessels ($p < 0.001$). The Spearman analysis showed a positive correlation between MPV and Gensini score (r = 0.189, $p < 0.001$), which was more significant in the diabetic subgroup (r = 0.232, $p < 0.001$). Receiver operating characteristic (ROC) curves were employed to assess the predictive value of MPV for high Gensini scores, using the median value of 32 points as the cutoff. MPV levels in the diabetes cohort exhibited a higher predictive value for high Gensini scores (area under the curve: 0.635 [0.614–0.657], $p < 0.001$). Multivariate linear regression analysis showed that diabetes and MPV were independently associated with Gensini scores. **Conclusion**: MPV levels in stable CHD patients can predict the severity of coronary artery stenosis. This correlation is more significant in the presence of diabetes.

Keywords

coronary artery disease; mean platelet volume; diabetes; Gensini score

Introduction

With the growing concern surrounding the challenges posed by an aging population, the incidence of coronary heart disease (CHD) is on a steady rise. In China, the death rate due to CHD reached 121.59/100,000 in urban areas and 130.14/100,000 in rural areas in 2019, marking a continuous upward trend since 2012 [1,2]. As the burden of CHD increases, there is an urgent need for early prediction and diagnosis of cardiovascular events in patients with CHD. Researchers worldwide are dedicated to this cause, striving to enhance prognosis and minimize the economic toll associated with CHD.

It is generally believed that coronary atherosclerosis is a chronic inflammatory disease, characterized by a complex interplay of inflammatory factors [3]. Among individuals with diabetes, insulin resistance and hyperglycemia result in oxidative stress and irreversible damage to endothelial cells. This damage leads to the release of various inflammatory factors, including C-reactive protein, tumor necrosis factor α, and interleukin-6 (IL-6), thereby increases the inflammatory response [4].

Platelets, essential for physiological processes such as thrombosis and hemostasis, also play a pivotal role in the pathophysiology of CHD [5]. When the endothelium of coronary artery is damaged, platelets aggregate at the site of injury, releasing a series of platelet-activating factors. This event stimulates further activation of surrounding platelets, resulting in increased inflammation and injury to vascular endothelial cells [5]. Consequently, antiplatelet therapy plays a central role in preventing thrombosis and ischemic events in CHD [6].

Activated platelets undergo morphological changes, transitioning from their typical disc-shaped form to a more spherical shape, with the formation of pseudopodia. This transformation corresponds with an increase in the mean platelet volume (MPV) [7]. MPV serves as a valuable pa-

rameter, reflecting the average platelet size in the bloodstream and offering a reliable means of assessing platelet activation [7].

While MPV has been the subject of numerous studies in field of CHD, the relationship between MPV and CHD in individuals with diabetes remains unknown [8,9]. This study sought to determine the association between MPV and the severity of coronary artery disease in stable CHD patients, both with or without diabetes.

Methods

Study Design and Patient Selection

This study is a single-center retrospective study, conducted within the Cardiology Department of Zhongshan Hospital, Fudan University, spanning from January 2019 to December 2021. The study enrolled a cohort of 2525 patients who had undergone coronary angiography (CAG) and received a diagnosis of stable coronary heart disease (CHD). The diagnostic criteria for stable CHD necessitated CAG was the presence of at least one major vascular stenosis with a severity of $\geq$50% in a major coronary artery, namely, the left anterior descending artery and its branches, the left circumflex artery and its branches, and the right coronary artery and its branches. Patients reported experiencing paroxysmal squeezing chest pain triggered by physical activity, emotional excitement, or other factors. The pain could radiate for several minutes and was alleviated with rest or the use of nitrates [6]. Type 2 diabetes (T2DM) was defined in accordance with the 2022 national standards of the American Diabetes Association, which included the presence of diabetes symptoms along with blood glucose levels exceeding 11.1 mmol/L at any time, fasting blood glucose levels surpassing 7.0 mmol/L, or blood glucose levels exceeding 11.1 mmol/L after two hours [10].

