

# Paradoxical Association Between Apolipoprotein B and Prognosis in Coronary Artery Disease: A 36,468 Chinese Cohort Study

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## Research Article

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# Abstract

## Background

Apolipoprotein B (ApoB) and low-density lipoprotein cholesterol (LDL-C) was identified as the target for blood lipid management among coronary artery disease (CAD) patients. Previous studies reported an inverse correlation between baseline LDL-C concentration and clinical outcomes. However, the association between baseline ApoB concentration and long-term prognosis is unknown.

## Methods

36,486 CAD patients admitted to Guangdong Provincial People's Hospital in China were enrolled in this study and patients were categorized into two groups: high concentration of ApoB ( $\geq 65$  mg/dL) group and low concentration of ApoB ( $< 65$  mg/dL) group. The association between ApoB levels and long-term all-cause mortality was evaluated by the Kaplan-Meier method and Cox regression analyses.

## Results

The overall mortality was 12.49% ( $n = 4,554$ ) over a median follow-up period of 5.01 years. According to Kaplan–Meier analysis, patients with low baseline ApoB levels were paradoxically more likely to get a worse prognosis. Multivariate Cox regression analyses were performed to adjust for confounding factors such as age, gender, and comorbidity, and there was no obvious difference in long-term all-cause mortality among ApoB patients (aHR: 1.07, 95% CI: 0.99-1.16). When CONUT and total bilirubin were adjusted, the risk of long-term all-cause mortality would reduce in the low-ApoB ( $< 65$ mg/dl) group (aHR: 0.86, 95% CI: 0.78-0.96). In the fully covariable-adjusted model, patients in the ApoB  $< 65$ mg/d group had a 10.00% lower risk of long-term all-cause death when comparing to patients with ApoB $\geq 65$ mg/dL (aHR: 0.90; 95% CI:0.81-0.99).

## Conclusion

This study found a paradoxical association between baseline ApoB concentration and long-term all-cause mortality. Malnutrition and bilirubin mainly mediate the ApoB paradox.

## Introduction

According to previous studies, it is a well-established association between dyslipidaemias and increased risk of adverse outcome in coronary artery disease (CAD)[1]. It is estimated that dyslipidaemias can increase 20-80% risk of long term mortality of CAD patients[2, 3]. In accordance with the guidelines for dyslipidemia management published by ESC in 2019, the control of low-density lipoprotein cholesterol[4] (LDL-C) is a primary goal among patients with CAD, and apolipoprotein B (ApoB) is regarded as a

secondary target for blood lipid management[5]. However, recent research illustrates that ApoB concentration can better reflect the risk of mortality than LDL-C, especially for patients treated with statin[6]. Several previous studies have reported a negative association of baseline LDL-C levels and prognosis[7–11]. For the situation of ApoB in CAD patients, limited studies explored the potential correlation between baseline ApoB concentration and long-term prognosis.

Therefore, our study attempts to elucidate the association between baseline ApoB and long-term all-cause mortality for CAD patients.

## Methods

### Study design and participants

Our study cohort stemmed from a previous retrospective cohort of 88,938 patients with coronary angiography (CAG) and percutaneous coronary intervention (PCI) treatment at Guangdong Provincial People's Hospital from January 2007 to December 2018. (Clinicaltrials.gov NCT04407936). The diagnosis of CAD was the basic condition of the patients enrolled in the current study. Patients who met the following criteria were excluded: under 18 years of age (n = 19), previous myocardial infarction (n = 3922), previous underwent percutaneous coronary intervention (n=4,996), previous underwent coronary artery bypass grafting (n = 328), cancer (n = 659), missing the data of ApoB (n=7,314), and lacking follow-up data about mortality (n = 5,961). Finally, 36,486 CAD patients without the conditions above were enrolled in the study (Figure 1). Guangdong Provincial People's Hospital approved the study proposal (No. GDREC2019555H[R1]). The study was implemented following the Declaration of Helsinki.

