

# Impact of Platelet-to-HDL-Cholesterol Ratio on Long-Term Mortality in Coronary Artery Disease Patients with or Without Type 2 Diabetes: Insights from a Chinese Multicenter Cohort

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**Background:** Inflammation contributes to the initiation and advancement of both coronary atherosclerosis and type 2 diabetes mellitus (T2DM). Recent evidence has underscored the platelet-to-HDL-cholesterol ratio (PHR) as a promising inflammatory biomarker closely linked to the severity of coronary artery disease (CAD). Nevertheless, the risk of adverse clinical outcomes remains unclear among CAD patients with varying PHR levels and glycemic status.

**Methods:** A total of 56,316 CAD patients were enrolled, primarily focusing on mortality outcomes. Patients were categorized into four subgroups based on median baseline PHR values and glycemic status: lower PHR (PHR-L) and higher PHR (PHR-H) with or without T2DM. Cox proportional hazard model and subgroup analysis were employed to investigate the association between PHR and glycemic status with mortality.

**Results:** Over a median 5.32-year follow-up, 8909 (15.8%) patients experienced all-cause mortality, with 3873 (6.9%) deaths attributed to cardiovascular causes. Compared to individuals in PHR-L/non-DM, those in PHR-H/non-DM, PHR-L/DM and PHR-H/DM groups exhibited a higher risk of all-cause death [adjusted hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.06–1.18; HR 1.21, 95% CI 1.14–1.29; HR 1.43, 95% CI 1.34–1.52, respectively], as well as cardiac mortality [HR 1.19, 95% CI 1.08–1.30; HR 1.58, 95% CI 1.44–1.74; HR 1.89, 95% CI 1.72–2.07, respectively]. Cox proportional hazard model also revealed the highest mortality risk among patients in PHR-H/DM compared to other groups ( $P < 0.05$ ). Restricted cubic spline regression analysis revealed a positive linear association between PHR and all-cause as well as cardiac mortality ( $P$  for non-linearity  $> 0.05$ ) after adjustment. Additionally, subgroup analysis indicated consistent effects on cardiac mortality within diverse subsets.

**Conclusion:** In this real-world observational cohort analysis, elevated PHR levels joint with T2DM were related to adverse long-term clinical outcomes in CAD patients. PHR levels may serve as a valuable tool for identifying high-risk individuals within this specific group.

**Trial Registration:** The Cardiorenal Improvement II registry NCT05050877.

**Keywords:** platelet-to-HDL-cholesterol ratio, coronary artery disease, diabetes, all-cause mortality, cardiovascular mortality

## Introduction

Inflammation plays a pivotal role in the initiation and progression of coronary atherosclerosis.<sup>1</sup> A growing body of evidence underscores a remarkable link between increased levels of inflammatory biomarkers and worse clinical outcomes among patients with coronary artery disease (CAD).<sup>2–6</sup> Notably, previous research has indicated the significance of platelets, functioning as both indicators of inflammation and core components in the coagulation cascade, in evaluating the co-occurrence and comorbidity of type 2 diabetes mellitus (T2DM) and CAD.<sup>7</sup> Furthermore, prior investigation indicated serum platelet counts within normal range ( $100\text{--}450\times 10^9/\text{L}$ ) were found to be positively correlated with new-onset T2DM.<sup>8</sup> In addition, another study demonstrated that higher platelet counts were observed in contrast-induced acute kidney injury (CI-AKI) group with DM compared to non-CI-AKI-DM group ( $224.8\pm 62.8\times 10^9/\text{L}$  vs  $197.9\pm 63.3\times 10^9/\text{L}$ ,  $P=0.014$ ) among invasively treated acute myocardial infarction patients, and elevated platelet counts were independent risk factors for CI-AKI-DM patients.<sup>9</sup>

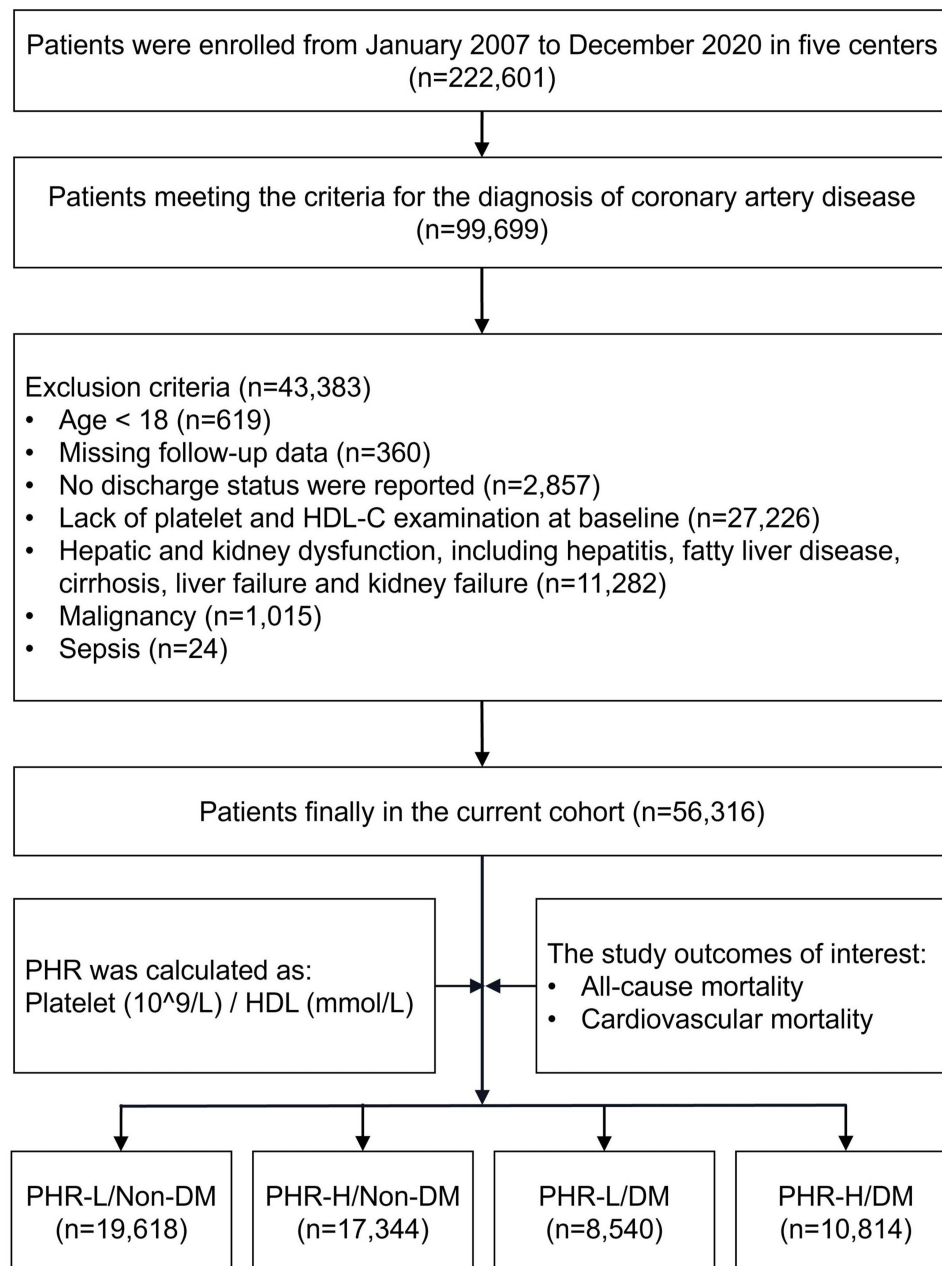
Conversely, high-density lipoprotein (HDL) has been shown to exhibit several anti-thrombotic effects.<sup>10,11</sup> Specifically, HDL plays a crucial role in facilitating the efflux of dietary cholesterol through the reverse cholesterol transport pathway and exerts anti-inflammatory as well as anti-coagulation effects.<sup>12–14</sup> Thus, reduced HDL levels may potentially contribute to the development of CAD by diminishing cholesterol efflux and anti-inflammatory capacities.<sup>15</sup> In addition, lower HDL levels were strongly related to a higher risk of composite cardiovascular events in a substantial sample of overweight or obese individuals diagnosed with T2DM.<sup>16</sup> Therefore, both platelet counts and HDL are critical indicators of hemorheological and inflammatory alterations. Recent publications have substantiated the significant association between the platelet-to-HDL-cholesterol ratio (PHR), comprising these two indicators, and a higher incidence of non-alcoholic fatty liver disease,<sup>17</sup> as well as an increased severity of metabolic syndrome.<sup>18</sup> Considering that T2DM represents a manifestation of metabolic syndrome, it is conceivable that PHR may be a potential biomarker to evaluate the severity of T2DM.