All patients included in this study were aged 18 years or older. Exclusion criteria consisted of the following: (1) patients with severe liver or kidney dysfunction, severe infection, systemic immune disease, malignant tumor, thyroid disease, or type 1 diabetes; (2) individuals with left main trunk disease; (3) incomplete data or CAG images for the patient.

Clinical Data Collection

The histories of patients were collected from the hospital's electronic medical record system. Subsequently, blood samples were drawn on the morning following admission which included glycated hemoglobin (HbA1c), white blood cell count (WBC), platelet count (PLT), platelet crit (PCT), MPV, platelet distribution width (PDW), total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

CAG and Gensini Score

CAG was performed through the patients' radial or femoral arteries, using the Jundkin method, which involved multi-angle and multi-position imaging. At least two cardiologists analyzed the CAG results to evaluate the degree of coronary stenosis in each patient. The Gensini score was employed as a quantitative measure of CHD severity [10]. The records were categorized as follows: Normal if no abnormality or $<$50% stenosis was observed, 1-vessel, 2-vessel and 3-vessel disease according to the number of major coronary vessels with stenosis $\geq$50%.

Statistical Analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Differences in continuous variables between groups were compared via *t*-tests or one-way ANOVA variance analysis. Categorical variables were represented in terms of frequency (n) and percentage (%), with inter-group comparisons analyzed using chi-square tests. Spearman correlation analysis was used to evaluate the correlation between MPV and Gensini scores in diabetes and non-diabetes patients. Receiver operation characteristic (ROC) curve analysis was conducted to assess the predictive value of MPV for the presence of high Gensini scores. High Gensini scores were defined using the median value of 32 points. In order to establish the independent relationship of MPV, diabetes status and Gensini score, potential confounding factors were included in the univariate regression analysis. Variables with $p < 0.05$ were further subjected to multi-factor linear regression analysis to calculate the standardized regression coefficient (β).

Statistical analysis was conducted using SPSS 26.0 software (IBM Corp., Armonk, NY, USA), and a two-tailed p value of $<$0.05 was considered statistically significant.

Results

Patient Data

Among the 2525 patients diagnosed with CHD, the median MPV was 10.9 fL, which was used as the cutoff point. Patients with MPV $\leq$10.9 fL were classified as the low MPV group (n = 1274), while those with MPV $>$10.9 fL were classified as the high MPV group (n = 1251). The unequal distribution of patients between the two groups may be attributed to the discrete nature of MPV values in the dataset, resulting in a concentration of patients around the median MPV value of 10.9 fL and eventually leading to unequal group sizes. The high MPV group exhibited significantly higher incidences of diabetes, Gensini score, coronary artery lesions, HbA1c, and PDW, all with $p < 0.001$. Conversely, PLT and PCT levels were lower in the high MPV group, also with $p < 0.001$. Among the en-

Table 1. Baseline characteristics stratified by MPV levels or the status of diabetes.

