Prognostic Impact of Remnant-like Particle Cholesterol in Patients with Differing Glucose Metabolic Status: an Observational Cohort Study from China

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Abstract

Background: It is uncertain whether remnant-like particle cholesterol (RLP-C) could predict residual risk in patients under different glucose metabolic status. This study aimed to evaluate the relationship between RLP-C and adverse prognosis in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention (PCI) and identify the potential impact of glucose metabolism on the predictive value of RLP-C.

Methods: The study enrolled 2419 patients with NSTE-ACS who underwent PCI at Beijing Anzhen Hospital from January to December 2015. RLP-C was calculated as follows: total cholesterol (TC) minus low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The primary endpoint was a composite of events as follows: all-cause death, non-fatal myocardial infarction (MI), and ischemia-driven revascularization.

Results: RLP-C was significantly associated with adverse prognosis in the total population [hazard ratio (HR) 1.291 per 1-SD increase of RLP-C, 95% confidence interval (CI) 1.119-1.490, $P < 0.001$], independent of confounding risk factors. However, subgroup analysis showed that increasing RLP-C was shown to be associated with a higher risk of adverse events in the diabetic population only [HR 1.385 per 1-SD increase of RLP-C, 95% CI 1.183-1.620, $P < 0.001$]. RLP-C failed to be a significant determinant of adverse prognosis in the pre-diabetic and non-diabetic population. The addition of RLP-C to the baseline model significantly enhanced the predictive value for adverse events both in the total and diabetic populations.

Conclusions: Higher RLP-C level is a significant and independent predictor of adverse prognosis in diabetic patients with NSTE-ACS who underwent PCI.

Background

As the most serious manifestation of atherosclerotic cardiovascular disease (ASCVD), acute coronary syndrome (ACS) leads to a consistently higher risk of recurrence of cardiovascular events despite the use of evidence-based secondary prevention therapies [1, 2]. Low-density lipoprotein cholesterol (LDL-C) has been extensively recognized as one of the important risk factors for ASCVD and reduction of serum LDL-C levels with statins is an effective therapy to reduce cardiovascular risks [3]. Despite regulating LDL-C with statins, residual risk for recurrence of cardiovascular events remains in patients with ACS [4-7], which indicates that there are factors other than LDL-C that determine risk. Identification of the residual risk factors is important in tailoring risk reduction strategies that match individual risk levels and developing new therapeutic targets.

Studies have reported that the residual risk can be partly ascribed to an increased level of remnant lipoproteins [2, 4, 8, 9]. Remnant lipoproteins are lipoproteins that are rich in triglycerides (TGs), components of which include very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and chylomicron [10]. The cholesterol content of remnant lipoproteins is defined as remnant-like particle cholesterol (RLP-C). Nowadays, the pattern of targeting LDL-C alone has changed, with recent guidelines

highlighting the important role of non-high-density lipoprotein cholesterol (non-HDL-C), which includes RLP-C, on the pathogenesis of atherosclerosis; and thus its availability as an additional therapeutic target [11]. As a component of non-HDL-C, it is of great significance to further clarify the role of RLP-C in the development of coronary atherosclerosis.

The relationship between RLP-C and adverse prognosis in the specific cohort with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention (PCI) were not fully investigated. Results from previous studies have revealed that the impact of RLP-C seems to be more prominent in high-risk patient groups such as patients with metabolic syndrome or type 2 diabetes [12-16]. It is worth exploring whether the predictive value of RLP-C for adverse outcomes varies among populations with different glucose metabolic states. Therefore, the present study was designed to investigate the prognostic impact of RLP-C in patients with NSTE-ACS undergoing PCI and the potential impact of glucose metabolic status on the predictive value of RLP-C.

Methods

Study population

This study retrospectively screened patients with NSTE-ACS who received PCI treatment in Beijing Anzhen Hospital (Beijing, China) from January to December 2015. NSTE-ACS consisted of non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA), whose definitions were determined by the corresponding guidelines [17]. The exclusion criteria were: (1) missing clinical, laboratory, and/or angiographic data; (2) history of cardiogenic shock, chronic inflammatory disease, or neoplasm; (3) evidence of active infection; (4) chronic renal insufficiency with estimated glomerular filtration rate (eGFR) < 30 mL/(min * 1.73 m^2) and severe hepatic disease; (5) other serious diseases; and (6) PCI failure, PCI-related complications, and in-hospital death. Ultimately, 2419 participants who met the inclusion criteria were enrolled.

Data collection and definitions

The enrolled patients' demographic and clinical characteristics, laboratory investigations, and coronary procedural results were retrieved and collected from the medical record system of Beijing Anzhen Hospital. Body mass index (BMI) was calculated as follows: weight (kilogram)/[height (meter)]^2. Participants previously diagnosed with diabetes (treated with diet, insulin, or oral agents) or whose glycosylated hemoglobin A1c (HbA1c) level ≥6.5% were considered to have diabetes. Non-diabetes was defined as a HbA1c level <5.7% and pre-diabetes was defined as an HbA1c level between 5.7% and 6.4% [18].

Venous blood samples were taken after overnight fasting before baseline PCI. Laboratory parameters including lipid profiles [TGs, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C)],

high-sensitivity C-reactive protein (hs-CRP), creatinine, uric acid, fasting blood glucose (FBG), HbA1c, and other biomarkers, were measured by standard methods in the central laboratory of the hospital. Concentrations of TC, HDL-C, and TGs were quantified by standard enzymatic techniques. LDL-C was determined by the homogeneous direct method. RLP-C levels were determined by subtracting LDL-C and HDL-C from TC, which was recommended by relevant dyslipidemia guidelines [19, 20]. The eGFR was calculated as follows: eGFR[mL/(min*1.73m^2)]=186*serum creatinine(mg/dL)$^{-1.154}$*age$^{-0.203}$(*0.742 if female) [21]. Left ventricular ejection fraction (LVEF) was evaluated by two-dimensional modified Simpson's method using an ultrasonic cardiogram (Philips Company, Eindhoven, The Netherlands).

Coronary angiographic data were analyzed and evaluated by visual measurements, and the results were documented and verified by at least two experienced cardiologists. A multi-vessel lesion was defined as more than two main branches with stenosis ≥50%. A chronic total occlusion lesion was defined as a total occlusion [thrombolysis in myocardial infarction (TIMI) flow grade 0] and an occlusion time ≥3 months. A diffuse lesion was defined as a single stenotic lesion with a length ≥20 mm. A bifurcation lesion was defined as the lesion involving the origin of an important side branch. Coronary procedures were carried out based on the current practice guidelines of China [22], and procedure strategies were selected by experienced interventional cardiologists.