Inflammation is recognized as a common underlying factor in the pathophysiology of both atherosclerosis and type 2 diabetes mellitus.<sup>3,19,20</sup> T2DM, widely recognized as a risk factor for CAD, consistently exhibits a close relationship with increased atherosclerotic plaque deposition and a heightened risk of unfavorable cardiovascular outcomes.<sup>21,22</sup> Nevertheless, the association between PHR level, glycemic metabolism, and long-term mortality among CAD patients remains relatively unexplored. To address this gap, the current research aimed to investigate the interplay between PHR and markers of glucose metabolism. Furthermore, it sought to evaluate the combined effect of PHR and T2DM on the long-term risk of mortality among patients with CAD.

## Methods

### Study Population

Data for this retrospective study were taken from the Cardiorenal Improvement II cohort registry (CIN-II, NCT05050877), a multi-center study that enrolled patients from five prominent tertiary hospitals in China. Over the period from January 2007 to December 2020, a total of 99,699 individuals were diagnosed with CAD. The study excluded individuals presenting with malignancy, sepsis, kidney failure and hepatic dysfunction, as well as those aged  $<18$  years, lacking baseline platelet counts and HDL values, discharge status and follow-up data, and/or other specific exclusion criteria (in-depth overview of the recruitment process shown in [Figure 1](#)). Eventually, 56,316 patients with CAD were enrolled in the current research and categorized into four subsets: PHR-L/Non-DM ( $N=19,618$ ), PHR-L/DM ( $N=8540$ ), PHR-H/Non-DM ( $N=17,344$ ) and PHR-H/DM ( $N=10,814$ ). This classification was based on the median of baseline PHR levels and diverse glycemic metabolism states. This study followed the principles of the Declaration of Helsinki and obtained approval from the Ethics Committee of Guangdong Provincial People's Hospital, with each participating site securing institutional review board clearance from local ethics committees. All identifiable personal information was removed from the database to safeguard patient privacy. Given the retrospective focus of this study, no additional intervention was required. The utilized data was anonymized, eliminating the necessity for patient informed consent.



**Figure 1** Flow Chart of the Study.

## Data Collection

This study collected data from the electronic clinical management system, which includes baseline information such as demographic features, coexisting conditions, laboratory tests, treatments during hospitalization, and discharge medications. For the test of PHR levels at admission, participants were required to undergo a fasting period (>8 h) prior to blood sample extraction. Routine blood tests, glycated haemoglobin (HbA1C), platelet counts, total cholesterol, triglycerides (TG), HDL and low-density lipoprotein (LDL) were taken on the same day and tested by standard laboratory methods. Platelet levels were assessed using Sysmex-XN9000 (Sysmex Co., Kobe, Japan). HDL, total cholesterol, TG and LDL levels were measured using an automatic biochemistry analyzer (Hitachi 7600, Tokyo, Japan) and assayed by an enzymatic method according to the manufacturer's instructions. The determination of comorbidities relied on preadmission diagnoses or diagnoses established during hospitalization. Follow-up information was obtained through the

alignment of survival data sourced from the Centers for Disease Control and Prevention. Senior cardiologists supervised quality control and performed periodic data verification procedures.

## Clinical Outcome and Definition

The study outcomes were cardiovascular and all-cause mortality. PHR was calculated as the plasma platelet counts ( $10^9/L$ ) divided by the plasma HDL-cholesterol level (mmol/L). CAD was confirmed through coronary angiography, with the main artery exhibiting stenosis exceeding 30%, and in one of the remaining three coronary vessels, stenosis exceeded 50%. The American Diabetes Association standards for HbA1c were employed in the definition of diabetes. Patients with HbA1c levels exceeding 47.5 mmol/L (6.4%) or with recorded hypoglycemic treatment were diagnosed with type II diabetes. Chronic kidney disease was identified as the discharge diagnosis and  $eGFR < 60 \text{ mL/min/1.73m}^2$ . Congestive heart failure (CHF) was defined as New York Heart Association class  $> 2$  or Killip class  $> 1$  and confirmed at discharge. Diagnoses of acute myocardial infarction, anemia, atrial fibrillation (AF), hypertension, hyperlipidemia, stroke, cancer, sepsis, hepatitis, fatty liver disease, liver cirrhosis and liver failure were ascertained in accordance with the International Classification of Diseases, the tenth revision.