### Procedures

The data of this study came from the Electronic medical record system. Baseline nutritional status data, coexistence conditions, demographic characteristics, laboratory examination, and medicine at discharge were collected. Blood samples were taken at admission for hematology and chemistry or collected before PCI/CAG, which was obeyed with standard clinical practice guidelines[12–14]. Follow-up data on patient mortality was obtained and recorded from the Public Security system of Guangdong Province

### Outcome and definition

In this study, all-cause mortality during the study period was considered as the primary outcome. CAD was confirmed by CAG (defined as >50% stenosis in at least one vessel) and differentiated in the 10th Revision Codes of the International Classification of Diseases. Additionally, comorbidities consist of several diseases. CHF was defined as Killip class  $\geq 2$  or New York Heart Association class  $\geq 3$ [15]. eGFR  $< 60$  ml/min per  $1.73 \text{ m}^2$  was defined as CKD (CKD stage 3 or worse)[16–18]. According to the World Health Organization, anemia was defined as hematocrit  $< 39\%$  in males and  $36\%$  in females[19]. Nutritional status was evaluated using the Controlled nutritional status (CONUT) scoring system. CONUT score is a comprehensive evaluation of serum albumin concentration, the total number of peripheral

blood lymphocytes, and total cholesterol concentration. Different scores correspond to different nutritional status (0-1 is normal; 2-4 represents mild malnutrition; > 4 for severe malnutrition)[20].

## Statistical analysis

Referring to the concentration of ApoB, patients were categorized into two groups: a group with a high concentration of ApoB ( $\geq 65$  mg/dL) and a group with a low concentration of ApoB ( $< 65$  mg/dL). The categorical variables of descriptive statistics are expressed as quantity (percentage), the continuous variables of the normal distribution are expressed as mean [standard deviation (SD)], and the continuous variables of abnormal distribution are expressed as median (quartile range [IQR]). Continuous and normally distributed variables were analyzed by independent sample Student t-test and Pearson chi-square tests for categorical ones. Kaplan-Meier method and log-rank t-test were selected to analyze the difference in survival between two groups. We conducted adjusted and unadjusted Cox proportional risk models to evaluate the link between apolipoprotein cholesterol levels and long-term all-cause mortality. We build a multivariate Cox regression model which incorporates baseline variables clinically relevant. In our study, we selected variables cautiously based on the given number of available events for assurance of the simplicity in the final model. We have successively constructed four models in turn, each of which has or has not been adjusted for concomitant variable: 1) univariate model; 2) adjusted age, gender, and complications including AMI, CHF, hypertension, diabetes mellitus, CKD, anemia, atrial fibrillation, COPD, and stroke; 3) adjusted nutritional status (CONUT) and total bilirubin; 4) adjusted for all covariates. The correlation between ApoB, nutritional status and total total bilirubin were analysed by using spearman analysis. Statistical analyses have been performed by using R software, version 4.0.3. Data would be considered statistically significant with an adjusted P-value less than 0.05.

## Results

### Patients' clinical characteristics

The final analysis consists of 36,468 CAD patients who met the criteria. Enrolled patients' baseline characteristics have been reported in Table 1. The average ages of patients with ApoB  $< 65$  mg/dL and the group of patients with ApoB  $\geq 65$ mg/dL were 64.50 years and 62.65 years, respectively. Patients with ApoB  $< 65$ mg/dL were more likely to develop comorbidities, worse nutrition status, and higher total bilirubin than patients with ApoB  $\geq 65$ mg/dL.

Table 1  
Baseline characteristics

Characteristic*	Overall (N=36,468)	ApoB < 65 mg/dL (N=5,840)	ApoB ≥ 65mg/dL (N=30,628)	P value
<b>Demographic characteristics</b>				
Age, year	62.95 (10.61)	64.50 (10.75)	62.65 (10.56)	<0.001
Age ≥75 years, n (%)	5319 (14.59)	1107 (18.96)	4212 (13.75)	<0.001
Male, n (%)	27359 (75.02)	4557 (78.03)	22802 (74.45)	<0.001
<b>Coexisting conditions</b>				
AMI, n (%)	8023 (22.00)	925 (15.84)	7098 (23.17)	<0.001
PCI, n (%)	26813 (73.52)	4071 (69.71)	22742 (74.25)	<0.001
CHF, n (%)	3462 (9.50)	444 (7.61)	3018 (9.87)	<0.001
Hypertension, n (%)	20536 (56.31)	3460 (59.25)	17076 (55.75)	<0.001
Diabetes mellitus, n (%)	9825 (26.94)	1708 (29.25)	8117 (26.50)	<0.001
CKD, n (%)	7588 (21.75)	1295 (23.22)	6293 (21.47)	0.004
Anemia, n (%)	11264 (31.84)	2309 (40.90)	8955 (30.11)	<0.001
Atrial fibrillation, n (%)	855 (2.34)	154 (2.64)	701 (2.29)	0.118
COPD, n (%)	311 (0.85)	57 (0.98)	254 (0.83)	0.298
Stroke, n (%)	2051 (5.62)	382 (6.54)	1669 (5.45)	0.001
<b>Nutritional status</b>				
Without malnutrition, n (%)	15276 (44.20)	561 (10.19)	14715 (50.64)	<0.001
Mild malnutrition, n (%)	15263 (44.16)	3739 (67.90)	11524 (39.66)	<0.001
Moderate malnutrition, n (%)	3812 (11.03)	1125 (20.43)	2687 (9.25)	<0.001
Severe malnutrition, n (%)	212 (0.61)	82 (1.49)	130 (0.45)	<0.001
<b>Laboratory examination</b>				
TBIL, mmol/L	14.54 (6.74)	14.91 (7.43)	14.48 (6.61)	<0.001

\* Data are presented as the mean value (standard deviation) or number of participants (percentage).