Follow-up and endpoint events

After baseline PCI had been performed, all patients received routine follow-up at 3, 6, and 12 months and then annually until 36 months. The prognostic information was obtained by means of telephone interviews with the patient and/or their family members. Corresponding medical records were referred to verify the authenticity in case that ambiguous information was obtained. Adverse events including all-cause death, non-fatal myocardial infarction (MI), and ischemia-driven revascularization were documented to perform the present analysis. The primary endpoint was the composite of adverse events mentioned above, and the secondary endpoint was each component of the primary endpoint. If participants experienced multiple adverse events during the 36-month follow-up, the most severe one (all-cause death>non-fatal MI>ischemia-driven revascularization) was applied to the present analysis. And for those who suffered from the same event multiple times, only the first instance of the event was selected.

Statistical analysis

Continuous variables were presented as mean±standard deviation (SD) or the median (25th and 75th percentiles: P25, P75), and differences between groups were examined by the independent-sample t-test or Mann-Whitney U test as appropriate. Nominal variables were expressed as counts (percentages) and compared by the Chi-square test (χ2 test) or Fisher’s exact test when appropriate. The correlations between RLP-C and other variables were assessed by Pearson correlation test or Spearman’s rank correlation test as appropriate. The Kaplan-Meier survival analysis was performed to evaluate the incidence of adverse events in groups stratified by the median of the RLP-C level. Then, survival curves

were plotted accordingly, and differences between groups were examined by the log-rank test. The univariate Cox proportional hazards analyses were primarily conducted to confirm the significant predictors of adverse events. The variables with statistical significance (P<0.05) in univariate analysis were analyzed with multivariate analysis to investigate the independent determinants of adverse events. The results of Cox proportional hazards analysis were expressed in terms of hazard ratio (HR) and 95% confidence intervals (CI). The HR was examined by 1-SD change in continuous variables except for age, heart rate, systolic blood pressure (SBP), and number of stents.

C-statistics that consisted of receiver-operating characteristic (ROC) curve analysis was applied to assess the additional discriminative performance of RLP-C on the basis of the baseline model that included traditional risk factors. Differences between the area under the ROC curve (AUC) of various models were compared by DeLong's test. Moreover, the incremental reclassification and discrimination ability of RLP-C on the basis of the baseline model for predicting adverse events was further determined by category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

The population was divided into three subgroups according to glycometabolic status: diabetic, pre-diabetic, and non-diabetic groups. Similar statistical analyses were performed for each subgroup. Statistical analyses were conducted by SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA), MedCalc version 19.1 (MedCalc Software, Belgium), and The R Programming Language (version 3.5.1). A two-tailed *P* value of 0.05 was applied to assess statistical significance.

Results

A total of 2419 patients (mean age: 60.08 ± 8.97 years; 71.8% men) were divided into with-event and without-event group. During the 36-month follow-up period, thirty-nine patients (1.6% of the total population) were lost to follow-up, and 454 (18.8%) patients experienced an adverse event, which comprised 21 (0.9%) all-cause deaths, 117 (4.8%) non-fatal MI, and 316 (13.1%) of ischemia-driven revascularization.

Baseline characteristics

The baseline characteristics of each groups were shown in Table 1. The RLP-C levels in participants with an adverse event were significantly higher than that in patients without (0.90±0.61 vs. 0.65±0.35, *P*<0.001). Patients with an adverse event exhibited higher age, BMI, heart rate, SBP, and higher prevalence of previous history of MI, PCI, stroke, and peripheral arterial disease (PAD). In terms of laboratory indicators, participants that developed adverse events had higher levels of TGs, TC, hs-CRP, creatinine, FBG, and HbA1c, but lower levels of HDL-C, eGFR, and LVEF. As for the angiographic findings, those with an adverse event showed higher proportions of left main artery disease, multi-vessel disease, and other characteristics of complex coronary artery lesion.

RLP-C levels were significantly higher in patients with diabetes than pre-diabetes (0.74±0.51 vs 0.68±0.36, *P*=0.003) and non-diabetes (0.74±0.51 vs 0.66±0.37, *P*<0.001). However, there was no significant disparity in RLP-C levels between pre-diabetic and non-diabetic populations (0.68±0.36 vs 0.66±0.37, *P*=0.339) (Figure 1). RLP-C levels were positively correlated with TGs (r=0.853, *P*<0.001), TC (r=0.455, *P*<0.001), and LDL-C (r=0.112, *P* < 0.001), while they were negatively correlated with HDL-C (r=-0.173, *P*<0.001).

Predictive value of RLP-C in total population

The study population was stratified into two groups according to the median of the RLP-C level. Kaplan-Meier curves for the incidence of the composite and each component of endpoint events according to the median of RLP-C were shown in Figure 2. Compared with patients with a lower median of RLP-C, those with a higher median of RLP-C presented with a significantly higher incidence of composite endpoint events (Figure 2A, Log-rank *P*<0.001). The difference was mainly driven by the increased incidence of non-fatal MI (Figure 2C, Log-rank *P*=0.002) and ischemia-driven revascularization (Figure 2D, Log-rank *P*<0.001). Kaplan-Meier curves for all-cause death between the lower and higher RLP-C group failed to reach statistical significance (Figure 2B, Log-rank *P*=0.260).

Multivariate Cox proportional hazard analysis that was adjusted for variables that were statistically significant (*P*<0.05, details shown in Table S1) were performed to assess the predictive value of RLP-C for the composite and each component of the endpoint events. After adjustment of the confounding factors, increased RLP-C levels were consistently observed to be an independent risk indicator of composite endpoint events, non-fatal MI, and ischemia-driven revascularization, despite regarding RLP-C as a nominal or continuous variable (Table 2).

The addition of RLP-C significantly enhanced the AUC obtained from the baseline model adjusted for traditional risk factors including age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease, and multi-vessel disease (AUC: baseline model, 0.798 vs. baseline model+RLP-C, 0.811, *P* for comparison <0.001) (Table 3). Moreover, adding RLP-C to the baseline model significantly promoted the discriminative performance for prediction of adverse events with a category-free NRI of 0.084 and an IDI of 0.017 (both *P*<0.05) (Table 3).