## Statistical Analysis

Continuous variates were summarized as means (SD) or medians (IQR), while categorical variates were presented as counts and percentages. The comparison among groups was evaluated utilizing one-way ANOVA, the Kruskal–Wallis test, and the Pearson chi-square test for continuous variates with normal or nonnormal distributions and categorical variates, respectively. The associations between baseline PHR, T2DM and clinical outcomes were illustrated by hazard ratio (HR, 95% CI) employed by Cox proportional hazard models. The PHR-L with Non-DM group served as the reference group. The study utilized stepwise Cox regression analysis and considered clinical importance to carefully select covariates included in the multivariate model. Three models were established sequentially: 1) without adjustment; 2) with adjustment for age and sex; 3) with further adjustment for covariates in Model 2, including LDL, TG, use of antiplatelets, use of statins, AF, anemia, chronic kidney disease, hypertension, CHF, stroke and percutaneous coronary intervention. Restricted cubic spline (RCS) was adopted to visualize the potential linear correlation between PHR and all-cause and cardiac mortality in CAD patients, adjusting for the same covariates as mentioned above. The correlation between PHR and other laboratory parameters (HbA1c, monocytes and procalcitonin) was evaluated by Pearson correlation test. Additionally, exploratory analyses were conducted for evaluating the impact of PHR and glycemic metabolism states on cardiac as well as all-cause mortality in specific subgroups and presented as a forest plot, stratified by various demographic characteristics, comorbidities as well as laboratory examinations, including age, sex, LDL, TG, acute myocardial infarction, hypertension, chronic kidney disease and stroke. Statistical analyses were conducted using R software (version 4.2.1), and GraphPad Prism software (version 9.4.1). Statistical significance was determined by a two-tailed P value below 0.05.

## Results

In total, 56,316 patients (63.2 $\pm$ 10.8 years, 75.4% male) meeting the inclusion criteria and successfully completing the follow-up were eventually included in the current research (Figure 1). Over a median follow-up of 5.32 (3.39–7.87) years, 8909 (15.8%) patients experienced all-cause mortality, with 3873 (6.9%) deaths attributed to cardiovascular causes.

## Baseline Characteristics

As shown in Table 1, participants were stratified into four subgroups based on the baseline PHR median level and their glycemic metabolism status, with the distribution in each subgroup as follows: PHR-L/Non-DM (N=19,618), PHR-L/DM (N=8540), PHR-H/Non-DM (N=17,344) and PHR-H/DM (N=10,814). Individuals with T2DM tended to be female when in contrast to those without T2DM. Compared with patients in the PHR-L/Non-DM group, ones in the remaining three subgroups exhibited a higher prevalence of percutaneous coronary intervention and comorbidities, such as hypertension, hyperlipidemia and anemia. Laboratory indices, including TG, fibrinogen, monocytes, procalcitonin and serum

**Table 1** Baseline Characteristics of Entire Population Stratified by PHR Levels and Glycemic Metabolism Status

Characteristics	Overall (N=56,316)	PHR-L/Non-DM (N=19,618)	PHR-H/Non-DM (N=17,344)	PHR-L/DM (N=8540)	PHR-H/DM (N=10,814)	P value
PHR	233.8±86.1	166.8±33.4	296.3±69.4	171.5±32.1	304.2±74.7	<0.0001
<b>Demographic characteristics</b>						
Age, years	63.2±10.8	64.7±10.7	60.7±11.1	65.5±9.8	62.8±10.2	<0.0001
Female, n(%)	13,864 (24.6)	4886 (24.9)	3235 (18.7)	2706 (31.7)	3037 (28.1)	<0.0001
<b>Coexisting conditions</b>						
CHF, n(%)	9069 (16.1)	3035 (15.5)	2549 (14.7)	1550 (18.1)	1935 (17.9)	<0.0001
CKD, n(%)	11,821 (21.0)	3714 (18.9)	3016 (17.4)	2200 (25.8)	2891 (26.7)	<0.0001
Hypertension, n(%)	31,055 (55.1)	9773 (49.8)	8942 (51.6)	5291 (62.0)	7049 (65.2)	<0.0001
Hyperlipemia, n(%)	38,001 (67.5)	9371 (47.8)	14,466 (83.4)	4736 (55.5)	9428 (87.2)	<0.0001
Atrial fibrillation, n(%)	2251 (4.0)	915 (4.7)	510 (2.9)	461 (5.4)	365 (3.4)	<0.0001
Anemia, n(%)	1013 (1.8)	303 (1.5)	278 (1.6)	162 (1.9)	270 (2.5)	<0.0001
Stroke, n(%)	3314 (5.9)	1097 (5.6)	867 (5.0)	555 (6.5)	795 (7.4)	<0.0001
AMI, n(%)	13,052 (23.2)	4343 (22.1)	4700 (27.1)	1671 (19.6)	2338 (21.6)	<0.0001
PCI, n(%)	40,978 (72.8)	13,246 (67.5)	13,196 (76.1)	6140 (71.9)	8396 (77.6)	<0.0001
<b>Laboratory examination</b>						
APOA (g/L)	1.2±0.3	1.3±0.3	1.1±0.2	1.2±0.3	1.0±0.2	<0.0001
APOB (g/L)	0.9±0.3	0.9±0.3	0.9±0.3	0.9±0.3	0.9±0.3	0.0065
TC (mmol/L)	4.6±1.3	4.8±1.3	4.5±1.2	4.8±1.3	4.4±1.2	<0.0001
TG (mmol/L)	1.7±1.2	1.4±0.9	1.8±1.2	1.6±1.3	2.0±1.4	<0.0001
LDL-C (mmol/L)	2.9±1.0	3.0±1.1	2.9±1.0	3.0±1.1	2.8±1.0	<0.0001
HDL-C (mmol/L)	1.0±0.3	1.2±0.3	0.9±0.2	1.1±0.2	0.9±0.2	<0.0001
HbA1c (%)	6.5 (1.5)	5.7±0.4	5.8±0.5	7.7±1.7	7.8±1.6	<0.0001
WBC (10 <sup>9</sup> /L)	8.8±55.7	8.7±71.9	8.9±25.4	8.2±12.8	9.5±75.0	0.3641
Monocytes (10 <sup>9</sup> /L)	0.6±0.3	0.6±0.3	0.7±0.3	0.6±0.3	0.7±0.3	<0.0001
Procalcitonin (ng/mL)	1.9±1.6	1.6±1.1	2.2±1.0	1.6±1.5	2.3±2.5	<0.0001
Hemoglobin (g/L)	134.2±17.2	135.5±16.2	135.4±17.0	133.1±17.4	130.8±18.4	<0.0001
Albumin (g/L)	37.5±4.4	38.0±4.3	37.2±4.4	37.6±4.4	36.8±4.6	<0.0001
Fibrinogen (g/L)	4.0±1.3	3.6±1.1	4.2±1.3	3.8±1.1	4.4±1.3	<0.0001
Platelet (10 <sup>9</sup> /L)	226.8±59.1	194.4±41.4	261.2±54.4	190.3±41.3	259.2±55.7	<0.0001
CKMB (U/L)	28.2±93.4	35.0±97.5	26.3±112.1	26.0±71.1	20.7±62.6	<0.0001
SCr (umol/L)	1.1±1.4	1.0±1.1	1.1±0.6	1.1±1.7	1.2±2.4	<0.0001
<b>Medicine</b>						
β-blockers, n(%)	43,871 (79.9)	14,434 (76.1)	13,898 (81.6)	6643 (80.1)	8896 (83.8)	<0.0001
Statins, n(%)	52,994 (96.5)	18,261 (96.3)	16,512 (96.9)	7968 (96.0)	10,253 (96.6)	0.0005
CCB, n(%)	10,206 (18.6)	3195 (16.8)	2844 (16.7)	1834 (22.1)	2333 (22.0)	<0.0001
ACEI/ARB, n(%)	38,881 (70.8)	12,734 (67.1)	12,110 (71.1)	6129 (73.9)	7908 (74.5)	<0.0001
Antiplatelets, n(%)	53,505 (97.4)	18,342 (96.7)	16,668 (97.8)	8062 (97.2)	10,433 (98.3)	<0.0001
<b>Events</b>						
All-cause mortality, n(%)	8909 (15.8)	2774 (14.1)	2501 (14.4)	1561 (18.3)	2073 (19.2)	<0.0001
Cardiovascular mortality, n(%)	3873 (6.9)	1025 (5.2)	982 (5.7)	790 (9.3)	1076 (10.0)	<0.0001

