Platelet-to-hemoglobin ratio as a valuable predictor of long-term all-Cause mortality in coronary artery disease patients with congestive heart failure

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Abstract

Background

The platelet-to-hemoglobin ratio (PHR) has emerged as a prognostic biomarker in coronary artery disease (CAD) patients after PCI but not clear in CAD complicated with congestive heart failure (CHF). Hence, we aimed to assess the association between PHR and long-term all-cause mortality among CAD patients with CHF.

Methods

Based on the registry at Guangdong Provincial People's Hospital in China, we analyzed data of 2,599 hospitalized patients who underwent coronary angiography (CAG) and were diagnosed with CAD complicated by CHF from January 2007 to December 2018. Low PHR was defined as 1.69 (group 1) and high PHR as ≥ 1.69 (group 2). Prognosis analysis was performed using Kaplan-Meier methods. To assess the association between PHR and long-term all-cause mortality, a Cox-regression model was fitted.

Results

During a median follow-up of 5.2 (3.1–7.8) years, a total of 985 (37.9%) patients died. On the Kaplan-Meier analysis, patients in high PHR group had a worse prognosis than low PHR group (log-rank, p = 0.0011). After adjustment for confounders, high PHR was correlated with an increased risk of long-term all-cause mortality in CAD patients complicated with CHF. (adjusted hazard ratio [aHR], 1.21; 95% confidence interval [CI], 1.03–1.41, p = 0.02).

Conclusion

Elevated PHR is correlated with an increased risk of long-term all-cause mortality in CAD patients with CHF. These results indicate that PHR may be a useful prognostic biomarker for this population. Meanwhile, it is necessary to take effective preventive measures to regulate both hemoglobin levels and platelet counts in this population.

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality globally. CAD complicated by heart failure especially carries considerable morbidity and poor prognosis[1].Those facts indicate that it is necessary to quest useful and simple indicators to evaluate the prognosis of CAD patients complicated with CHF for effective and timely intervention strategies.

A growing body of literature has illustrated the prognostic utility of various complete blood counts in predicting adverse outcomes in cardiovascular disease[2, 3]. High circulating platelet counts have been reported to be associated with poor outcomes in cardiovascular disease[4–6], the mechanism of which may be inflammatory response[7, 8] and platelet activation[9]. In contrast, low hemoglobin levels were considered as poor prognostic factors of cardiovascular disease[10, 11], owing to worsening myocardial ischemia[12], neurohormonal activation, increased cardiac output[13, 14], and adverse left ventricular (LV) remodeling[14, 15].

Platelet-to-hemoglobin ratio has emerged as a novel and readily available prognostic parameter[16, 17]. Zheng et al[17]reported that PHR was an independent predictor of adverse outcomes in CAD patients who underwent percutaneous coronary intervention (PCI) and was considered as a stronger predictor than platelet counts or hemoglobin levels alone. However, the association of PHR and all-cause mortality in CAD patients with congestive heart failure is not clear. In this context, this study aims to investigate the relationship between PHR and long-term all-cause mortality of CAD patients with CHF.

Population And Methods

Data sources and study population

This is an observational cohort, single-center, retrospective study. The data we used in this study was based on the electronic clinical management records system of the Guangdong Provincial People's Hospital (ClinicalTrials.gov NCT04407936). We collected data on all-cause mortality through the Guangdong Provincial Public Security and then matched to the electronic clinical management system of the Guangdong Provincial People's Hospital records. The baseline data included demographic characteristics, medical history, laboratory test results and medication use. We included patients undergoing coronary angiography (CAG) and with a final diagnosis of CAD complicated by CHF in accordance with the 10th Revision Codes of the International Classification of Diseases (ICD-10; I20.xx–I25.xx, I50.00001, and I91.40001, Supplemental Table S1) from January 2007 to December 2018. Percutaneous coronary intervention (PCI) or coronary angiography (CAG) was performed in accordance with authoritative clinical practice guidelines[18, 19]. All blood samples were collected in the early morning after overnight fasting. We excluded patients who lacked platelet counts, hemoglobin levels, and follow-up information. Finally, 2,599 were enrolled in this analysis (Figure 1). The study population was dichotomized based on the PHR on admission according to the median, and we define PHR□1.69 as low PHR (group 1), PHR≥1.69 as high PHR (group 2).

Clinical definition

CHF was defined as New York Heart Association (NYHA) class>2 or Killip class>1[20]. Acute myocardial infarction (AMI) was defined as having a medical history of an ST-elevated myocardial infarction (STEMI) or Non-STEMI cardiac events. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m^2. eGFR was calculated according to the Modification of Diet in

Renal Disease (MDRD) equation. Hypertension (HT) and diabetes mellitus (DM) were defined following the 10th Revision Codes of the International Classification of Diseases.