Predictive value of RLP-C in subgroups with various glycometabolic status

The predictive value of RLP-C was further evaluated in subgroups with various glycometabolic status [non-diabetic population (n=926), pre-diabetic population (n=645), diabetic population (n=848)]. Kaplan-Meier curves for the incidence of the composite and each component of the endpoint events according to the median of RLP-C in various subgroups were summarized in Figure 3. In patients with diabetes, the incidence of composite endpoint events, non-fatal MI, and ischemia-driven revascularization in the higher

RLP-C group was significantly higher than that in the lower RLP-C group [Figure 3(i-l)]. The difference was not found in pre-diabetic [Figure 3(e-h)] and non-diabetic [Figure 3(a-d)] patients.

In multivariate Cox proportional hazard analysis, increasing RLP-C levels were shown to be significantly correlated to a higher risk of adverse events in the diabetic population. However, RLP-C failed to be a significant determinant of adverse prognosis in the pre-diabetic and non-diabetic populations (Table 4).

The increased AUC resulting from the addition of RLP-C to the baseline model (AUC: baseline model, 0.788 vs. baseline model+RLP-C, 0.836, *P* for comparison <0.001) was significant in the diabetic population. By contrast, the addition of RLP-C did not show an incremental effect on AUC in the pre-diabetic and non-diabetic populations (Table 5, Figure 4). Furthermore, adding RLP-C to the baseline model prominently promoted the reclassification and discrimination ability for predicting adverse events in the diabetic population with a category-free NRI of 0.155 and an IDI of 0.040 (both $P<0.05$), but the additional effect was not found in the pre-diabetic and non-diabetic populations (Table 5).

Discussion

The present study demonstrated a strong and independent relationship between fasting RLP-C levels and adverse prognosis in patients with NSTE-ACS treated with PCI. Further subgroup analyses elucidated that RLP-C showed a better predictive value in the diabetic population. However, RLP-C failed to be a significant determinant of adverse prognosis in the pre-diabetic and non-diabetic populations. The addition of the RLP-C level had a significant incremental effect on the predictive value for adverse events.

It has been widely demonstrated that LDL-C is one of the most significant risk indicators for ASCVD, and reduction of serum LDL-C levels with statins is a well-established therapy to reduce the ASCVD risk. However, many patients whose LDL-C levels are well controlled by statins continue to suffer recurrent cardiovascular events [3-7]. In recent years, factors related to obesity and metabolic syndrome, such as triglycerides rich lipoproteins (TRLs), have been considered as potential metabolism-related risk factors for cardiovascular diseases and a possible cause of residual risks other than LDL-C. As the cholesterol component of the subset of TRLs, RLP-C has been demonstrated to be a causal risk factor for ischemic heart disease (IHD) [23-25]. Clinical studies also revealed that higher RLP-C levels showed favorable predictive value for the risk of recurrent cardiovascular events in patients with either stable coronary artery disease (SCAD) or ACS, regardless of the baseline treatment of statins and level of LDL-C [12, 26-29]. The current analyses extend these findings to a cohort of patients with NSTE-ACS treated with PCI and indicate that elevated RLP-C is significantly associated with adverse prognosis.

Previous studies have also demonstrated the significant association of RLP-C with plaque characteristics of the coronary arteries, such as plaque burden, composition, and vulnerability. Lina et al. revealed that RLP-C levels were significantly related to coronary atherosclerotic burden evaluated by computed tomography coronary angiography (CTCA), even in patients with optimal LDL-C levels [30]. Puri et al. demonstrated that non-HDL-C levels were closely correlated with the progression and regression of atherosclerotic plaque burden assessed by intravascular ultrasound (IVUS), independent of LDL-C levels

[31]. Matsuo et al. found that in statin-treated patients, RLP-C levels, as opposed to LDL-C levels, were strongly associated with the proportion of plaque necrosis (a marker of plaque vulnerability) evaluated by IVUS [32]. These findings provide important confirmation and interpretation of results from previous clinical studies, suggesting that a high RLP-C level is one of the risk factors for cardiovascular events. Additionally, this correlation between RLP-C and plaque characteristics was observed in the statin-treated and optimal LDL-C level group, indicating that high RLP-C levels may be a residual risk factor in the statin-treated population.

In this study, the LDL-C level did not show predictive value for poor prognosis, which was consistent with previous studies [5, 13, 29]. The underlying causes can be complex. Firstly, most participants that were enrolled in the present study underwent statin therapy, whose lipid-lowering effects in conjunction with other effects may have potential impacts on the association of LDL-C levels with adverse events. Moreover, patients with complex coronary lesions or clinical conditions may be inclined to receive more intensive lipid-lowering therapy. Such treatment selection bias or so-called “confounding by indication” may have a certain influence on the predictive ability of LDL-C. Additionally this may lead to a paradox phenomenon, such as the phenomenon that the use of angiotensin-converting enzyme inhibitors (ACEI) could predict adverse events, which was also present in our study. The present study revealed that RLP-C levels remained a predictor of adverse prognosis despite the probable influence of statin treatment on RLP-C levels, which indicated that RLP-C may have greater atherogenicity than other serum lipid parameters. TGs, TC, and HDL-C lost their predictability in the multivariate Cox proportional hazard analysis using covariates, including RLP-C, in the present study; which can partly be attributed to the strong correlation between them and RLP-C levels.

Results from previous studies have revealed that the impact of RLP-C seems to be more prominent in high-risk patients, such as those with metabolic syndromes or type 2 diabetes [12-16]. Our study also shows that RLP-C has predictive value for poor outcomes only in patients with diabetes, which indicates that there is significant interaction between glycometabolic status and RLP-C level on the risk of an adverse prognosis. Diabetic patients have more complex lipid metabolism disorders than non-diabetic patients characterized by increased TGs levels and decreased HDL-C levels [33]. Therefore, in addition to LDL-C, other lipid-metabolic indicators may also have a certain impact on the cardiovascular risk of diabetic patients. Previous studies have proven that hypertriglyceridemia and high TRLs play an important role in the development of coronary artery disease (CAD) [2, 4, 9]. TGs is predominantly carried by TRLs, which binds to arterial endothelium, where lipoprotein lipase initiates TGs hydrolysis, finally leading to the production of remnant lipoproteins. Thus, the concentrations of TGs are closely related to the cholesterol content of remnant lipoproteins, that is, RLP-C [34, 35]. The association of RLP-C with the TGs level was also verified in the present study. Studies have also shown that RLP-C levels increased in patients with diabetes compared with non-diabetic patients [12, 26, 35], which was consistent with our study. These phenomena may magnify the predictive value of RLP-C for adverse prognosis in patients with recognized diabetes.