**Abbreviations:** PHR, platelet-to-HDL-cholesterol ratio; CHF, congestive heart failure; CKD, chronic kidney disease; AMI, acute myocardial infarction; PCI, percutaneous coronary interventions; APOA, apolipoprotein A-I; APOB, apolipoprotein B; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; WBC, white blood cell; CKMB, creatine kinase MB; SCr, serum creatinine; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

creatinine, exhibited significantly elevated levels in individuals with higher PHR levels combined with T2DM, while levels of apolipoprotein A, HDL, total cholesterol, LDL, hemoglobin, albumin and Creatine Kinase-MB were relatively lower.

## Prognostic Significance of PHR in Conjunction with Glycemic Metabolism Status on All-Cause Mortality

The occurrence of all-cause mortality across the four subgroups was as follows: PHR-L/Non-DM: 14.1% (2774/19,618), PHR-H/Non-DM: 14.4% (2501/17,344), PHR-L/DM: 18.3% (1561/8540) and PHR-H/DM: 19.2% (2073/10,814). As shown in Table 2, Cox regression analysis was employed to assess the prognostic value among patients with varying PHR levels, with or without T2DM. In the crude model, PHR-H/Non-DM, PHR-L/DM and PHR-H/DM patients showed an increased risk of overall mortality (HR 0.98, 95% CI 0.93–1.04,  $P=0.502$ ; HR 1.29, 95% CI 1.21–1.37,  $P<0.001$ ; HR 1.38, 95% CI 1.31–1.47,  $P<0.001$ ; respectively) compared to those in the reference group. After adjustment for age, sex, LDL, TG, use of antiplatelets, use of statins, anemia, AF, chronic kidney disease, CHF, hypertension, stroke and percutaneous coronary intervention, the result remained statistically robust in multivariate analysis (adjusted HR 1.12, 95% CI 1.06–1.18,  $P<0.001$ ; adjusted HR 1.21, 95% CI 1.14–1.29,  $P<0.001$ ; adjusted HR 1.43, 95% CI 1.34–1.52,  $P<0.001$ ; respectively). Additionally, Cox proportional regression analysis also indicated that patients with PHR-H/DM exhibited the highest risk of all-cause mortality in contrast to other groups, which was consistent with the observed trend in cardiovascular mortality (Figure 2A and B,  $P<0.001$ ). Furthermore, RCS analysis unveiled a linear correlation between PHR and the risk of all-cause death after adjustments (Figure 3A,  $P$  for non-linearity  $>0.05$ ).

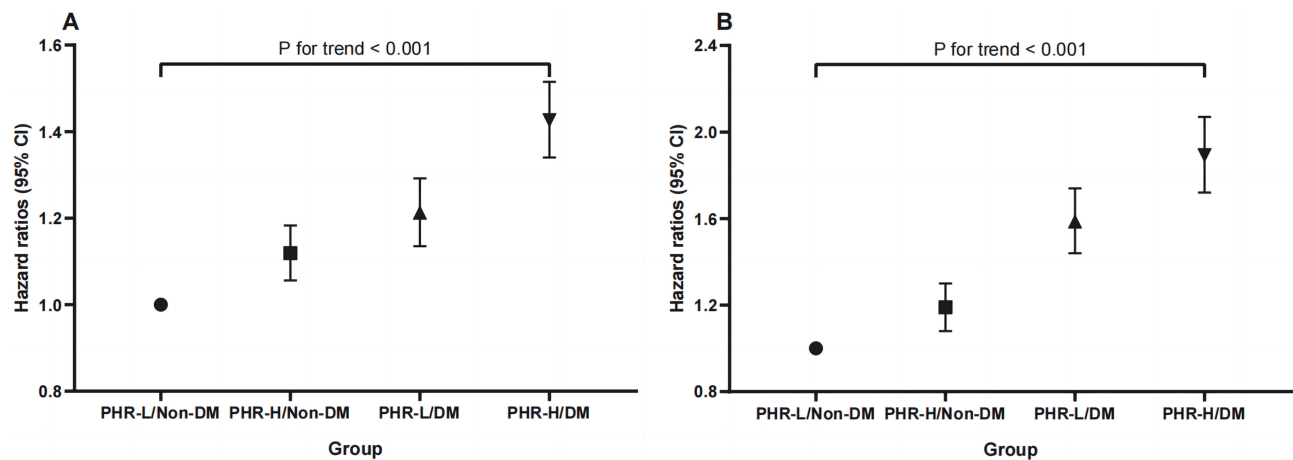
## Association of PHR Combined with Glycemic Metabolism Status with Cardiovascular Mortality