Study endpoints and clinical follow-up

Long-term all-cause mortality was the primary endpoint of this study which was defined as any death recorded from the date of enrollment to the date of the last follow-up visit. Follow-up time and data on long-term all-cause mortality were obtained from the Guangdong Provincial Public Security and then matched to the electronic Clinical Management System of the Guangdong Provincial People's Hospital records.

Statistical Analysis

Descriptive statistics on baseline variables are presented as the mean (standard deviation [SD]), median (interquartile range [IQR]), or number and percentage as appropriate. Differences in baseline characteristics between groups were analyzed by Student's t-test when appropriate. The categorical data was analyzed by Pearson chi-squared tests. Restricted cubic splines were used to investigate the associations of PHR and long-term all-cause death. Survival times were plotted using Kaplan-Meier survival curves, the log-rank test was used to compare differences in survival.

The usefulness of PHR for independently predicting long-term all-cause mortality among CAD patients with CHF was analyzed by the Cox regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Those related to mortality on the basis of clinical experience were further controlled using multivariable Cox regression in 3 different models. Model 1 was unadjusted, model 2 adjusts for age and gender, and model 3 included model 2 variables, medical history (CKD, HT, AMI, Stroke, DM, pre-acute myocardial infarction, PCI and anemia), drugs information (angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, aspirin, β-blockers, clopidogrel and statins). Subgroup analysis was performed among 8 prespecified subgroups (age≥75 or age<75, male or female, non-CKD or CKD, non-PCI or PCI) to assess the association of PHR with long-term all-cause mortality among CAD patients with CHF.

All P values were calculated with two-sided tests, a threshold of p-value<0.05 was set to represent statistical significance. All data analyses were performed by R software (version 4.0.3; R Core Team, Vienna, Austria).

Results

Clinical characteristics

A total of 2,599 patients were included in the study. The baseline clinical characteristics of the patients are shown in table 1. Among the whole study population, the mean age was 66.3±10.9 years, and 660 (25.4%) were female. A total of 1,857 (71.5%) patients underwent PCI treatment, 1,290 (49.7%) patients were diagnosed as AMI, 1,117 (43.0%) patients were identified as having CKD, 921 (35.5%) patients had

DM. Patients in high PHR group were more likely to be female (31.3%) and positively associated with the prevalence of AMI, DM, HT, CKD and was negatively associated with admission ALB, eGFR, HGB levels. There was a significantly higher use of statins, clopidogrel, aspirin and calcium channel blockers in the high PHR group. More details of the baseline characteristics of patients enrolled are shown in table 1.

Primary outcomes

During a median follow-up of 5.2 (3.1-7.8) years, a total of 985 (37. 9%) patients died (p=0.001; Figure 2). Restricted cubic splines showed HR for the primary endpoint was positively associated with PHR, but the relationship between them was nonlinear (Figure 3). As determined by Kaplan-Meier analysis, the high PHR group had a higher incidence of long-term all-cause mortality, the statistically significant differences between KM curves were measured by the log-rank test (log-rank, p=0.0011; Figure 4).

The relationship between high PHR and long-term all-cause mortality was evaluated using Cox proportional hazards models. Our results demonstrated that high PHR was associated with a higher risk of all-cause death than low PHR even after full adjustment by major confounders. (model 1: HR 1.23, 95%CI 1.09-1.40, p<0.001; model 2: HR 1.26, 95%CI 1.11-1.43, p<0.001; model 3: HR 1.21, 95%CI 1.03 -1.41, p=0.02; table 2). In a subgroup analysis, the Cox regression analysis revealed that high PHR had a consistently higher relative risk of mortality among age<75, male, non-CKD, PCI (Figure 5).

Discussion

To our knowledge, it is the first study to demonstrate the association of PHR with all-cause mortality among CAD patients with CHF. Our study showed that long-term all-cause mortality of this population was approximately 40% with a median follow-up of 5.2 years and high PHR increased long-term all-cause mortality by 21% after adjusting major confounders among those patients.

CAD is often complicated by heart failure and leads to a worse prognosis[21, 22]. Some scholars found that about 20 ~ 30% of long-term all-cause mortality with a median follow-up of ~ 2 years[23, 24], which were lower than our data. It suggested that more information about endpoints may be attained with a longer follow-up time. CAD is a common reason for HF development[25]. Either AMI or chronic ischemia leads to LV remodeling, ischemic mitral regurgitation, and LV dysfunction[26, 27]. In acute heart failure syndromes, the high LV diastolic pressure and low systemic blood pressure often result in subendocardial ischemia and lead to worse outcomes[28]. Patients with CAD complicated by LV dysfunction carry a high risk for sudden cardiac death because of recurrent myocardial injury or the abrupt onset of ventricular arrhythmias[29, 30]. Thus, physicians need some simple indicators to evaluate the outcomes among CAD patients complicated with CHF.