Several pathophysiologic mechanisms may account for the association between high RLP-C levels and the increased prevalence of recurrent adverse events which was observed in the current study. These include: (1) RLP-C can upregulate the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, which further induces the migration of monocytes into the arterial wall [36]; (2) RLP-C increases the generation of tissue factors (TF), which is essential for the formation of thrombus in vessels [36]; (3) There is evidence that RLP-C can enhance the aggregation of platelets [37]; (4) RLP-C promotes the propagation of smooth muscle cells that is independent from the impact of oxidative stress [38]; (5) RLP-C is causally related to low-grade inflammation, with a nearly three-fold increase in CRP level for each 1 mmol/L increase in RLP-C [39]; (6) RLP-C was demonstrated to be a risk indicator for endothelial vasomotor dysfunction [16, 40]; and (7) High concentrations of RLP-C were proven to be correlated to inflammation in the arterial wall in cases of endothelial injury [41]. The pro-inflammatory and pro-atherothrombotic roles of RLP-C listed above may be the explanation for the relationship between high RLP-C levels and future adverse prognosis observed in the current study.

Studies have shown that less than a quarter of patients exhibited an LDL-C level below the guideline-recommended target, despite remaining on statin therapy during the secondary prevention period [28, 42]. This so-called “treatment gap” between the target value and clinical practice is common in the real world. In this context, while regarding LDL-C as the primary target, the exploration of residual risk factors can also provide complementary therapeutic strategies for reducing cardiovascular risk. The relationship between high RLP-C levels and increased incidence of recurrent adverse events in diabetic patients with NSTE-ACS treated with PCI demonstrated by the present study shows that RLP-C may be a complementary risk predictor and therapeutic target.

Previous reports showed that lipid-lowering agents, such as fibrates, ezetimibe, and statins, as well as diet adaptation, proper aerobic exercise, and obesity reduction, may effectively decrease RLP-C levels to varying degrees [26, 43, 44], thus enabling RLP-C as a therapeutic target. However, in addition to statin treatment for LDL-C, it is uncertain whether RLP-C should be a therapeutic target in recognized CAD patients. Clinical trials of non-statin, lipid-lowering treatments have shown significant benefit in reducing residual risk, but none have specifically targeted RLP-C. Newer agents, such as potent omega-3 fatty acid derivatives [45] or antisense oligonucleotide to apolipoprotein C-III [46], were proven to have the potential to reduce TRLs significantly and may provide useful tools for answering this question. In JELIS (Japan EPA Lipid Intervention Study), eicosapentaenoic acid (an omega-3 fatty acid derivative) combined with low-dose statins reduced triglycerides by about 5% and coronary events by 19% compared to low-dose statins alone [47]. Novel inhibitors of apolipoprotein C-III, a key regulator of remnant metabolism, have also shown promising results [48]. Furthermore, antibodies to PCSK9, although primarily intended to lower LDL-C concentrations, was also proven to reduce the cholesterol contained in TRLs to some extent [49].

Nowadays, the pattern of targeting LDL-C alone has changed, with recent guidelines highlighting the important role of non-high-density lipoprotein cholesterol (non-HDL-C), which includes RLP-C, on the

pathogenesis of atherosclerosis and thus its availability as an additional therapeutic target [11]. Therefore, it is necessary to develop new therapies targeting RLP-C and conduct randomized trials evaluating whether lowering the RLP-C level can regulate plaque morphology and reduce the residual risk of substantial cardiovascular events.

The major strengths of present study were the long-term follow-up period and the large number of the enrolled subjects. This observational cohort study also expanded the relationship between RLP-C and poor outcomes to a specific cohort of patients with NSTE-ACS undergoing PCI. Additionally, the prognosis impact of RLP-C was evaluated in patients with differing glucose metabolic status. However, there are some limitations to our study: (1) Remnant lipoproteins mainly contain VLDL and chylomicron remnants. In the fasting state of the present study, VLDL remnants are the major constituent of circulating remnants, so that the contribution of chylomicron remnants to atherosclerosis and plaque burden may have been underestimated [50]. (2) Although potentially not as accurate as direct measurement, calculated remnant cholesterol as used in our study can be easily performed on a standard lipid profile without any additional cost. (3) Although evidence-based statin treatment was administrated, no specific statin agent or dose was specified. (4) Finally, although sequential surveillance may provide more information, only baseline lipid profiles before PCI were obtained in our study.

Conclusions

Increased RLP-C levels was a significant and independent predictor of adverse prognosis in diabetic patients with NSTE-ACS undergoing PCI, as opposed to in the subgroup of pre-diabetic and non-diabetic populations. The addition of the RLP-C levels had a significant incremental effect on the predictive value for adverse events, especially in diabetic patients. The current study indicated that the measurement of RLP-C may be important, not only for evaluating the risk of adverse prognosis, but also for tailoring treatment to prevent impending cardiovascular events in specific populations, such as diabetic patients. Further studies investigating whether appropriate therapeutic strategies targeting RLP-C levels can significantly improve the prognosis of CAD patients are needed to be proceeded.

Abbreviations

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; ACS: acute coronary syndrome; RLP-C: remnant-like particle cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; HbA1c: glycosylated hemoglobin A1c; TGs: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; HR: hazard ratio; CI: confidence intervals; SD: standard deviation; ROC: receiver-operating characteristic; BMI: body mass index; SBP: systolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; FBG: fasting blood glucose; LVEF: Left ventricular ejection fraction; AUC: area under the curve; NRI: net reclassification improvement; IDI: integrated discrimination improvement; TRLs: triglycerides rich lipoproteins; IVUS: intravascular ultrasound; CAD: coronary artery disease; VLDL: very-low-density lipoprotein.

Declarations

Ethics approval and consent to participate

Given the retrospective nature of the current study, the requirement for informed consent was waived. The study protocol was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed for this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

QZ (first author) and TYZ made substantial contributions to study design, data collection, data analysis, and manuscript writing. YJZ (corresponding author) made substantial contributions to study design and intellectual direction. They contributed equally to this work. YJC, YM, YKX, JQY made contributions to data collection and analysis. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline clinical characteristics of the study population.