The incidence of cardiovascular mortality was observed as follows: PHR-L/Non-DM, PHR-L/DM, PHR-H/Non-DM and PHR-H/DM were 5.2% (1025/19,618), 9.3% (790/8540), 5.7% (982/17,344) and 10.0% (1076/10,814). After adjustment for potential confounders (Table 2), multivariate Cox regression analysis demonstrated that the PHR-H/Non-DM, PHR-L/DM and PHR-H/DM groups were consistently correlated with a gradually increased likelihood of cardiovascular mortality when compared to the reference group. The HRs and 95% CIs were as follows: PHR-H/Non-DM – HR 1.19, 95% CI 1.08–1.30,  $P<0.001$ ; PHR-L/DM – HR 1.58, 95% CI 1.44–1.74,  $P<0.001$ ; PHR-H/DM – HR 1.89, 95% CI 1.72–2.07,  $P<0.001$ . Additionally, RCS analysis indicated a linear relationship between PHR and the risk of cardiovascular mortality after adjustments (Figure 3B,  $P$  for non-linearity  $=0.292$ ).

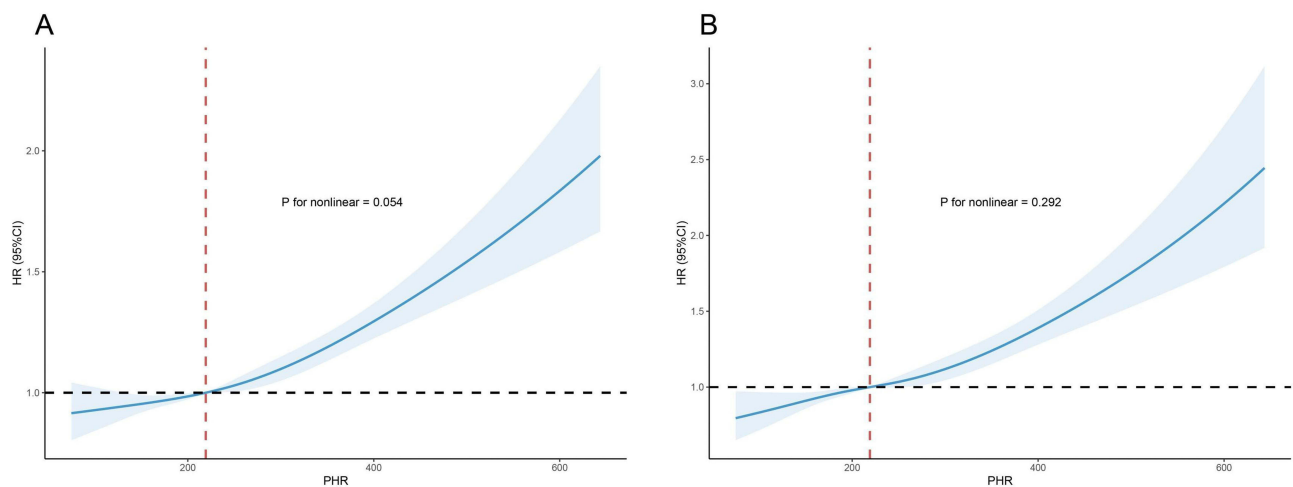
**Table 2** Predictive Value of the PHR Level and Glycemic Metabolism Status for All-Cause and Cardiovascular Mortality

PHR	Events/Subjects	Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>All-cause mortality</b>	8909/56,316						
PHR-L/Non-DM	2774/19,618	Ref	–	Ref	–	Ref	–
PHR-H/Non-DM	2501/17,344	0.98 (0.93–1.04)	0.502	1.14 (1.08–1.20)	<0.001	1.12 (1.06–1.18)	<0.001
PHR-L/DM	1561/8540	1.29 (1.21–1.37)	<0.001	1.27 (1.19–1.35)	<0.001	1.21 (1.14–1.29)	<0.001
PHR-H/DM	2073/10,814	1.38 (1.31–1.47)	<0.001	1.52 (1.43–1.61)	<0.001	1.43 (1.34–1.52)	<0.001
<b>Cardiovascular mortality</b>	3873/56,316						
PHR-L/Non-DM	1025/19,618	Ref	–	Ref	–	Ref	–
PHR-H/Non-DM	982/17,344	1.04 (0.95–1.14)	0.363	1.26 (1.15–1.37)	<0.001	1.19 (1.08–1.30)	<0.001
PHR-L/DM	790/8540	1.76 (1.61–1.93)	<0.001	1.74 (1.58–1.90)	<0.001	1.58 (1.44–1.74)	<0.001
PHR-H/DM	1076/10,814	1.95 (1.79–2.12)	<0.001	2.19 (2.01–2.39)	<0.001	1.89 (1.72–2.07)	<0.001

**Notes:** Model 1: Not adjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, LDL, TG, use of antiplatelets, use of statins, AF, anemia, chronic kidney disease, hypertension, CHF, stroke and percutaneous coronary intervention.



**Figure 2** Hazard ratios (95% CIs) for all-cause (A) and cardiovascular mortality (B) according to four subgroups. The analysis adjusted for age, sex, low-density lipoprotein, triglycerides, use of antiplatelets, use of statins, atrial fibrillation, anemia, chronic kidney disease, hypertension, congestive heart failure, stroke and percutaneous coronary intervention.



**Figure 3** The association between PHR and glycemic metabolism status with all-cause (A) and cardiovascular mortality (B). Model adjusted for age, sex, low-density lipoprotein, triglycerides, use of antiplatelets, use of statins, atrial fibrillation, anemia, chronic kidney disease, hypertension, congestive heart failure, stroke and percutaneous coronary intervention.

## Correlation Analysis of PHR and HbA1c/Monocytes/Procalcitonin

Pearson correlation analysis was conducted to assess the correlation between PHR and glycemic metabolism status (Table 3). PHR was positively correlated with admission HbA1c in the whole cohort ( $R = 0.080$ ,  $P < 0.001$ ), and the results were consistent between the T2DM cohort and non-T2DM cohort ( $R = 0.041$ ,  $P < 0.001$ ;  $R = 0.019$ ,  $P = 0.001$ ). Furthermore, we evaluated the correlation between PHR and monocytes as well as procalcitonin, which are considered as inflammatory indicators. Results demonstrated PHR showed modestly positive correlations with monocytes and procalcitonin ( $R = 0.166$ ,  $P < 0.001$ ;  $R = 0.240$ ,  $P < 0.001$ , respectively).