	MPV ≤10.9 fL	MPV >10.9 fL	*p*	Non-Diabetes	Diabetes	*p*
	(n = 1274)	(n = 1251)		(n = 1605)	(n = 920)	
Gender, male	971 (76.2%)	944 (75.5%)	0.580	1217 (75.8%)	698 (75.9%)	0.967
Age, years	64.82 ± 10.11	65.07 ± 10.70	0.435	64.70 ± 10.54	65.39 ± 10.13	0.033
BMI, kg/m^2	24.70 ± 3.60	24.72 ± 3.56	0.835	24.66 ± 3.46	24.80 ± 3.79	0.228
Smoking, n (%)	710 (55.7%)	671 (53.6%)	0.167	881 (54.9%)	500 (54.3%)	0.727
Hypertension	582 (45.7%)	574 (45.9%)	0.896	674 (42.0%)	482 (52.4%)	<0.001
T2DM, n (%)	371 (27.3%)	549 (43.9%)	<0.001	-	-	-
Gensini score	28.0 [12.0–50.0]	36.0 [15.0–74.0]	<0.001	28.0 [12.0–56.0]	36.0 [18.0–68.0]	<0.001
1-vessel disease	701 (55.0%)	578 (46.2%)		875 (54.5%)	404 (43.9%)	
2-vessel disease	377 (29.6%)	378 (30.2%)	<0.001	448 (27.9%)	307 (33.4%)	<0.001
3-vessel disease	196 (15.4%)	295 (23.6%)		282 (17.6%)	209 (22.7%)	
HbA1c, %	6.29 ± 1.11	6.61 ± 1.39	<0.001	5.84 ± 0.60	7.51 ± 1.43	<0.001
WBC, 10^9/L	7.20 ± 2.36	7.28 ± 2.51	0.249	7.22 ± 2.44	7.28 ± 2.43	0.456
PLT, 10^9/L	222.76 ± 60.02	190.52 ± 55.31	<0.001	208.60 ± 58.62	204.33 ± 62.31	0.023
PCT, %	0.23 ± 0.06	0.22 ± 0.06	<0.001	0.22 ± 0.05	0.22 ± 0.06	0.203
MPV, fL	10.09 ± 0.57	11.87 ± 0.74	<0.001	10.80 ± 1.09	11.25 ± 1.07	<0.001
PDW, %	11.39 ± 1.32	14.26 ± 2.44	<0.001	12.62 ± 2.41	13.07 ± 2.40	<0.001
TC, mmol/L	3.83 ± 1.03	3.85 ± 1.11	0.418	3.76 ± 1.06	3.89 ± 1.07	<0.001
TG, mmol/L	1.53 [1.07–2.24]	1.51 [1.06–2.24]	0.118	1.62 [1.14–2.40]	1.47 [1.02–2.16]	<0.001
LDL-C, mmol/L	2.34 ± 0.92	2.36 ± 0.97	0.423	2.26 ± 0.94	2.39 ± 0.94	<0.001
HDL-C, mmol/L	1.10 ± 0.31	1.05 ± 0.30	<0.001	1.03 ± 0.29	1.10 ± 0.31	<0.001

Data were presented as either n (%), mean ± SD, or median [interquartile range]. Statistical analysis for continuous data across multiple groups involved employing ANOVA or non-parametric tests. Categorical data were assessed using the chi-square test or the Fisher exact two-tailed test. *p*-values less than 0.05 were regarded as statistically significant. BMI, body mass index; T2DM, type 2 diabetes mellitus; HbA1c, glycated haemoglobin; WBC, white blood cell count; PLT, platelet count; PCT platelet crit; MPV, mean platelet volume; PDW, platelet distribution width; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

tire cohort, 920 patients (36.4%) had a history of diabetes. Patients with diabetes displayed significantly higher MPV levels compared to those without diabetes ($p < 0.001$). In addition, age, history of hypertension, Gensini score, number of coronary vessels with stenosis >50%, HbA1c, PLT, PDW, TC, TG, LDL-C, HDL-C also exhibited statistically significant differences between the two groups ($p < 0.05$) (Table 1).

Comparison of CAG Results at Different MPV Levels

The Gensini score of patients with high MPV was significantly higher than that of patients with low MPV (Fig. 1). Additionally, there was a significant increase in MPV as the number of vessels with stenosis greater than 50% increased (Fig. 2). These trends were particularly pronounced among patients with diabetes (Fig. 1b, Fig. 2b).

Correlation analysis using Spearman's method involving MPV and Gensini scores revealed a positive correlation (r = 0.189, $p < 0.001$, Fig. 3a). This positive correlation was more pronounced among patients with diabetes (r = 0.232, $p < 0.001$, Fig. 3b). In contrast, within the non-diabetic cohort, the observed correlation, while still significant, was comparatively weaker, suggesting a less robust relationship between MPV and Gensini scores in this subgroup (r = 0.141, $p < 0.001$, Fig. 3c).

To evaluate the predictive value of MPV for high Gensini scores, we used ROC curves and defined high Gensini scores by the median value, which was 32 points. The optimal cut-points of MPV were determined to be 10.8, 10.9, and 10.7 fL for the whole cohort, diabetes patients, and non-diabetes patients, respectively. Notably, MPV levels in the diabetes cohort provided a more accurate prediction for high Gensini scores compared to the entire cohort (Area under the ROC curve (AUC): 0.635 [0.614–0.657] *vs*. 0.696 [0.662–0.729]) (Fig. 4).