The clinical importance of other parameters composed of complete blood count has been shown in cardiovascular medicine. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been reported to be useful markers to predict poor prognosis in CAD patients[2, 31]. Zheng et al[17]showed that PHR was an independent prognostic marker for CAD patients after PCI with better

prognostic value than absolute platelet counts or hemoglobin levels. It is acknowledged that CAD patients with CHF are at high risk for adverse outcomes. Nevertheless, evidence of the prognostic value of PHR for this population is lacking. As a complement, our study indicated that PHR was significantly associated with poor outcomes among CAD patients with CHF.

The role of PHR in the deterioration of CAD with CHF remains unclear. On one hand, persistent inflammation is a hallmark of coronary artery disease and congestive heart failure[7, 8]. The release of various mediators during a proinflammatory state results in megakaryocyte proliferation and increased platelet counts in circulation[9, 32, 33], which may indicate elevated platelet activation and a prothrombotic state[34, 35]. These processes may cause thrombosis-related complications in CHF patients[4, 5]. In terms of CAD, activated platelets play a vital role in the development and progression of atherosclerosis[36], the instability of atherosclerotic plaques and thrombus formation in the case of vascular endothelium injury and plaque rupture[32, 37, 38]. On the other hand, low hemoglobin levels indicate decreased oxygen-carrying capacity, which may worsen the myocardial ischemic injury[12]. Subsequent tissue hypoxia may result in the activation of sympathetic nervous system and renin-angiotensin-aldosterone systems, which eventually results in elevated cardiac output[13, 14]. These changes may chronically lead to adverse LV remodeling[14, 15] and a vicious cycle of HF progression[26].

Complete blood count is routinely performed upon admission and frequently repeated during hospitalization in all CAD patients. PHR is an easily calculated, readily available, reproducible biomarker with no further cost for the patient or healthcare system. CAD complicated by CHF carries considerable morbidity and poor prognosis, it is necessary to take some measures to improve the prognosis of this population, such as secondary prevention of CAD and appropriate management of congestive heart failure. As to high PHR patients, controlling the progression of the inflammatory response, the administration of antiplatelet or anticoagulant medications and supplement of erythrotropin analogs or iron for improvement of anemia are essential and beneficial to postpone ventricular remodeling and improve prognosis.

Limitations

This study for the first time examined the significance of PHR on long-term all-cause death among CAD patients with CHF. There are several limitations to this study. First, information about cause-specific death was not available in this study, which restricted our ability to examine the significance of PHR with cause-specific death, such as cardiovascular disease mortality. Second, only in-hospital baseline platelet counts and hemoglobin levels were contained in our study. Therefore, we could not know the status of platelet counts and hemoglobin levels after discharge and the effects of changes in them. Third, although we have adjusted for many confounders in the analyses, residual confounding due to unmeasured factors should be considered.

Conclusions

High PHR is a novel, independent predictor of long-term all-cause mortality in CAD patients with CHF. It is helpful for risk stratification in CAD patients complicated by CHF to identify high-risk patients for further targeted intervention. However, prospective multi-center cohort studies are required to provide high-level of evidence and validate our findings.

Abbreviations

PHR
platelet-to-hemoglobin ratio
CAD
coronary artery disease
CHF
congestive heart failure
CAG
coronary angiography
PCI
percutaneous coronary intervention
LV
left ventricular
NYHA
New York Heart Association
CKD
Chronic kidney disease
eGFR
estimated glomerular filtration rate
MDRD
Modification of Diet in Renal Disease
AMI
Acute myocardial infarction
STEMI
ST-elevated myocardial infarction
DM
diabetes mellitus
HT
hypertension

Declarations

Ethics approval and consent to participate

All protocols of this study were approved by the institutional Ethics Research Committee of Guangdong Provincial People's Hospital (No. GDREC2019555H). The study was performed according to the declaration of Helsinki. Written informed consent for this study was also waived by the Guangdong Provincial People's Hospital Ethics Committee.

Consent for publication

Consent for publication is not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KB, HH and GH performed the scientific literature search, and contributed to the figures and the writing of the manuscript. All authors participated in the data analysis and reviewed the manuscript. KC, LC and SC conceived and designed the study and wrote the manuscript. YL, JW, WC, YP, JL, YY and ZH helped in revising the manuscript. All authors read and approved the final manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Tables

Table 1. Baseline characteristics of the study groups.