## Subgroup Analysis

Further analysis of post-hoc subgroup data demonstrated consistent interactions in relation to cardiac mortality across every subset and covariates (sex, age, LDL, TG, hypertension, stroke, acute myocardial infarction and chronic kidney disease) (Figure 4 and Table S1). Among CAD patients, those with both PHR-H and combined with T2DM exhibited a significantly increased risk of mortality, irrespective of the stratification of the aforementioned covariates. Upon closer inspection of age and TG levels ( $P$ -value for interaction  $< 0.05$ ), patients in the subset of age under 65 years and TG levels

**Table 3** Correlation Analysis of PHR and HbA1c/Monocytes/Procalcitonin

Variables	R	P value
<b>Whole cohort</b>		
HbA1c, %	0.080	<0.001
Monocytes, 10 <sup>9</sup> /L	0.166	<0.001
Procalcitonin, ng/mL	0.240	<0.001
<b>T2DM cohort</b>		
HbA1c, %	0.041	<0.001
Monocytes, 10 <sup>9</sup> /L	0.151	<0.001
Procalcitonin, ng/mL	0.194	<0.001
<b>Non-T2DM cohort</b>		
HbA1c, %	0.019	0.001
Monocytes, 10 <sup>9</sup> /L	0.173	<0.001
Procalcitonin, ng/mL	0.310	<0.001

**Abbreviations:** PHR, platelet-to-HDL-cholesterol ratio; HbA1c, glycosylated hemoglobin A1c.

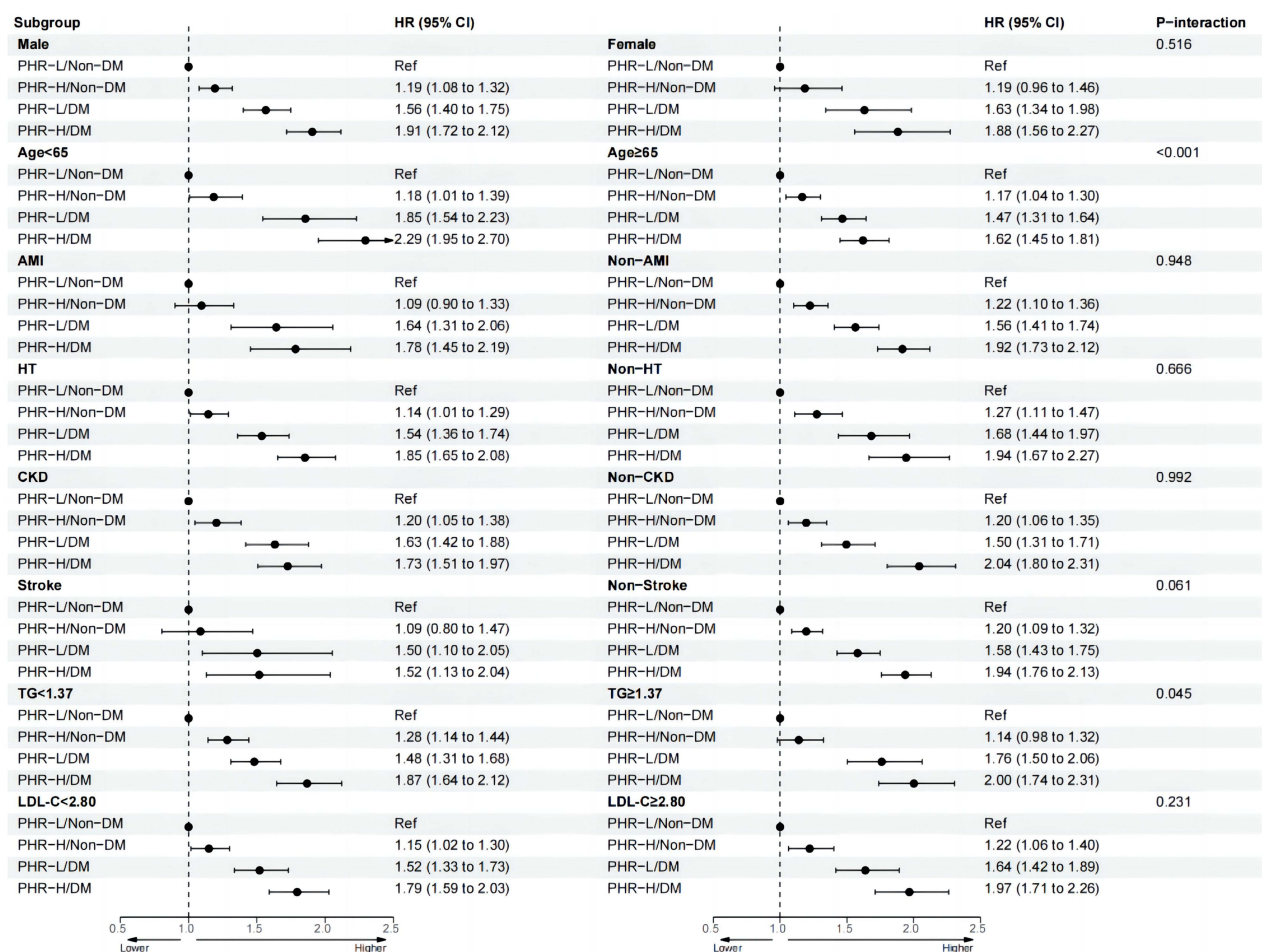
≥1.37 mmol/L were notably correlated with increased cardiac mortality events. Additionally, patients with PHR-L/DM, PHR-H with or without T2DM exhibited consistent characteristics in relation to all-cause mortality across most subsets, except for those with TG levels below 1.37 mmol/L, compared to individuals in the reference group. An interaction effect was observed considering all-cause death among subgroups based on baseline age (age <65 and ≥65) and LDL levels (LDL <2.80 mmol/L and ≥2.80 mmol/L) (P for interaction <0.05) ([Figure S1](#) and [Table S2](#)).