Multivariate Linear Regression Analysis Results of MPV and Gensini Scores

To investigate the correlation between MPV and the severity of coronary stenosis, both univariate and multivariate linear regression analyses were performed, with the Gensini score as the dependent variable, as presented in Table 2. The univariate linear regression analysis revealed significant correlations between male gender, smoking, dia-

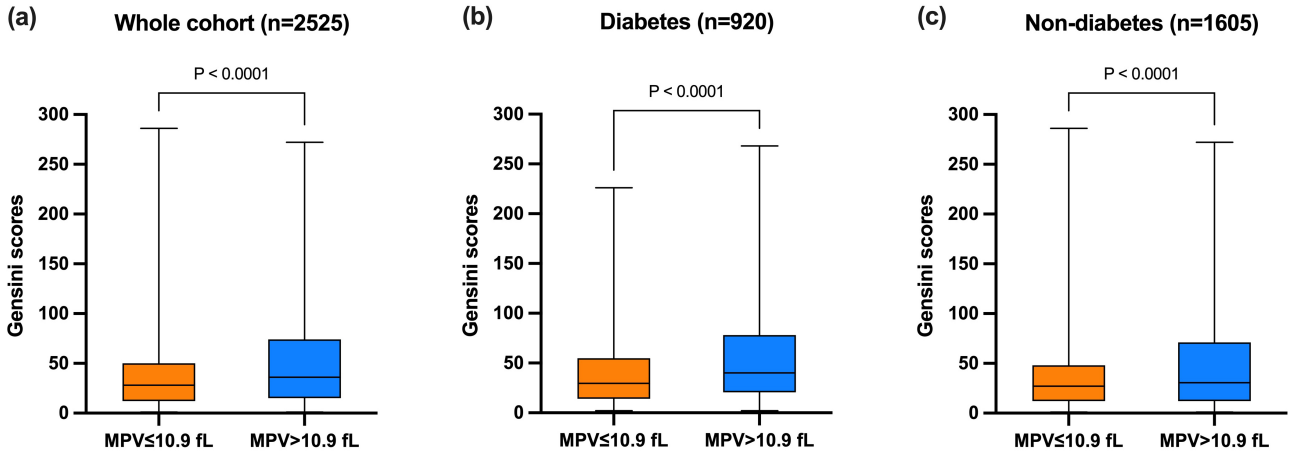

Fig. 1. Gensini score stratified by median value of MPV in patients with or without diabetes. Symbols and error bars represent the medians and interquartile ranges respectively due to skewed distribution of Gensini scores. (a) whole cohort; (b) diabetes cohort; (c) non-diabetes cohort. MPV, mean platelet volume.