Characteristic	Overall	Group1	Group2	P-value
(n=2599)	PHR<1.69	PHR≥1.69		
	(n=1299)	(n=1300)		
Demographic characteristics				
Age, years, mean (SD)	66.26 (10.91)	66.29 (10.76)	66.24 (11.07)	0.907
Age≥75, (%)	651 (25.0)	334 (25.7)	317 (24.4)	0.462
Female, n (%)	660 (25.4)	253 (19.5)	407 (31.3)	<0.001
Medical history				
DM, n (%)	921 (35.5)	405 (31.2)	516 (39.7)	<0.001
AMI, n (%)	1290 (49.7)	592 (45.6)	698 (53.7)	<0.001
HT, n (%)	1504 (57.9)	698 (53.8)	806 (62.0)	<0.001
CKD, n (%)	1117 (43.0)	523 (40.3)	594 (45.7)	0.006
Hyperlipidemia, n (%)	1726 (69.5)	855 (69.1)	871 (69.9)	0.703
LVEF (mean (SD))	48.55 (14.50)	48.57 (14.94)	48.53 (14.06)	0.957
Anemia, n (%)	1319 (50.8)	471 (36.3)	848 (65.2)	<0.001
Stroke, n (%)	213 (8.2)	108 (8.3)	105 (8.1)	0.877
PCI, n (%)	1857 (71.5)	904 (69.6)	953 (73.3)	0.040
Laboratory tests				
WBC, 109/L, mean (SD)	9.57 (4.08)	9.25 (4.05)	9.88 (4.08)	<0.001
HGB, g/L, mean (SD)	126.07 (20.42)	134.13 (17.51)	118.03 (19.94)	<0.001
PLT, 109/L, mean (SD)	227.00 (85.61)	172.66 (39.05)	281.29 (85.03)	<0.001
ALB, g/L, mean (SD)	33.09 (4.87)	33.81 (4.73)	32.36 (4.92)	<0.001
eGFR, ml/min/1.73 m2, mean (SD)	62.87 (28.12)	65.40 (25.60)	60.31 (30.25)	<0.001
HbA1c, %, mean (SD)	6.82 (1.60)	6.70 (1.48)	6.95 (1.69)	0.003
CHOL, mmol/L, mean (SD)	4.52 (1.25)	4.52 (1.21)	4.52 (1.28)	0.983
TRIG, mmol/L, mean (SD)	1.50 (0.92)	1.46 (0.98)	1.53 (0.86)	0.047
HDL-C, mmol/L, mean (SD)	0.97 (0.27)	0.98 (0.27)	0.96 (0.27)	0.125
LDL-C, mmol/L, mean (SD)	2.83 (1.03)	2.84 (1.01)	2.82 (1.04)	0.562
Medications				
Beta-blocker, n (%)	1781 (77.6)	903 (77.7)	878 (77.5)	0.940
ACEI/ARB, n (%)	1137 (49.5)	596 (51.3)	541 (47.7)	0.098
Clopidogrel, n (%)	1954 (85.1)	956 (82.3)	998 (88.1)	<0.001
Aspirin, n (%)	1987 (86.6)	983 (84.6)	1004 (88.6)	0.006

Characteristic	Overall	Group1	Group2	P-value
Statins, n (%)	2069 (90.2)	1025 (88.2)	1044 (92.1)	0.002
CCB, n (%)	437 (19.0)	190 (16.4)	247 (21.8)	0.001

Abbreviation: DM, diabetes mellitus; AMI, acute myocardial infarction; HT, hypertension; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; ALB: albumin; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; CHOL, cholesterol; TRIG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blockers.

Table 2. Cox proportional hazards model for the association between PHR and long-term all-cause mortality

Groups	N	HR, 95% Cl, p-value		
		Model 1*	Model 2$	Model 3§
Low PHR	1299	ref	ref	ref
High PHR	1300	1.23 (1.09-1.40), <0.0001	1.26 (1.11-1.43), <0.0001	1.21 (1.03-1.41), 0.02

*Unadjusted

$ Adjusted for age and gender.

§Adjusted for full multivariate: age, gender, chronic kidney disease, hypertension, acute myocardial infarction, pre-acute myocardial infarction, stroke, diabetes mellitus, percutaneous coronary intervention, anemia, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, β-blockers, aspirin, statins and clopidogrel.