## Discussion

Derived from a real-world, multi-center observational study encompassing a substantial cohort from China, the study investigated the prognostic implication of T2DM on long-term mortality in individuals with different PHR levels. The current analysis demonstrated that diabetic patients with elevated PHR levels exhibited a significant increase in all-cause and cardiac mortality in comparison to individuals in lower PHR groups. Additionally, lower PHR levels in non-diabetic individuals revealed a reduced risk of adverse clinical outcomes compared to ones with higher PHR levels and T2DM. Cox proportional regression analysis further demonstrated that individuals with PHR-H and T2DM experienced the utmost risk of mortality in comparison to other sets. Furthermore, in subgroup analysis, the study identified interactions between adverse outcomes among subgroups based on baseline age (age <65 and ≥65) and TG levels (TG <1.37 mmol/L and ≥1.37 mmol/L) (P for interaction <0.05), suggesting potential clinical trials for specific therapeutic interventions. These findings emphasize the crucial necessity for more accurate risk assessment in diabetic patients with elevated PHR levels.

Platelets, produced by megakaryocytes in the bone marrow, contribute to the pathogenesis of inflammation and thromboembolic processes, thereby actively participating in the development of coronary atherosclerosis.<sup>1,23,24</sup> Numerous studies have previously clarified the connection between platelets and inflammation in the advancement of atherogenesis and CAD.<sup>25–27</sup> For instance, a prospective study recently demonstrated that circulating platelet levels independently correlated with worse clinical outcomes in myocardial infarction patients.<sup>28</sup> Another study offers mechanistic evidence that pathological states of platelets in T2DM might contribute to an increased risk for cardiovascular events.<sup>7</sup> Platelets could function as excellent, sensitive cellular indicators for the co-occurrence and comorbidity of T2DM and CAD.<sup>7,8</sup> Additionally, a study involving 135 participants indicated that metabolic syndrome patients have exhibited higher platelet levels, which may serve as markers of a prothrombotic and proinflammatory state and contributors to atherothromboembolic risk.<sup>29</sup>





**Figure 4** Forest plot of cardiovascular mortality according to different subgroups. The analysis with adjustment for age, sex, low-density lipoprotein, triglycerides, use of antiplatelets, use of statins, atrial fibrillation, anemia, chronic kidney disease, hypertension, congestive heart failure, stroke and percutaneous coronary intervention. **Abbreviations:** AMI, acute myocardial infarction; HT, hypertension; CKD, chronic kidney disease; TG, Triglyceride; LDL-C, low density lipoprotein cholesterol.

HDL, the predominant protein in human extracellular fluid, serves as a crucial component in various physiological functions, acting as an anti-inflammatory lipoprotein, a mediator of cholesterol efflux, as well as a repressor of platelet activation and adhesion.<sup>30,31</sup> Numerous observational studies and meta-analyses have consistently illustrated a correlation between reduced serum HDL levels and adverse cardiovascular outcomes.<sup>32,33</sup>

Given the robust association of plasma platelets and HDL as useful inflammatory biomarkers for cardiovascular events, investigating the reciprocal relationship between these two biomarkers, like PHR, may provide a novel approach for identifying high-risk individuals within the CAD population, particularly among those with T2DM.

The platelet-to-HDL-cholesterol ratio, comprising the readily measurable biomarkers aforementioned, emerges as a novel indicator for evaluating the clinical outcomes of patients with metabolic syndrome.<sup>18</sup> As a prospective serum biomarker, PHR has demonstrated superior sensitivity and specificity in predicting cardiovascular risk when compared to platelet and HDL alone.<sup>18,34</sup> To date, some studies have underscored the prognostic value of PHR in various clinical contexts.<sup>17,34,35</sup> For instance, noteworthy findings from Jialal et al found that elevated PHR values in patients progressing towards metabolic syndrome significantly correlated with all cardio-metabolic features, suggesting its potential as both a marker for metabolic syndrome and a promising predictor of cardiovascular risk and thrombotic incidents.<sup>18</sup> Furthermore, Szymańska et al observed significantly higher PHR levels in subgroups with elevated blood glucose ( $P = 0.041$ ) and increased body mass index ( $P = 0.001$ ), highlighting its potential in stratifying patients based on glucose and body mass index.<sup>35</sup> In addition to its correlation with metabolic syndrome and cardiovascular risk, prior investigations

have shown that elevated PHR levels are associated with stenosis in multiple coronary arteries, correlating with CAD severity measured by Gensini score.<sup>34</sup>

Moreover, substantial evidence has established the well-acknowledged pathological mechanism of chronic inflammation underlying both T2DM and cardiovascular disease (CVD).<sup>3,36</sup> Notably, prior studies have indicated that T2DM considerably elevates worse clinical events in CVD patients.<sup>37,38</sup> Our study unveiled a positive association between PHR and the glycemic metabolism index marker (HbA1c) in our CAD cohort. This underscores the importance of investigating the combined impact of PHR and T2DM on prolonged negative outcomes in individuals with CAD. Nevertheless, there is insufficient literature on the intricate interplay among PHR, diverse glycemic metabolism and the occurrence of mortality. In addition to PHR, C-peptide, released alongside insulin, serves as an indicator of pancreatic  $\beta$  cell reserve has been shown to reverse adverse impacts of high glucose levels on vasculature through its anti-inflammatory and antioxidant properties.<sup>39,40</sup> In a study by Toprak et al, the impact of C-peptide and DM on coronary artery ectasia (CAE) and long-term cardiovascular outcomes in patients undergoing coronary angiography was investigated. Results indicated that higher C-peptide levels were independently associated with CAE, and both CAE and C-peptide emerged as independent predictors for major adverse cardiovascular events.<sup>41</sup> Furthermore, Toprak et al assessed the role of HbA1c/C-peptide ratio (HCR) for high thrombus burden (HTB) and short-term mortality in ST-elevation myocardial infarction (STEMI) patients. HCR was found significantly higher in the HTB group and strongly correlated with short-term mortality, suggesting its potential as a prognostic marker in STEMI patients.<sup>42</sup>

To the best of our knowledge, our study was the first to reveal a strong association between elevated PHR levels and impaired glycemic metabolism with heightened long-term risks of both all-cause and cardiac mortality. Specifically, non-diabetic patients with lower PHR levels exhibited a diminished risk of adverse clinical outcomes in comparison to those with PHR-H and T2DM. Multivariate Cox proportional hazard model further affirmed the highest incidence of cardiac and all-cause mortality in the PHR-H and T2DM group than others, as indicated by a statistically significant trend ( $P < 0.001$ ).

Given the significant clinical implication of inflammation and diabetes on cardiac risk complications, the simultaneous assessment of diabetes and PHR holds potential clinical enlightenment for effectively managing high-risk populations within the PHR-H/DM group. Nevertheless, to date, no therapeutic approach has been specifically designed for long-term regulation of PHR levels. Further research is essential to ascertain whether individuals with CAD, particularly those with concurrent T2DM, could derive further benefit from future treatments targeting PHR.