Abbreviations: ApoB, apolipoprotein B; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TBIL, total bilirubin; DBIL, direct bilirubin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RASi, renin angiotensin system inhibitor.

Characteristic*	Overall (N=36,468)	ApoB < 65 mg/dL (N=5,840)	ApoB ≥ 65mg/dL (N=30,628)	P value
HCT	0.40 (0.05)	0.39 (0.05)	0.40 (0.05)	<0.001
Lymphocyte, 10 <sup>9</sup> /L	1.94 (0.71)	1.81 (0.68)	1.97 (0.71)	<0.001
Total cholesterol, mmol/L	4.60 (1.21)	3.29 (0.68)	4.85 (1.13)	<0.001
HDL-C, mmol/L	1.00 (0.26)	0.99 (0.28)	1.00 (0.26)	<0.001
LDL-C, mmol/L	2.86 (0.97)	1.74 (0.42)	3.07 (0.90)	<0.001
Triglyceride, mmol/L	1.67 (1.23)	1.33 (1.42)	1.73 (1.18)	<0.001
ApoB, mg/dL	0.87 (0.24)	0.56 (0.07)	0.93 (0.22)	<0.001
ALB, g/L	36.37 (4.23)	36.14 (4.21)	36.42 (4.23)	<0.001
<b>Medicine</b>				
RASi, n (%)	17553 (48.94)	2675 (46.94)	14878 (49.32)	0.001
β-blocker, n (%)	28856 (80.45)	4479 (78.59)	24377 (80.80)	<0.001
Statins, n (%)	33921 (94.57)	5319 (93.33)	28602 (94.81)	<0.001
<b>Events</b>				
All-cause mortality, n (%)	4554 (12.49)	903 (15.46)	3651 (11.92)	<0.001
* Data are presented as the mean value (standard deviation) or number of participants (percentage).				
Abbreviations: ApoB, apolipoprotein B; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TBIL, total bilirubin; DBIL, direct bilirubin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RASi, renin angiotensin system inhibitor.				

## Primary outcomes

During the whole follow-up period with a median time of 5.01 years (IQR 2.96-7.65), The all-cause mortality rate of the patients surveyed was 12.49% (n = 4,554). Kaplan-Meier analysis indicated the phenomenon that patients with low ApoB (< 65mg/dl) had a worse prognosis (Figure 2). Multivariate Cox regression analyses were performed to adjust for confounding factors between patients with low ApoB (< 65mg/dl) and patients with high ApoB levels (≥ 65mg/dL) (Figure 3). After adjusting for age, gender, and comorbidity (model 2), there was no obvious difference in long-term all-cause mortality among ApoB patients (aHR: 1.07, 95% CI: 0.99-1.16, Figure 3). Nevertheless, when CONUT and total bilirubin (model 3) were adjusted, the risk of long-term all-cause mortality would reduce for the patients with low-ApoB (< 65mg/dl) (aHR: 0.86, 95% CI: 0.78-0.96, Figure 3). In the fully covariable-adjusted model (model 4), patients in the ApoB < 65mg/d group had a 10.00% lower risk of long-term all-cause death when comparing to patients with ApoB≥65mg/dL(aHR: 0.90; 95% CI:0.81-0.99, Figure 3). The result above

indicating nutrition state and total bilirubin were the most important confounders in associating low ApoB levels with clinical outcomes.

## **Correlations between ApoB, total bilirubin, nutritional status and its components**

The correlations between ApoB and total bilirubin, nutritional status evaluated by CONUT score and components of CONUT score were shown in Figure 4. ApoB did not show a significant correlation with total bilirubin ( $r = -0.023$ ,  $p < 0.001$ ). Although ApoB show a strong correlation with total cholesterol ( $r = 0.838$ ,  $p < 0.001$ ) and LDL-C ( $r = 0.864$ ,  $p < 0.001$ ), there was no strong correlation between ApoB and nutritional status which was evaluated by CONUT score ( $r = -0.38$ ,  $p < 0.001$ ). Additionally, ApoB was not strongly correlated with lymphocyte count and albumin ( $r = 0.117$  and  $0.092$ ).