	Total population, n = 2419	Without event, n = 1965	With event, n = 454	*P*
Age, years	60.08 ± 8.97	59.60 ± 8.72	62.16 ± 9.70	**< 0.001**
Male, n (%)	1737 (71.8)	1422 (72.4)	315 (69.4)	0.203
BMI, kg/m²	26.21 ± 3.45	26.13 ± 3.40	26.55 ± 3.61	**0.019**
Heart rate, bpm	69.77 ± 10.15	69.44 ± 10.00	71.17 ± 10.69	**0.002**
SBP, mmHg	130.30 ± 16.52	129.80 ± 15.99	132.44 ± 18.50	**0.005**
DBP, mmHg	77.05 ± 9.90	77.00 ± 9.68	77.25 ± 10.80	0.661
Smoking, n (%)	1381 (57.1)	1127 (57.4)	254 (55.9)	0.585
Drinking, n (%)	562 (23.2)	468 (23.8)	94 (20.7)	0.157
Family history of CAD, n (%)	254 (10.5)	203 (10.3)	51 (11.2)	0.572
Medical history, n (%)				
Hypertension	1511 (62.5)	1210 (61.6)	301 (66.3)	0.061
Prior MI	527 (21.8)	348 (17.7)	179 (39.4)	**< 0.001**
Prior PCI	414 (17.1)	280 (14.2)	134 (29.5)	**< 0.001**
Prior CABG	55 (2.3)	23 (1.2)	32 (7.0)	**< 0.001**
Prior stroke	281 (11.6)	204 (10.4)	77 (17.0)	**< 0.001**
Prior PAD	84 (3.5)	63 (3.2)	21 (4.6)	0.137
Glycometabolic status				
Non-diabetes	926 (38.3)	829 (42.2)	97 (21.4)	**< 0.001**
Pre-diabetes	645 (26.7)	531 (27.0)	114 (25.1)	0.406
Diabetes	848 (35.1)	605 (30.8)	243 (53.5)	**< 0.001**
Laboratory results				
TGs, mmol/L	1.84 ± 1.32	1.69 ± 1.05	2.47 ± 2.00	**< 0.001**
TC, mmol/L	4.17 ± 1.06	4.14 ± 1.05	4.33 ± 1.07	**0.001**

LDL-C, mmol/L	2.50 ± 0.88	2.50 ± 0.89	2.50 ± 0.85	0.962
HDL-C, mmol/L	0.98 ± 0.23	0.99 ± 0.24	0.92 ± 0.21	**< 0.001**
RLP-C, mmol/L	0.69 ± 0.42	0.65 ± 0.35	0.90 ± 0.61	**< 0.001**
hs-CRP, mg/L	1.29 (0.58, 3.31)	1.22 (0.53, 3.06)	1.87 (0.77, 4.29)	**< 0.001**
Creatinine, μmol/L	76.00 ± 16.95	75.68 ± 16.49	77.42 ± 18.76	**0.048**
eGFR, ml/(min*1.73m²)	93.49 ± 20.36	94.09 ± 20.11	90.91 ± 21.22	**0.003**
Uric acid, μmol/L	346.22 ± 82.64	346.45 ± 81.45	345.21 ± 87.69	0.774
FBG, mmol/L	6.20 ± 1.94	6.01 ± 1.71	7.03 ± 2.57	**< 0.001**
HbA1c, %	6.29 ± 1.21	6.14 ± 1.08	6.96 ± 1.51	**< 0.001**
LVEF, %	63.92 ± 6.81	64.50 ± 6.20	61.42 ± 8.56	**< 0.001**
Initial diagnosis, n (%)				**0.001**
UA	2018 (83.4)	1662 (84.6)	356 (78.4)	
NSTEMI	401 (16.6)	303 (15.4)	98 (21.6)	
Medical treatment, n (%)				
ACEI	734 (30.3)	577 (29.4)	157 (34.6)	**0.029**
ARB	948 (39.2)	753 (38.3)	195 (43.0)	0.068
Aspirin	2417 (99.9)	1963 (99.9)	454 (100.0)	0.496
Clopidogrel	2415 (99.8)	1963 (99.9)	452 (99.6)	0.109
β-Blocker	2199 (90.9)	1780 (90.6)	419 (92.3)	0.255
Statins	2366 (97.8)	1922 (97.8)	444 (97.8)	0.985
Oral hypoglycemic agents	437 (18.1)	314 (16.0)	123 (27.1)	**< 0.001**
Insulin	232 (9.6)	154 (7.8)	78 (17.2)	**< 0.001**
Angiographic data, n (%)				
Left main disease	110 (4.5)	64 (3.3)	46 (10.1)	**< 0.001**

Multi-vessel disease	1631 (67.4)	1225 (62.3)	406 (89.4)	**< 0.001**
Chronic total occlusion	345 (14.3)	202 (10.3)	143 (31.5)	**< 0.001**
Diffuse lesion	605 (25.0)	431 (21.9)	174 (38.3)	**< 0.001**
Bifurcation lesion	492 (20.3	368 (18.7)	124 (27.3)	**< 0.001**
Number of stents	1.96 ± 1.29	1.87 ± 1.14	2.33 ± 1.76	**< 0.001**

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PAD, peripheral arterial disease; TGs, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c glycated hemoglobin A1c; LVEF, left ventricular ejection fraction; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Multivariate Cox analysis evaluating the predictive value of RLP-C for composite and each component of endpoint events in the total population.

	RLP-C as a nominal variable*			RLP-C as a continuous variable**		
	HR	95% CI	*P*	HR	95% CI	*P*
Primary endpoint	1.960	1.558-2.465	**< 0.001**	1.291	1.119-1.490	**< 0.001**
All-cause death	2.207	0.612-7.959	0.226	1.829	0.837-3.995	0.130
Non-fatal MI	1.883	1.195-2.966	**0.006**	1.330	1.002-1.764	**0.048**
Ischemia-driven revascularization	1.836	1.395-2.416	**< 0.001**	1.208	1.016-1.438	**0.033**

Multivariate Cox analysis was adjusted for confounders that are significant (P <0.05) in univariate analysis (details shown in Table S1).

* The HR was examined regarding the lower median of RLP-C as reference.

** The HR was examined by per 1-SD increase of RLP-C.

RLP-C, remnant-like particle cholesterol; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.

Table 3. C-statistics for discrimination ability of the various predictive model for composite endpoint events in the total population.

	ROC curve analysis			Category-free NRI		IDI	
	AUC	95% CI	*P*	index	*P*	index	*P*
Baseline model*	0.798	0.781-0.814	reference	-	reference	-	reference
+ RLP-C	0.811	0.795-0.826	**< 0.001**	0.084	**0.048**	0.017	**0.030**

* Baseline model includes traditional risk factors: age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease.

ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement; RLP-C, remnant-like particle cholesterol.

Table 4. Multivariate Cox analysis evaluating the predictive value of RLP-C for composite and each component of endpoint event in subgroups with different glycometabolic status.

	RLP-C as a nominal variable*			RLP-C as a continuous variable**		
	HR	95% CI	*P*	HR	95% CI	*P*
Non-diabetic population						
Primary endpoint	1.193	0.681-2.092	0.538	0.957	0.548-1.670	0.876
All-cause death	0.344	0.001-229.549	0.748	4.143	0.240-71.536	0.328
Non-fatal MI	1.189	0.382-3.703	0.766	1.092	0.309-3.855	0.892
Ischemia-driven revascularization	1.292	0.664-2.513	0.451	0.812	0.421-1.568	0.535
Pre-diabetic population						
Primary endpoint	1.335	0.852-2.092	0.208	0.898	0.577-1.397	0.633
All-cause death	2.882	0.337-24.651	0.334	1.132	0.305-4.202	0.853
Non-fatal MI	1.346	0.532-3.404	0.530	1.152	0.535-2.483	0.718
Ischemia-driven revascularization	1.312	0.750-2.293	0.341	0.725	0.405-1.297	0.278
Diabetic population						
Primary endpoint	4.247	2.941-6.135	**< 0.001**	1.385	1.183-1.620	**< 0.001**
All-cause death	1.571	0.247-9.996	0.632	0.753	0.329-1.723	0.502
Non-fatal MI	6.072	2.669-13.815	**< 0.001**	1.392	0.975-1.988	0.069
Ischemia-driven revascularization	3.683	2.397-5.657	**< 0.001**	1.327	1.100-1.600	**0.003**

Multivariate Cox analysis was adjusted for confounders that are significant (P <0.05) in univariate analysis (details shown in Table S1).

* The HR was examined regarding the lower median of RLP-C as reference.

** The HR was examined by per 1-SD increase of RLP-C.

RLP-C, remnant-like particle cholesterol; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.

Table 5. C-statistics for discrimination ability of the various predictive model for composite endpoint events in subgroups with different glycometabolic status.

	ROC curve analysis			Category-free NRI		IDI	
	AUC	95% CI	*P*	index	*P*	index	*P*
Non-diabetic population							
Baseline model*	0.836	0.810-0.859	reference	-	reference	-	reference
+RLP-C	0.838	0.813-0.861	0.311	0.022	0.517	0.002	0.169
Pre-diabetic population							
Baseline model*	0.781	0.747-0.812	reference	-	reference	-	reference
+RLP-C	0.781	0.747-0.812	0.581	0.017	0.842	0.001	0.642
Diabetic population							
Baseline model*	0.788	0.759-0.815	reference	-	reference	-	reference
+RLP-C	0.836	0.809-0.860	**< 0.001**	0.155	**0.010**	0.040	**< 0.001**

* Baseline model includes traditional risk factors: age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease.

ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement; RLP-C, remnant-like particle cholesterol.

Figures

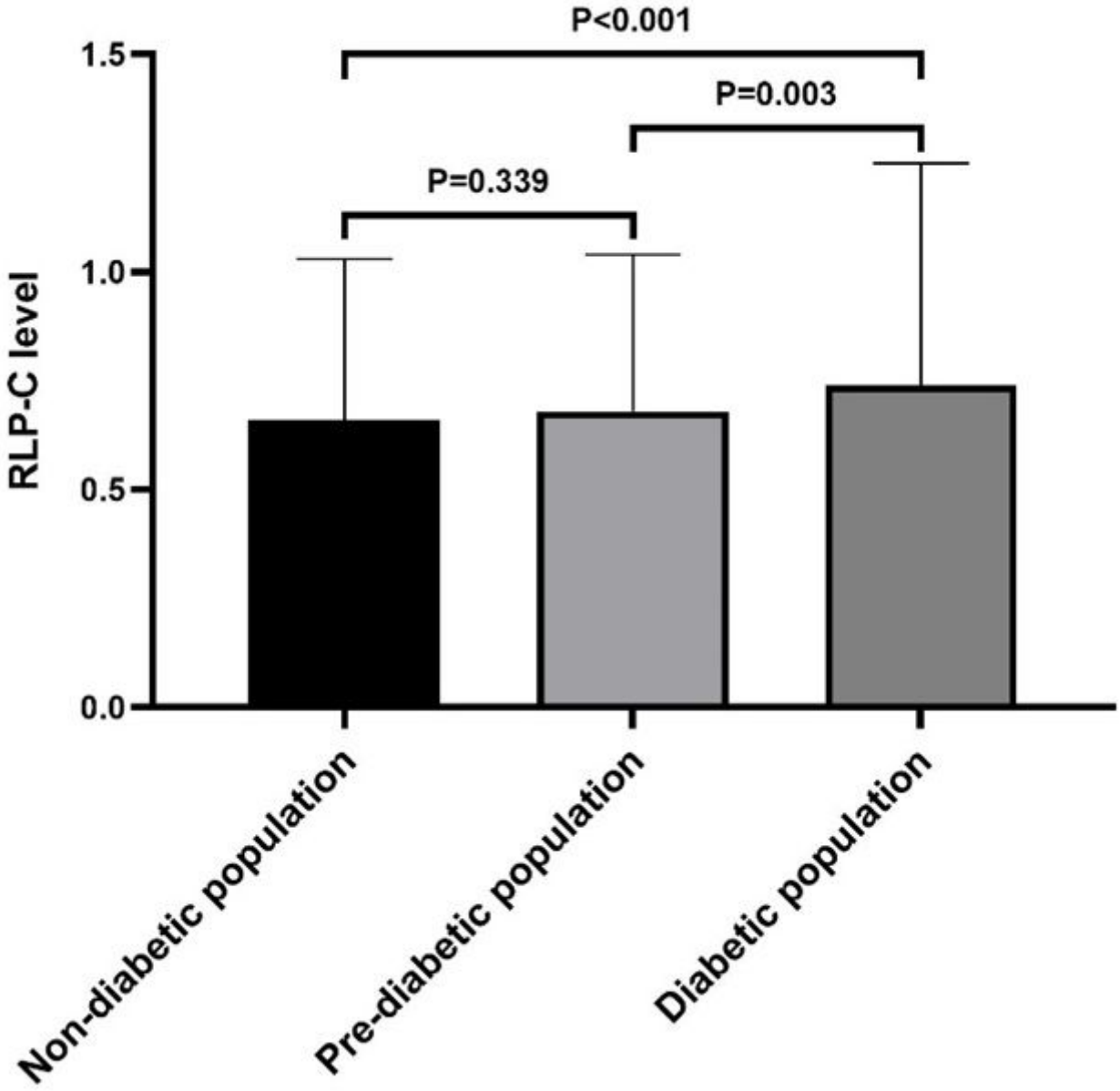

Figure 1

RLP-C levels in different glycometabolic status. RLP-C, remnant-like particle cholesterol.