This study conducted subgroup analysis to delve further into the contribution of specific factors and assess subsets in which patients exhibit heightened clinical relevance. Our observations revealed that patients in PHR-H with or without T2DM, and PHR-L with T2DM consistently displayed similar clinical characteristics across every subgroup. Remarkably, the current analysis observed significant statistical differences related to cardiac mortality among patients categorized by age ( $<65$  and  $\geq 65$ ) and TG levels ( $<1.37$  mmol/L and  $\geq 1.37$  mmol/L) ( $P$  for interaction  $<0.05$ ). Of note, the cardiovascular death was higher in subgroup of TG levels  $\geq 1.37$  mmol/L than TG  $<1.37$  mmol/L.

Therefore, this approach may enable researchers to design clinical trials for precision therapies (eg, eicosapentaenoic acid ethyl ester (EPA EE), apolipoprotein C3 (APOC3) inhibitors, inclisiran) tailored to specific subgroups, providing more precise guidance for subsequent treatments towards individuals with higher PHR levels and T2DM. In particular, the REDUCE-IT trial (NCT04181996) sought to assess the effect of EPA EE on major adverse cardiac events reduction by lowering TG levels. The outcomes, specifically in patients with T2DM and CAD in this randomized clinical trial have substantiated the safety and efficacy of EPA EE.<sup>43</sup> In conjunction with outcomes of our research, we anticipate favorable outcomes from the diabetic subgroup in the REDUCE-IT trial. Furthermore, the ARO-APOC3 (siRNA) trial (NCT05021835) was particularly conducted to investigate whether inhibiting APOC3 would diminish the risk of cardiac events in individuals with higher TG levels.<sup>44</sup> Studies have shown that patients with T2DM exhibit elevated circulating plasma levels of APOC3 than control patients without diabetes, matched for body mass index.<sup>45</sup> The ongoing trials, VICTORION-2 Prevent (NCT05030428) and ORION-4 (NCT03705234), aim to provide insights into whether low dose inclisiran therapy could potentially confer positive benefits in patients with both clinical CAD and elevated LDL despite statin therapy. However, based on subgroup analysis within this study, it appears evident that addressing inflammation and managing diabetes remain crucial, even in patients with low LDL, which merits further consideration. Notably, any suggestions made here are preliminary, given the inherent constraints of observational research.

Additionally, another crucial aspect for consideration involves potential mechanisms underlying the connection between PHR and T2DM and their impact on unfavorable prognosis. Firstly, earlier research established that activated platelets could upregulate the atherogenic potential of endothelial cells, leading to increased formation of platelet-leukocyte aggregates in plaques.<sup>26,46,47</sup> Furthermore, platelet-released chemokines facilitate the recruitment of immune cells to the plaques, fostering a pro-inflammatory and atherogenic milieu.<sup>48</sup> Additionally, evidence from previous studies suggested that platelets play a crucial role in inflammation, chronic atherogenesis and acute thrombosis, contributing to the progression of CVD, including peripheral arterial disease.<sup>1,24</sup>

Secondly, several basic research studies have proven that physiological state of serum HDL could mitigate endothelial adhesion and activation of leukocytes and platelets.<sup>49</sup> The anti-inflammatory properties of HDL are attributed to its ability to mitigate inflammation and immune activation at atherosclerotic sites, hinting at its athero-protective potential.<sup>12,50</sup> Thirdly, inflammation serves as a common precursor of both atherosclerosis and diabetes.<sup>3,36</sup>

In alignment with prior studies, our results revealed a positive association between PHR and specific glycemic markers. The potential link between T2DM and PHR has been deliberated in earlier discussions.<sup>51,52</sup> Consequently, additional investigations are warranted to explore these potential mechanisms. Moreover, the significance of regular screening for emerging glycemic indicators and inflammatory biomarkers could not be underestimated.

This research presents several limitations. To begin with, the assessment of PHR levels was confined to baseline measurements, lacking an exploration of dynamic variations of this novel biomarker after percutaneous coronary intervention and throughout the follow-up period. Additionally, given the prolonged duration of our study, the biological variations may have impacted platelet counts.<sup>53</sup> It is essential to acknowledge that this study was conducted to provide insights into the role of PHR in long-term mortality among CAD patients. Further investigations are requested to assess if these outcomes could be extrapolated to other cohorts. Secondly, due to the inherent nature of observational studies, it was challenging to adequately adjust for potential confounders. Consequently, additional randomized clinical trials are imperative to validate these results. Thirdly, the CIN-II cohort lacks data regarding GENSINI or SYNTAX scores, risk assessment tools utilized to assess the severity and complexity of CAD. Thus, the potential association between PHR levels and CAD severity could not be explored in this study. Another limitation of our study is that due to insufficient data on C-peptide and insulin, the evaluation of their potential association with adverse clinical outcomes was not available. Moreover, it's essential to acknowledge that this study was carried out exclusively among CAD patients across China and the generalizability of these findings to other populations remains uncertain.

## Conclusion

In this real-world cohort study, elevated PHR levels in conjunction with T2DM appeared to be correlated with unfavorable long-term clinical events in patients with CAD. The measurement of PHR levels may emerge as a valuable tool for identifying specific high-risk population, which deserves more precise risk assessment and management.

## Abbreviations

HDL, High-density lipoprotein; PHR, Platelet-to-HDL-cholesterol ratio; DM, Diabetes mellitus; CAD, Coronary artery disease; CHF, Congestive heart failure; AF, Atrial fibrillation; RCS, Restricted cubic spline; T2DM, Type 2 diabetes mellitus; HbA1c, Glycated haemoglobin; LDL, Low-density lipoprotein; TG, Triglycerides; CVD, Cardiovascular disease; CAE, Coronary artery ectasia; CI-AKI, Contrast-induced acute kidney injury; HCR, HbA1c/C-peptide ratio; HTB, High thrombus burden; STEMI, ST-elevation myocardial infarction; EPA EE, Eicosapentaenoic acid ethyl ester; APOC3, Apolipoprotein C3.

## Data Sharing Statement

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

## Ethics Approval and Consent to Participate

The research obtained ethics approval from the Ethics Committee of the Guangdong Provincial People's Hospital (No. GDREC2019-555H-2). To safeguard patient privacy, all identifiable information was expunged from the analytical

dataset. Institutional review board approval was obtained from respective ethics committees at participating sites. Our database remains inaccessible to the public to uphold participant confidentiality. Given the retrospective nature of our study, no further intervention was undertaken. Patient information was anonymized, obviating the need for informed consent.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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