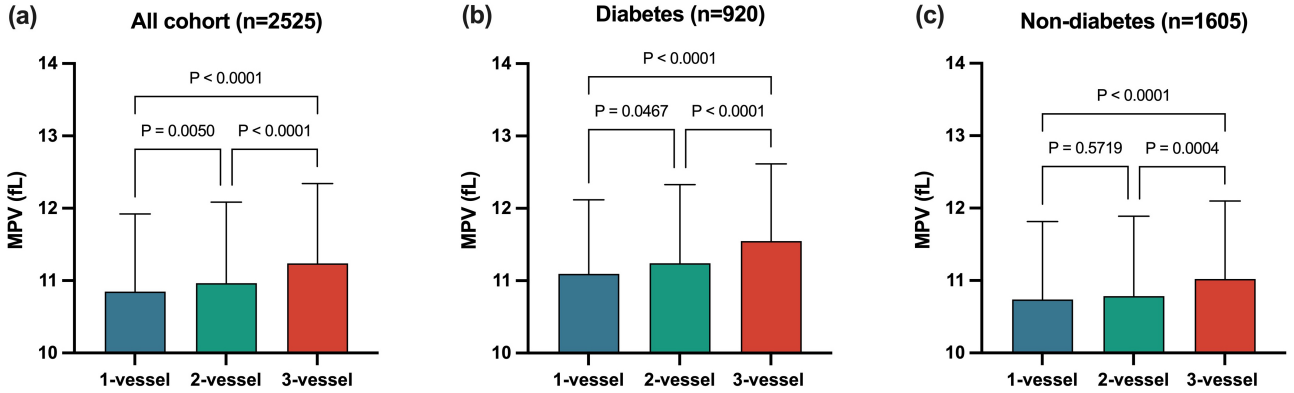

Fig. 2. MPV levels by the number of major coronary vessels with stenosis. Symbols and error bars represent the mean and standard deviation of MPV. 1-vessel, 2-vessel and 3-vessel refer to the number of major coronary vessels with stenosis over 50%. (a) whole cohort; (b) diabetes cohort; (c) non-diabetes cohort. MPV, mean platelet volume.

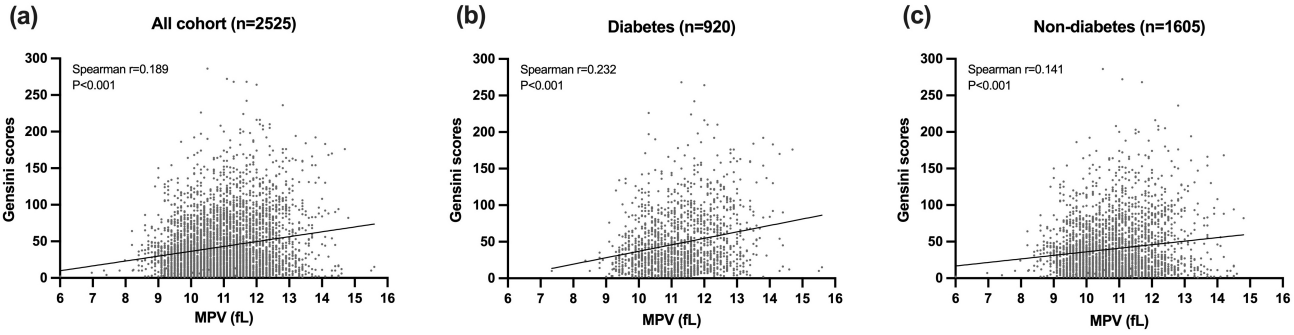

Fig. 3. Association between MPV and Gensini scores according to diabetes status. Spearman's correlation analyses were employed to show the association between MPV and Gensini scores. (a) whole cohort; (b) diabetes cohort; (c) non-diabetes cohort. MPV, mean platelet volume.

betes, LDL-C, HDL-C with Gensini scores. Subsequently, the multivariate analysis incorporated variables with $p < 0.05$, including men, smoking, diabetes, MPV, LDL-C, and HDL-C. Diabetes, MPV, and Gensini scores remained independently and positively correlated (diabetes: $\beta = 0.192$, $p < 0.001$; MPV: 0.208, $p < 0.001$). Additionally, it was identified that LDL-C also constituted an independent risk factor for high Gensini scores ($\beta = 0.103$, $p < 0.001$).