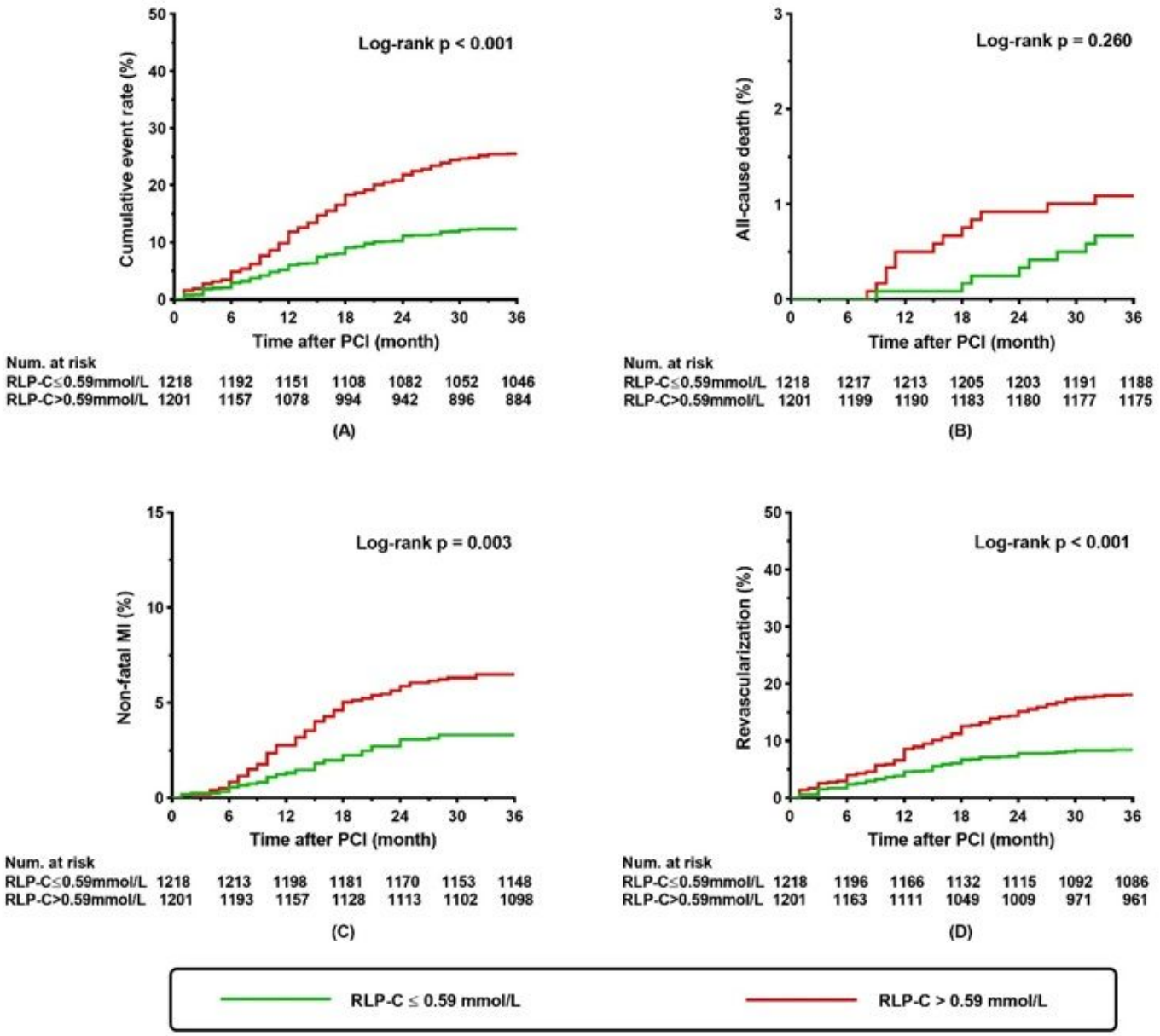

Figure 2

Kaplan-Meier curves for cumulative event rate according to RLP-C levels in the total population. Kaplan-Meier curves for (A) composite endpoint event; (B) all-cause death; (C) non-fatal MI; (D) ischemia-driven revascularization. RLP-C, remnant-like particle cholesterol; PCI, percutaneous coronary intervention; MI, myocardial infarction.