## **Discussion**

To the best of our knowledge, no previous study has demonstrated the relationship between long-term all-cause mortality and baseline serum ApoB concentration in CAD patients. According to the Kaplan-Meier curve, there is a paradoxical association between baseline ApoB concentration and long-term prognosis, in which low baseline ApoB was associated with a high risk of poor outcomes. Considering the baseline discrepancies including age, sex, and comorbidities, the association between low ApoB level and worse prognosis was not significant. After taking nutrition status and total bilirubin level into consideration, high baseline serum concentration of ApoB was one of the factors which can affect long-term all-cause mortality independently. The apolipoprotein paradox has been observed in CHD patients in previous studies, but it would no longer exist by taking the effects of malnutrition and bilirubin into account. The paradoxical association between ApoB and worse prognosis was mainly mediated by the effect of bilirubin and underlying malnutrition.

According to our findings, baseline plasma apolipoprotein levels were inversely associated with long-term prognosis in unadjusted analysis. Although no previous studies have reported similar phenomena, previous studies have reported paradoxical relations between baseline LDL-C level and long-term prognosis [4, 7–10]. Additionally, ApoB is highly correlated with LDL-C [21]. These previous studies illustrated that baseline confounders caused the cholesterol paradox of LDL-C. Cho et al. found AMI patients owing lower LDL-C levels ( $< 1.8$  mmol/L) on admission would be prone to have higher mortality in crude short-term [7].

Meanwhile, patients in the lower LDL-C group were older and had a higher proportion of comorbidities. After adjusting for covariates, the level of LDL-C was not connected strongly to short-term mortality. Another study conducted by Wang et al. showed that ACS patients' low baseline LDL-C concentration will increase the risk of mortality among hospitalized patients [7]. Similarly, after adjustment for baseline confounders, the paradoxical association disappeared, and no apparent relationship between LDL-C levels and in-hospital mortality. The other three trials showed that the reduction of baseline LDL-C concentration was correlated to the increase of mortality in unadjusted and adjusted models [4, 9, 10].

All of these studies have found a paradoxical relationship between hyperlipidemia and well prognosis, but these studies have not found causes for the phenomenon. A study conducted by Wallner et al. indicated that lipid profile would be altered in hyperbilirubinemia patients, characterized by a lower ApoB and LDL-C[22]. Previous studies also demonstrated that the bilirubin concentration was negatively associated with LDL-C level[23, 24], and ApoB was the primary structural protein of low-density lipoprotein (LDL)[25]. Moreover, increased bilirubin level was associated with an increased risk of poor prognosis[26–28]. In an observational study retrospectively conducted by Huang et al. recruiting 3013 patients, the results suggested a positive correlation between serum total bilirubin concentration and short-term mortality in AMI patients[26]. At the same time, it also showed that increased serum total bilirubin level might increase the number of long-term deaths[26]. In another observational study including 1167 patients with STEMI who underwent PCI, Baumann et al. found that high levels of total bilirubin ( $\geq 12$  mg/L) were associated with a 128% increased risk of major adverse cardiac events (MACEs) during hospitalization[27]. In addition, Wu et al. demonstrated that for patients with severe systolic heart failure, patients with higher bilirubin levels had conspicuously higher all-cause mortality[28]. Since there was a tight connection between ApoB and total cholesterol, which is an evaluation index for nutritional status[20, 21], low ApoB may also indicate potential malnutrition. The CONUT score is an effective and objective tool to assess patients' nutritional status in hospital [20, 29]. Roubín et al., Wada et al., and Chen et al. found that the nutritional status obtained by CONUT score can be considered as one of the indicators to predict long-term clinical outcomes of CAD patients[30–32].