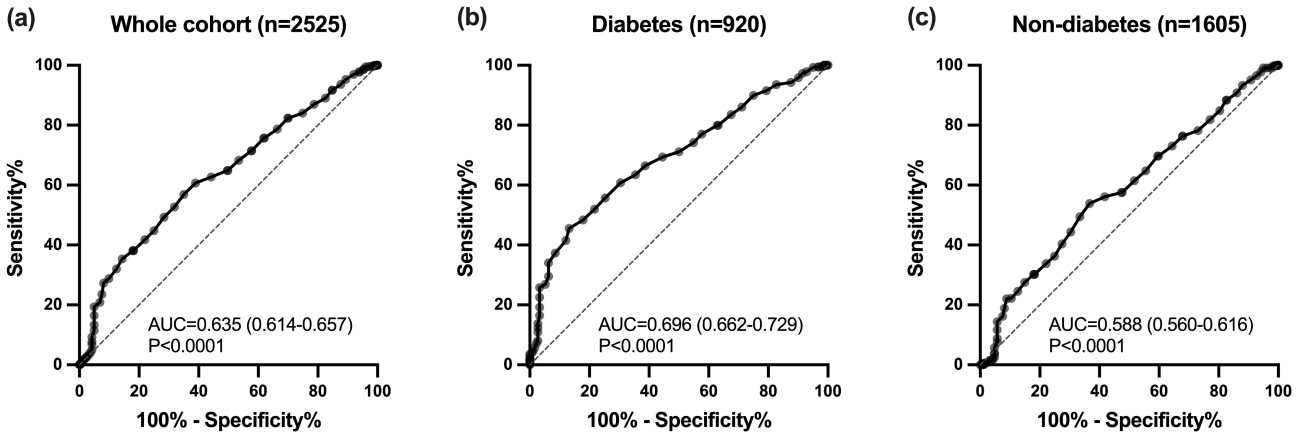

Fig. 4. ROC curves for MPV to determine high Gensini scores stratified by the status of diabetes. Data were expressed as area under ROC curve (AUC) (95% confidence intervals). High Gensini scores were defined by the median value, set at 32 points. (a) whole cohort; (b) diabetes cohort; (c) non-diabetes cohort. ROC, receiver-operating characteristic; MPV, mean platelet volume.

Table 2. Linear regression of MPV and Gensini scores.

Variable	Univariate		Multivariate	
	β	*p*	*β*	*p*
Gender, male	0.105	<0.001	0.075	<0.001
Age	–0.005	0.723		
BMI	0.020	0.184		
Smoking	0.071	<0.001	0.018	0.330
Hypertension	–0.001	0.940		
Diabetes	0.171	<0.001	0.192	<0.001
WBC	0.010	0.741		
PLT	0.021	0.154		
PCT	0.027	0.072		
MPV	0.189	<0.001	0.208	<0.001
PDW	–0.001	0.947		
TC	0.043	0.166		
TG	0.018	0.235		
LDL-C	0.128	<0.001	0.103	<0.001
HDL-C	–0.078	0.012	–0.059	0.143

BMI, body mass index; T2DM, type 2 diabetes mellitus; WBC, white blood cell count; PLT, platelet count; PCT platelet crit; MPV, mean platelet volume; PDW, platelet distribution width; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Discussion

CHD represents a significant global health burden [1]. Diabetes is a well-established independent risk factor for coronary atherosclerosis, and platelet activation plays an important role in coronary artery inflammation and thrombosis [4,5].

The findings of this study align with previous research, underscoring a significant correlation between MPV and Gensini score [8,9]. In addition, MPV has the potential to provide valuable insights for managing not only individuals with CHD but also healthy populations. Notably, the CHD group exhibited significantly elevated MPV levels compared to the non-CHD group [11]. This correlation extends beyond stable CHD patients to those with acute coronary syndrome (ACS), where the relationship between MPV and the degree of coronary stenosis is even more pronounced [12,13]. Studies by Ekici *et al*. [14] and Vogiatzis *et al*. [15] corroborated a positive correlation between MPV and the SYNTAX score in ACS patients.

The stratification of our patient population into subgroups based on the presence or absence of diabetes mellitus is based on a substantial body of scientific evidence that underscores the intricate interplay between diabetes and platelet reactivity. Individuals with diabetes, particularly those with T2DM, commonly present with heightened platelet reactivity, a phenomenon attributed to a range of underlying mechanisms [16]. Hyperglycemia directly influences platelet reactivity by promoting the glycation of platelet proteins [17]. This glycation process reduces membrane fluidity, thereby increasing the propensity for platelet activation [18]. Furthermore, the activation of protein kinase C intensifies this elevation in platelet reactivity due to hyperglycemia [19]. Notably, insulin resistance, frequently observed in individuals with type 2 diabetes, contributes to elevated platelet reactivity [20]. Ordinarily, insulin plays an antagonistic role in countering platelet activation [21]. However, in cases of insulin resistance or deficiency, this antagonistic effect is compromised, ultimately leading to heightened platelet reactivity [21]. Diabetes is also associated with systemic abnormalities, including oxidative stress and inflammation, which further increase platelet reactivity [22]. For example, superoxide, a byproduct of oxidative stress, augments platelet reactivity by enhancing intraplatelet calcium release and inhibiting the biological activity of nitric oxide [23]. These effects promote platelet

activation. Diabetes may directly induce the production of reactive oxygen species via glucose metabolism and auto-oxidation reactions, thereby stimulating the expression of IL-6 that further activate platelets [24].