Figures

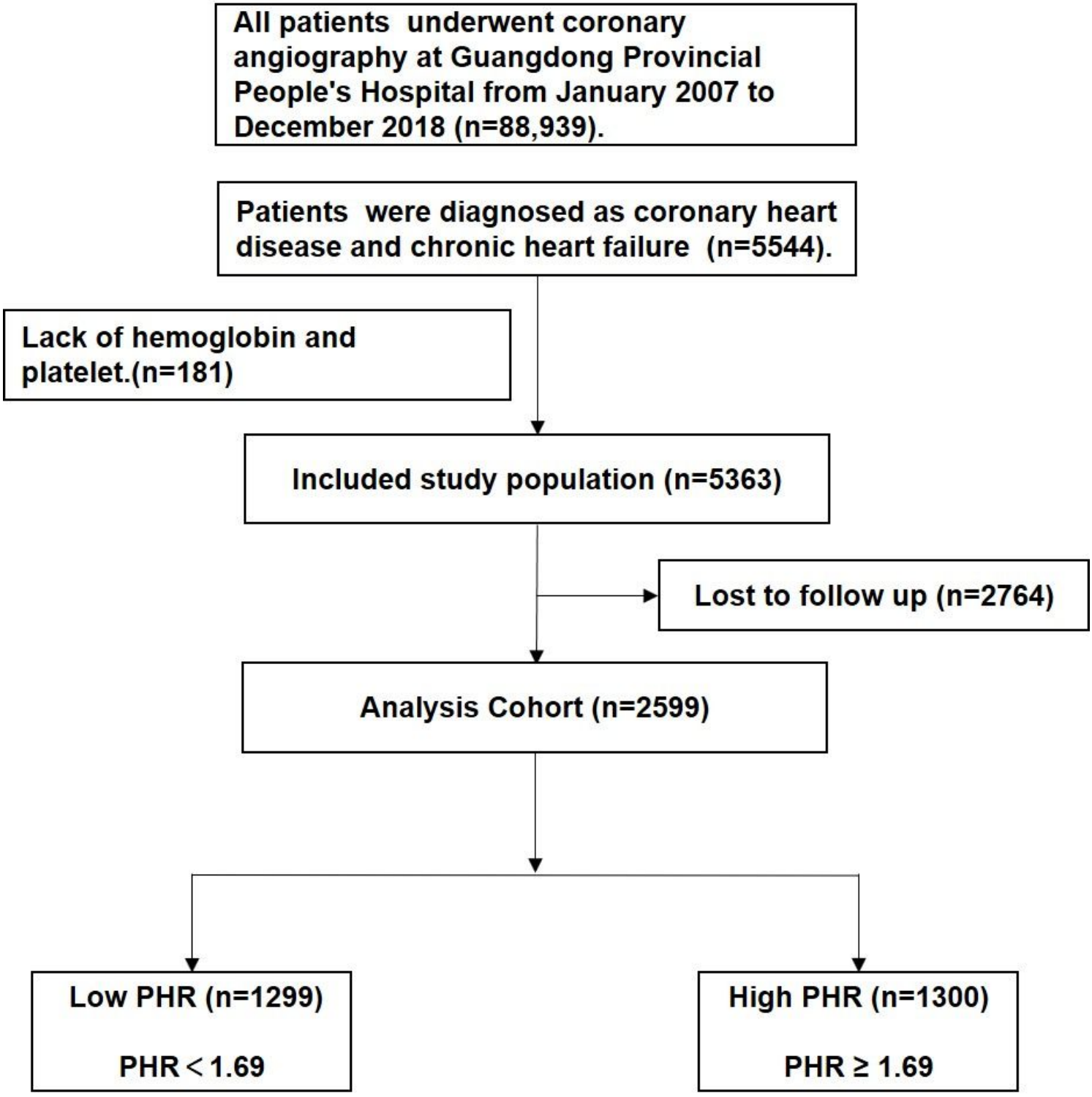


Figure 1

Patients flow diagram.