Several reasons may explain the result of the present study. Firstly, according to the baseline, patients with low levels of ApoB ( $< 65$  mg/dL) were more elderly and complicated with more comorbidities. These confounders were highly associated with poor prognosis. Compared with patients having high levels of ApoB ( $\geq 65$  mg/dL), patients with low ApoB ( $< 65$  mg/dL) had higher prevalence of elderly patients (18.96% vs. 13.75%), hypertension (59.25% vs. 55.75%), CKD (23.22% vs. 21.47%), diabetes mellitus (29.25% vs. 26.50%) and anemia (43.2% vs. 30.3%). Thus, our study constructed model 2 in Cox regression which adjusted for age, male, and comorbidities. The results showed baseline ApoB concentration was not relevant to long-term all-cause mortality when taking age, male, and comorbidities into account. Secondly, patients with ApoB  $< 65$  mg/dL had higher bilirubin which may affect the prognosis. Bilirubin, the ultimate breakdown of hemoglobin, is an endogenous antioxidant with anti-inflammatory properties[33]. As a strong antioxidant, bilirubin can inhibit the generation of atherogenic lipid such as oxidized-LDL. It may directly affect lipid metabolism through several pathways, including hepatic very low-density lipoprotein (VLDL) assembly and cholesterol synthesis, bile cholesterol excretion, and intestinal cholesterol transport[34, 35]. Meanwhile, ApoB is a direct measure of circulating numbers of atherogenic lipoproteins and is the main apolipoprotein of cholesterol within LDL, VLDL, and intermediate-density lipoprotein (IDL) particles[21, 36, 37]. Thus, it is not surprising that bilirubin was negatively associated with ApoB. Thirdly, patients with ApoB  $< 65$  mg/dL had a higher proportion of worse nutrition states. In the present study, the prevalence of mild, moderate, severe malnutrition in the low ApoB group ( $< 65$ mg/dL) was 67.90%, 20.43%, and 1.49%, respectively. While, it was 39.66%, 9.25% and 0.45% in high ApoB group ( $\geq 65$ mg/dL), respectively. Emerging studies demonstrated that

malnutrition and increased bilirubin level were highly associated with increased risk of poor long-term outcomes. The result of model 3 (adjusted for nutrition state, bilirubin) and model 4 (adjusted for all covariates including nutrition state, bilirubin) illustrated a normal association between baseline ApoB concentration and long-term all-cause death.

Lipid management is one of the critical points of secondary prevention in patients with CAD. ApoB as the secondary target should be paid attention to risk stratification. The nutrition state and the concentration of bilirubin should also be considered.

## **Limitation**

There are also several limitations that should be considered. Firstly, the data of the present study was a single-center observational study from China. However, the data of the present study was from a large real-world cohort. Secondly, the data of the included patients were limited, and information such as body weight, BMI, waist circumference, and obesity that might be helpful to evaluate the nutritional status of the patients was missing comprehensively. To compensate for this, we chose the CONUT score based on laboratory examination as a tool to assess nutritional status. This may also help us perform an objective appraisal on patients about their nutritional status. Thirdly, this study only enrolled the ApoB values collected from the patients at admission, making it tougher to evaluate the effect of changes in ApoB levels on clinical endpoints during follow-up. In summary, our study mainly focuses on the clinical importance of baseline ApoB level on prognosis among CAD patients.

## **Conclusion**

Among CAD patients, there is a paradoxical association between ApoB concentration and the risk of all-cause mortality. Nutrition state and bilirubin levels mediate this abnormal association. Conversely, after considering these two factors, ApoB is still a risk factor for long-term all-cause mortality of CAD patients.

## **Declarations**

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Data relevant to this study are available from the corresponding authors upon reasonable request.

### **Competing interests**

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

## Ethical approval

This study was conducted following the Declaration of Helsinki and was approved by the Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences Research Ethics Committee (No. GDREC2019555H[R1]). All personal identifiers were removed from the analytic dataset to protect the privacy of patients.

## Founding

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## Authors' contributions

Substantial contributions to the conception and design of the study (HQL, WB, CSQ); data collection (ZLM, SJY,ZYZ,LWG,QL,HYL); data analysis and/or interpretation of data for the work (SQC, YL, JYC,YQY, JRD, JL,NT); drafting of the work or revising it critically for important intellectual content (HQL, BW, ZLM, SJY, SQC, LQ,YQY, JRD, JL, YL, JYC); final approval of the version to be published (all the authors).