Our rationale for establishing subgroups based on the presence or absence of diabetes is supported by a substantial body of literature. A comprehensive meta-analysis, which incorporated findings from 39 studies, consistently emphasized the association between increased MPV levels and diabetes, as well as impaired glucose tolerance [25]. This conclusion was further affirmed by a large prospective cross-sectional study in China. In the highest quantile of MPV, there was a significant risk of diabetes [26]. These results solidify the relationship between diabetes and altered platelet reactivity and emphasize the significance of our subgroup analysis in exploring this intricate relationship.

In addition, this study found a correlation between LDL-C and Gensini score through multivariate linear regression analysis. Elevated levels of LDL-C represent crucial risk factors for coronary plaque formation [27]. LDL-C assumes a role in the formation of oxidized low-density lipoprotein (ox-LDL) under conditions of oxidative stress. Ox-LDL interacts with platelets through receptors such as CD36 and LOX-1, expediting plaque rupture and thrombus formation. Diabetes, characterized by insulin resistance, shifts energy usage toward fatty acids rather than glucose, contributing to elevated rates of total cholesterol (TC) and triglyceride (TG) synthesis in the liver. Consequently, diabetes patients often exhibit higher blood lipid levels [24].

In summary, this study underscores the positive correlation between MPV, a routine platelet parameter, and the Gensini score, indicative of the severity of coronary artery disease. This implies that MPV could complement conventional risk factors in clinical decision-making. This relationship is more pronounced in diabetes patients, suggesting that patients with diabetes may require more potent and sustained antiplatelet therapy. Moreover, for patients with diabetes, stringent blood glucose control is crucial to reduce the occurrence of adverse cardiovascular events. These findings offer novel insights for future clinical diagnosis and treatment strategies, encouraging personalized care in CHD management that potentially leads to more effective interventions and improved patient outcomes. Furthermore, our results provide opportunities to explore tailored treatment approaches, such as high-dose statins or PCSK9 inhibitors, for specific patient subgroups based on their MPV levels or diabetes status, resulting in improved cardiovascular care.

This study has several limitations. First, based on the single-center retrospective nature, the study may entail inherent biases in the patients' selection process, potentially affecting the generalizability of the findings. Second, the analysis may not encompass a comprehensive array of laboratory indicators, particularly those related to platelet activation, such as P-selectin and CD36. These parameters are known to play a significant role in the development of CHD. Future studies may consider including these additional indicators to provide a more comprehensive assessment. It is important to note that our study specifically focused on stable CHD patients, and did not study patients with acute coronary syndrome. Further research will be necessary to validate our conclusions in patients with ACS.

Conclusion

In conclusion, our study illuminates a significant correlation between MPV levels and the severity of coronary artery stenosis in CHD patients. Through a retrospective analysis of a substantial patient cohort, we identified a noteworthy elevation in Gensini scores among individuals with higher MPV, particularly in the diabetic subgroup. The positive correlation between MPV and Gensini scores underscores the potential of MPV levels as a predictive marker for assessing the extent of coronary artery disease. Our findings advocate for the inclusion of MPV in risk stratification protocols, especially for those with diabetes, offering valuable insights for enhanced clinical management and tailored interventions in stable CHD patients.

Availability of Data and Materials

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

Author Contributions

QQ was involved in the original draft preparation, while QQ and GZ took responsibility for materials, data collection, and analysis. GP and LW contributed to the analysis and interpretation of the data. HL and YX managed the data collection and processing. WZ and YS contributed to the acquisition of the data and conducted the literature review. YY, QL and QW contributed to the concepetion and design of the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University, under the ethics

number B2022-78R, with approval granted on February 21, 2022. Given the retrospective design of the investigation, patient informed consent forms were exempted as per the Ethics Committee's guidelines.

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Conflict of Interest

The authors declare no conflict of interest.

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