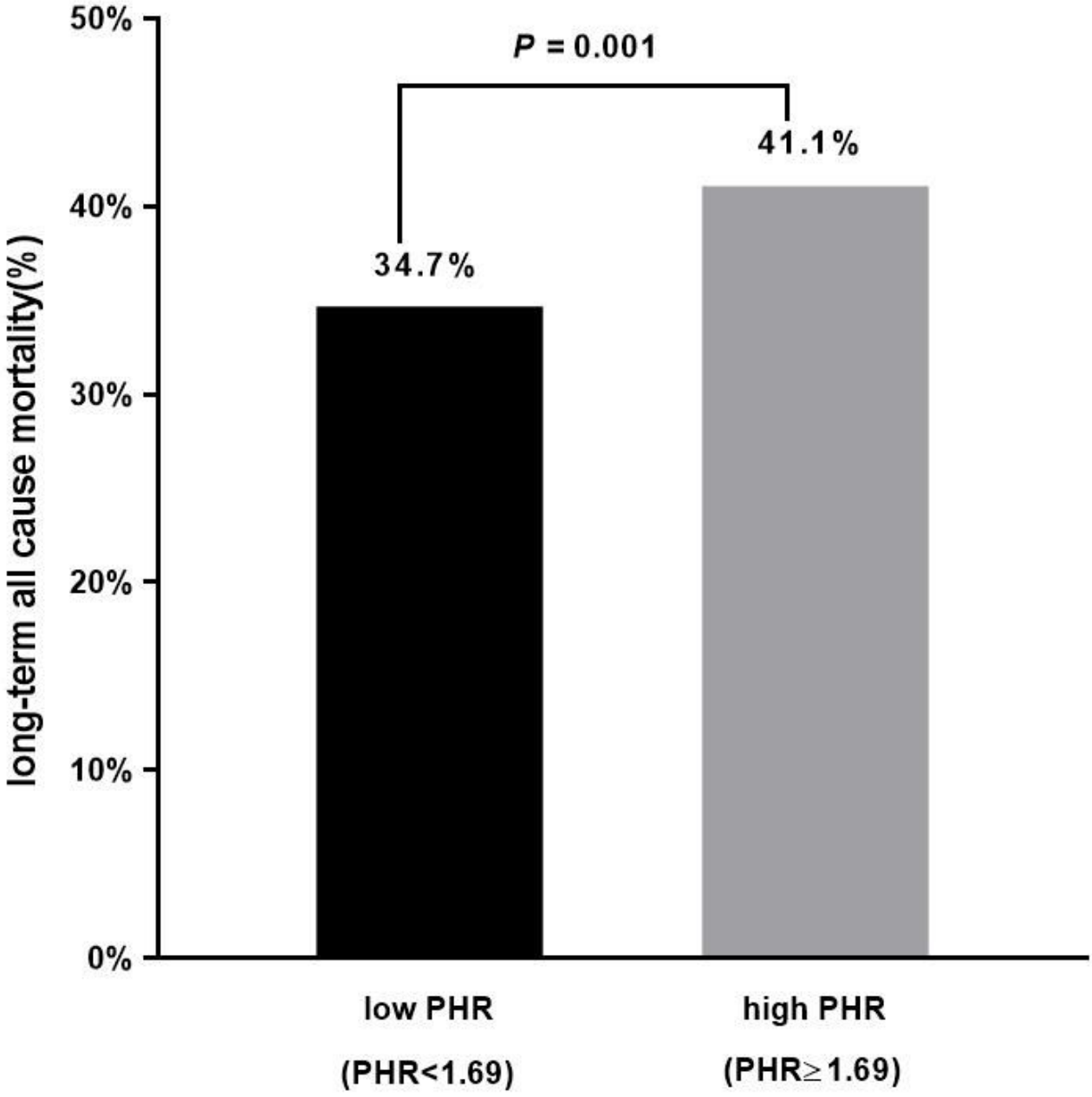


Figure 2

Bar chart for long-term all-cause mortality of PHR.