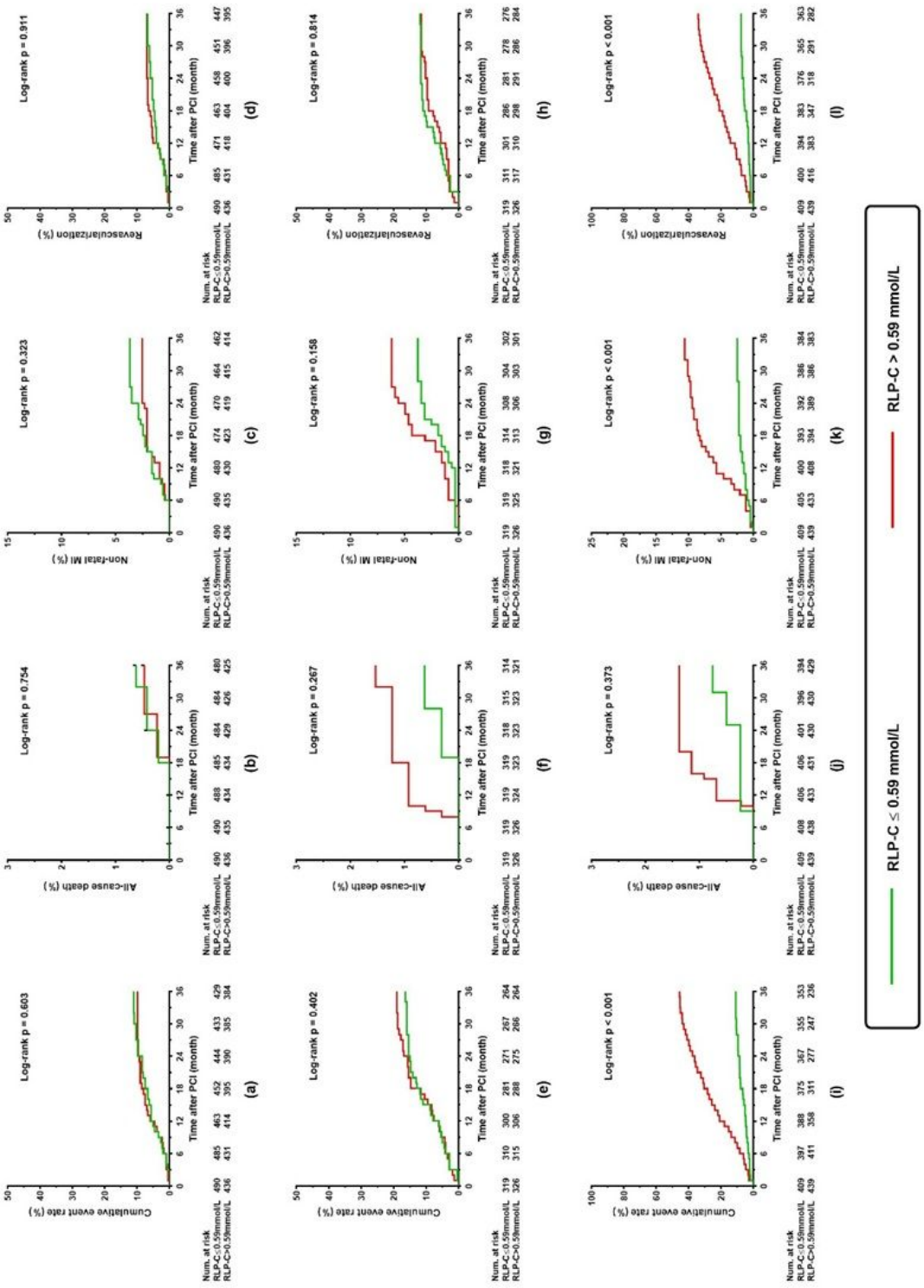

Figure 3

Kaplan-Meier curves for cumulative event rate according to RLP-C levels in various subgroups with different glycometabolic status. Kaplan-Meier curves for cumulative event rate in (a-d) non-diabetic population; (e-h) pre-diabetic population; (i-l) diabetic population. RLP-C, remnant-like particle cholesterol; PCI, percutaneous coronary intervention; MI, myocardial infarction.

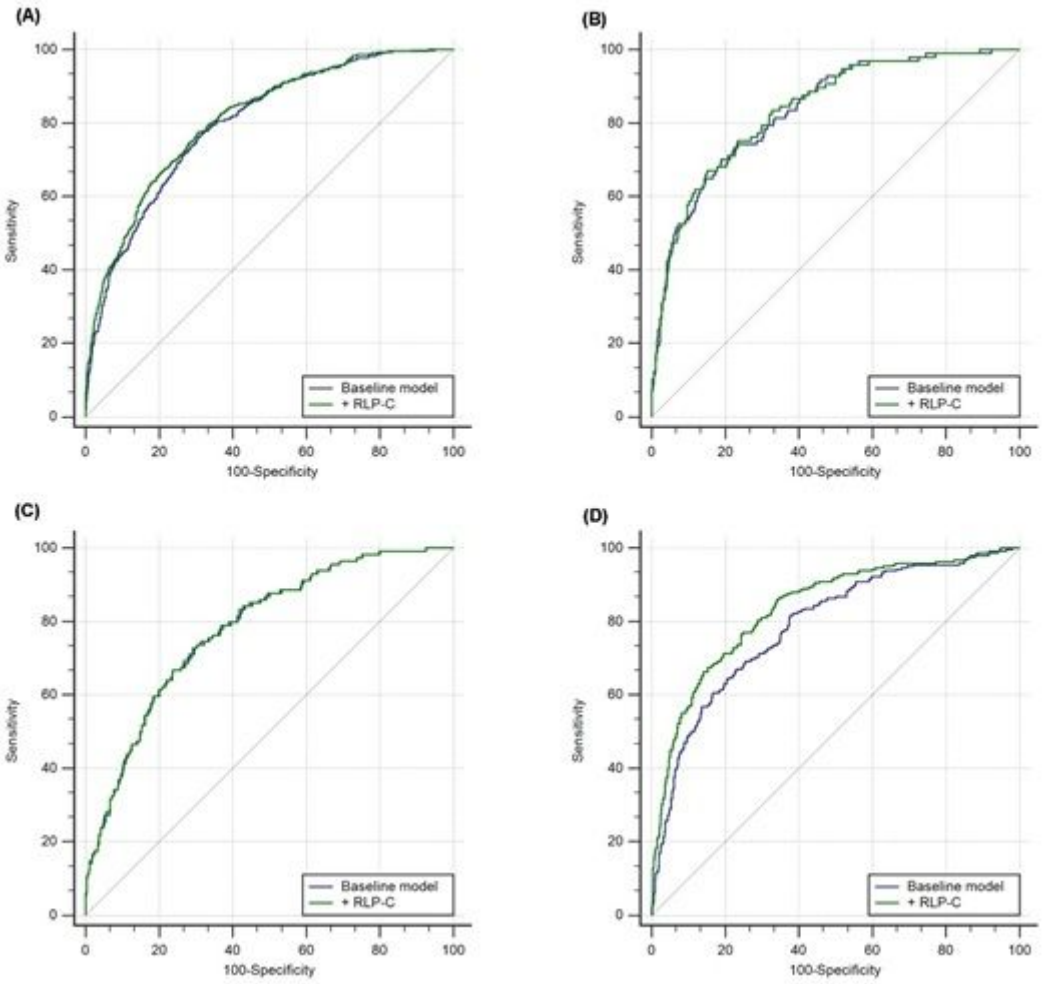

Figure 4

ROC curve evaluating the predictive value of various models for composite endpoint events in total population and subgroups. (A) Total population; (B) Non-diabetic population; (C) Pre-diabetic population; (D) Diabetic population. The baseline model includes traditional risk factors: age, sex (female), smoking, hypertension, prior MI, prior PCI, eGFR, HbA1c, TC, HDL-C, LVEF, left main disease and multi-vessel disease. RLP-C, remnant-like particle cholesterol.

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