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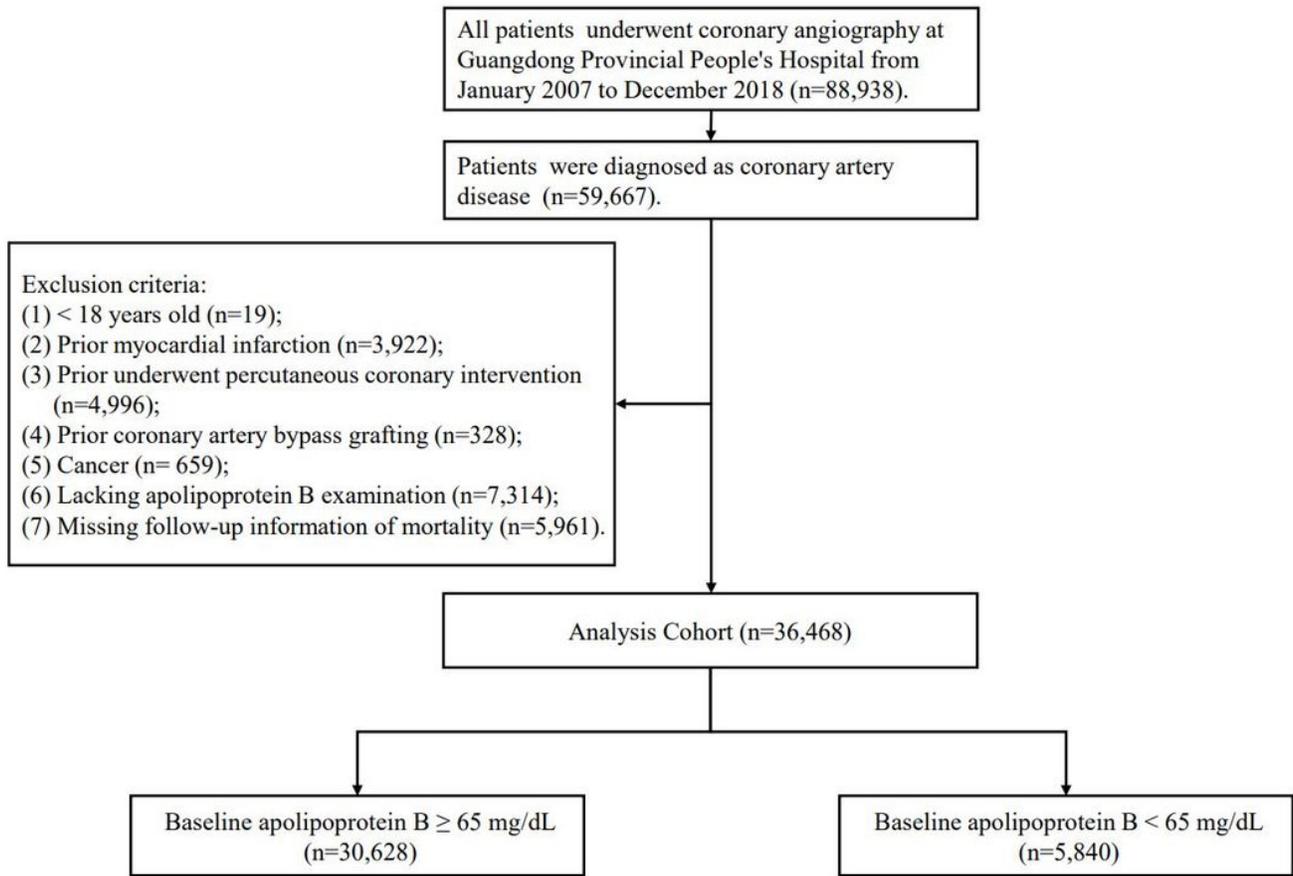
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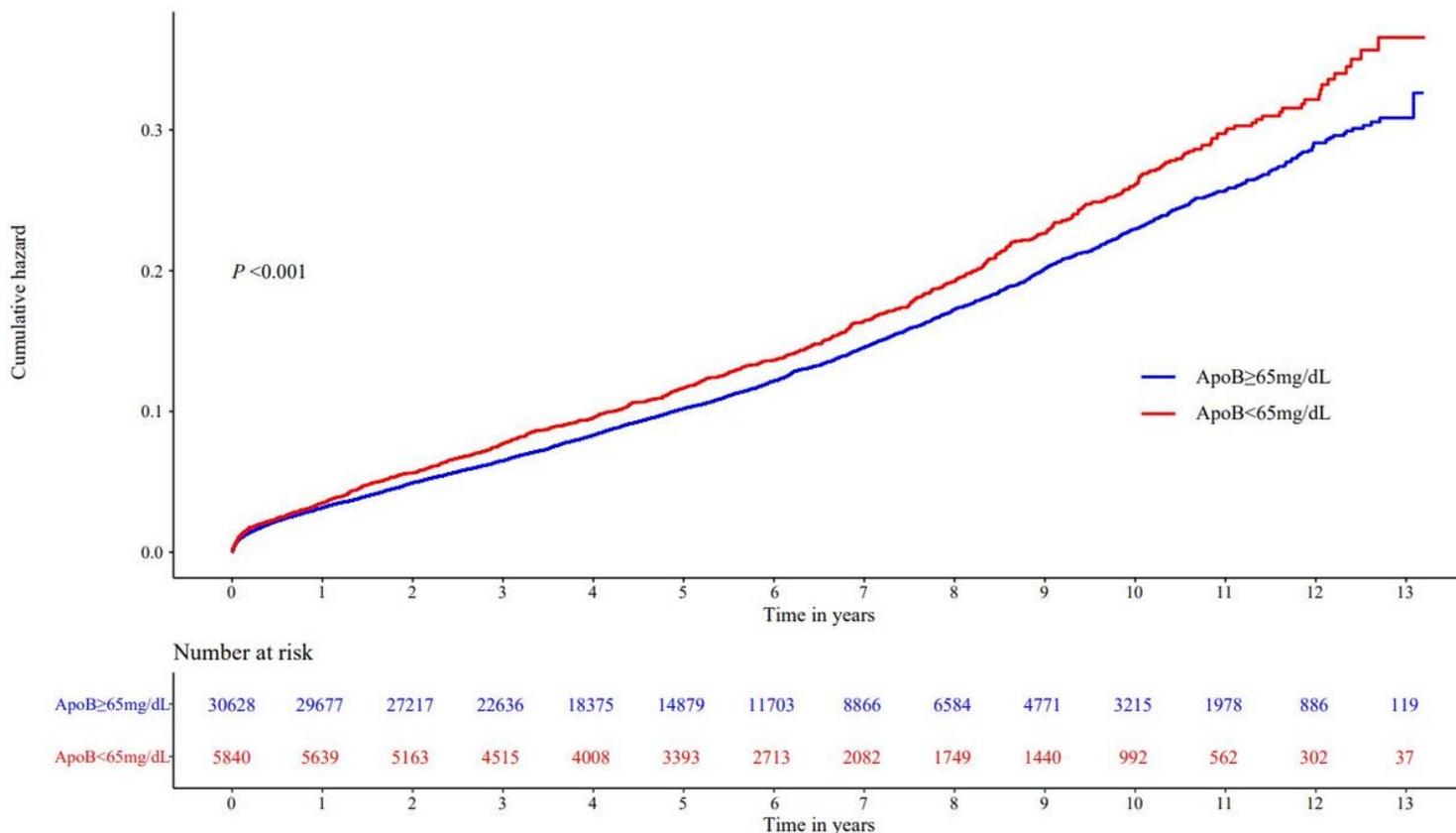
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## Figures