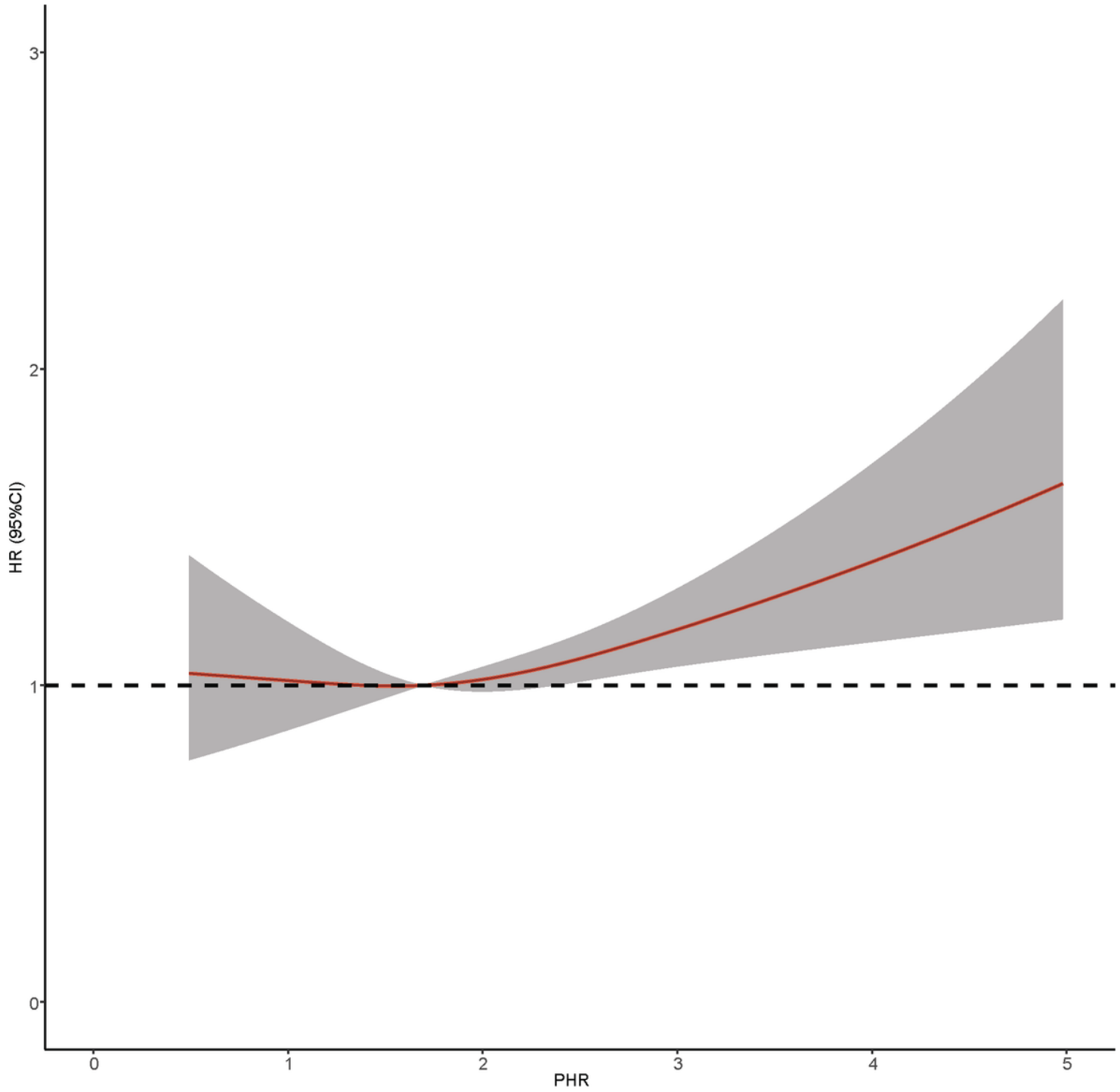
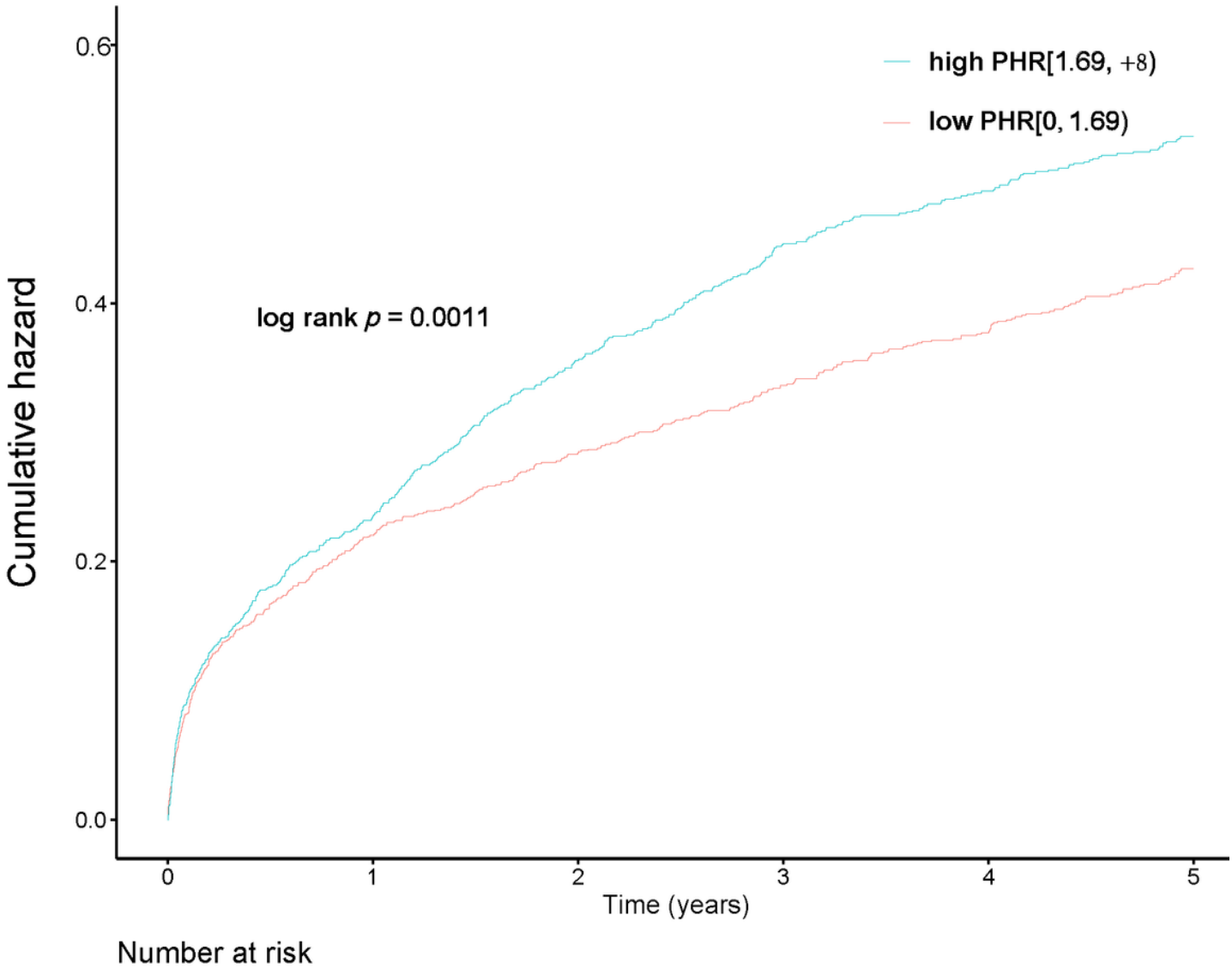