**Figure 1**

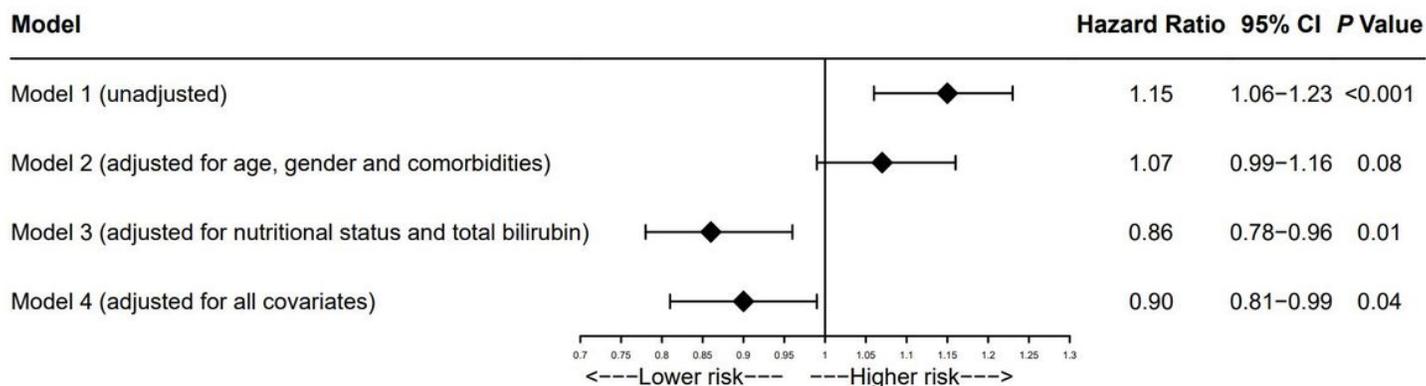
Study flow chart.



**Figure 2**

Cumulative incidence of all-cause death for ApoB < 65mg/dL group vs. ApoB ≥ 65mg/dL group in CAD patients.

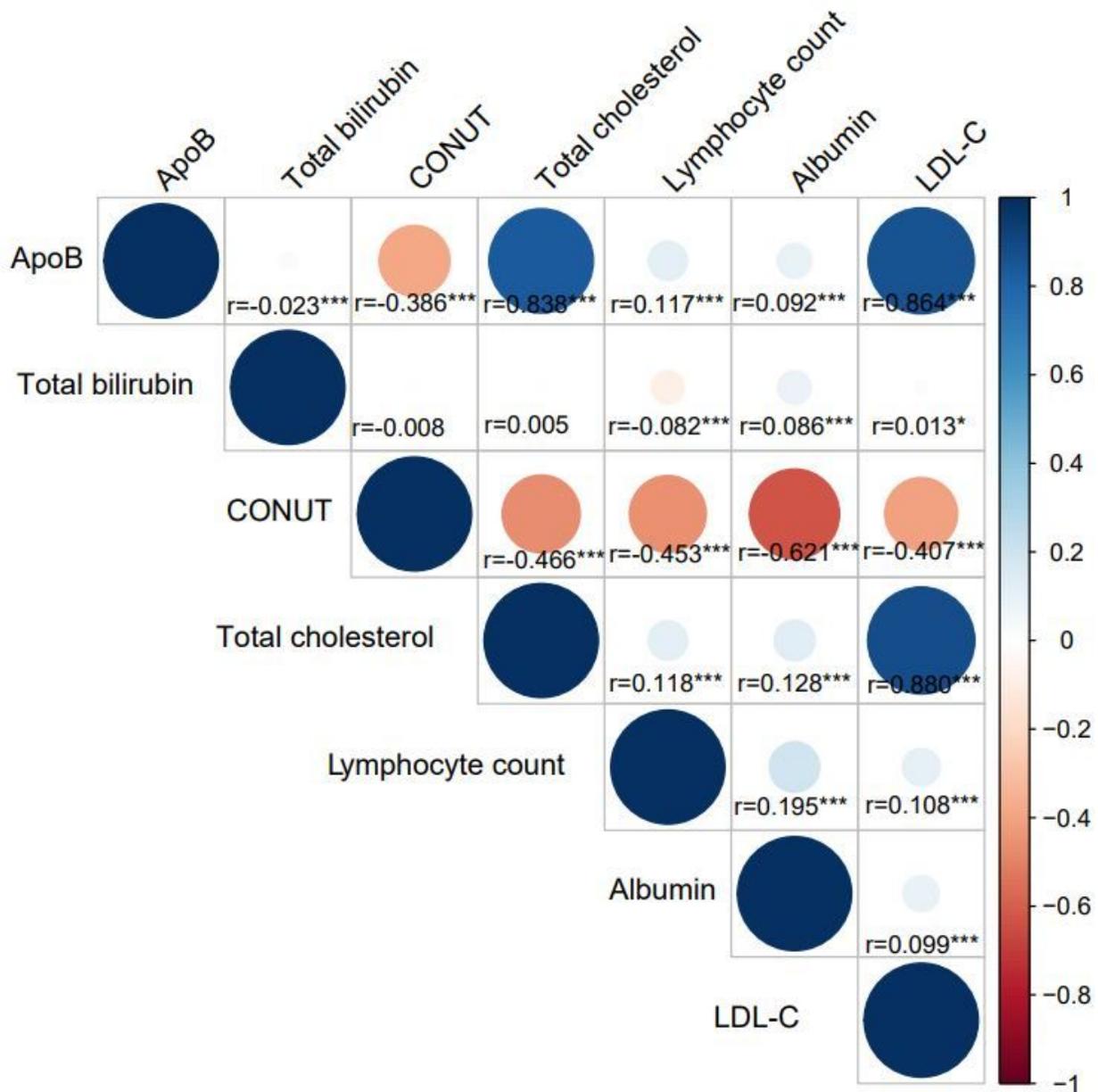
### HR(95%CI) for long-term all-cause mortality



**Figure 3**

Unadjusted and adjusted HRs and 95% CIs for the primary end point (long-term all-cause mortality) of ApoB < 65mg/dL group vs. ApoB ≥ 65mg/dL group in CAD patients. Model 1: Unadjusted model. Model 2: Adjusted for age ≥ 75 years, sex, PCI and comorbidities including AMI, CHF, hypertension, diabetes

mellitus, CKD, anemia, atrial fibrillation, COPD and stroke. Model 3: Adjusted for malnutrition. Model 4: Adjusted for all covariates: age  $\geq$  75 years, sex, PCI and comorbidities including AMI, CHF, hypertension, diabetes mellitus, CKD, anemia, atrial fibrillation, COPD, stroke and malnutrition.



**Figure 4**

Correlations between ApoB, total bilirubin, nutritional status and its components Nutritional status is assessed by Controlling Nutritional Status (CONUT) score. Total cholesterol, lymphocyte count and albumin are components of CONUT score. p values $<0.05$  \*; p values $<0.01$ \*\*; p values $<0.001$ \*\*\*.