Figure 3

Restricted spline curve for the PHR hazard ratio.



Number at risk

low PHR	1299	1042	978	928	891	848
high PHR	1300	1028	911	833	799	766

Figure 4

Kaplan-Meier curves for long-term all-cause mortality of PHR.

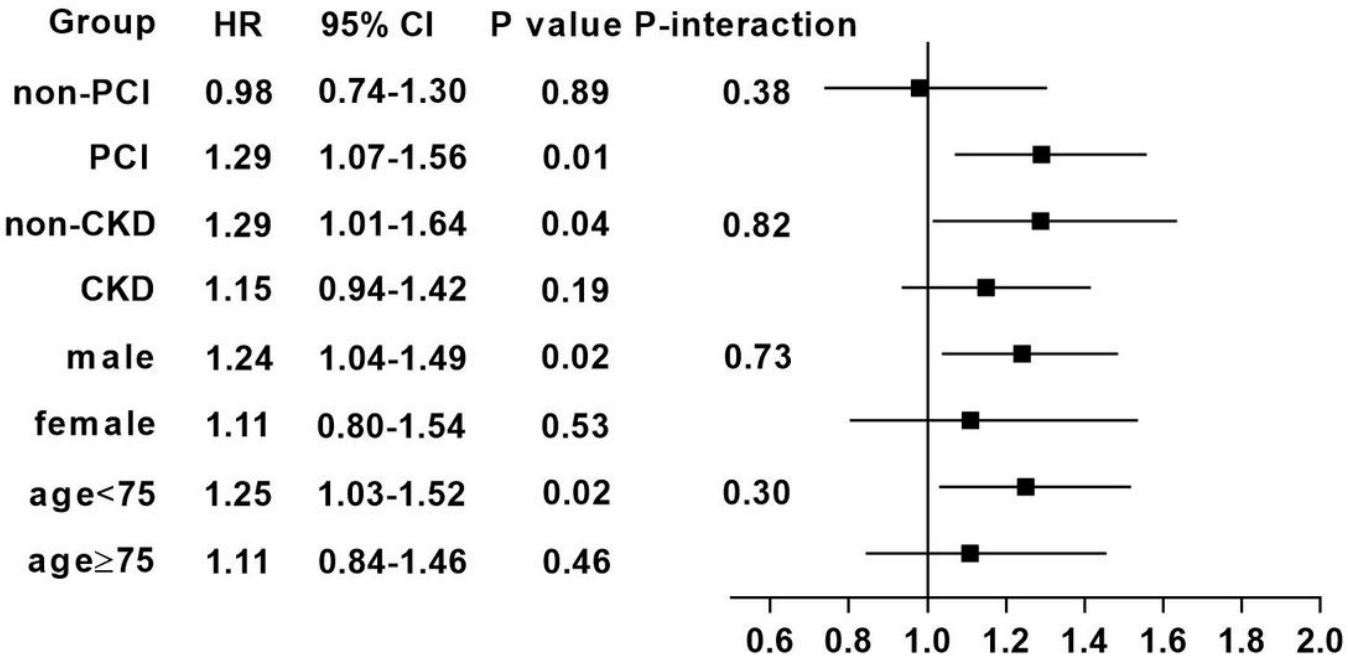


Figure 5

Forest plots of hazard ratios for the primary endpoint in different subgroups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable1.docx