

# A Novel and Simply Calculated Cardiac Load Index Correlates With Coronary Artery Disease

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## Research

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# Abstract

**Background:** No cardiac load index (CLI) has been established for patients with coronary artery disease (CAD). We propose a simple method for calculating CLI and explore the association of CLI with CAD.

**Methods:** We enrolled 4145 consecutive inpatients with suspected stable CAD from December 2011 to June 2017 at the Chengde Medical University Affiliated Hospital. All patients were divided into the CAD (n=2914) and the NCAD groups (n=1231) according to coronary computed tomography angiography. We retrospectively collected data and calculated the CLI values of all patients. The receiver operating characteristic diagnostic test analysis was performed with  $CLI \geq 77$ ,  $CLI \geq 125$ ,  $CLI \geq 171$ ,  $CLI \geq 217$ , and  $CLI \geq 264$ , respectively. Multivariate logistic regression models were established to determine the risk factors of CAD.

**Results:** The CLI was significantly higher in the CAD group than in the NCAD group and higher in the male than in the female subgroup (both  $P < 0.001$ ).  $CLI \geq 171$  was the diagnostic cut-off value. The predictive power of  $CLI \geq 171$  for CAD improved after considering other risk factors.  $CLI \geq 171$  is a new independent risk factor for CAD, and is an independent risk factor for CAD in males and females (all  $P < 0.001$ ).

**Conclusions:** Increased CLI is an independent risk factor for CAD, it may be used as a predictor for the prevalence for CAD to improve diagnosis and prevention.

## Background

In previous decades, cardiovascular researchers have conducted extensive basic and clinical research to explore the pathophysiology of coronary artery disease (CAD) [1,2]. Although the prevention, treatment, and care of CAD patients have greatly improved and adverse cardiovascular events and mortality have declined, the aging population experiences improved quality of life and reduced physical activity, which contributes to the prevalence of CAD remaining high and being the leading cause of death in patients with cardiovascular disease[3]. The pathogenesis of CAD is not fully understood; in addition to visceral fat, inflammatory factors, and classic clinical risk factors, researchers are committed to exploring new risk factors and biomarkers for CAD, such as the atherogenic index of plasma and the triglyceride glucose index[4,5].

Myocardial oxygen consumption depends on the wall tension, heart rate, myocardial contractility, and ejection time[6]. Systolic blood pressure (SBP) multiplied by heart rate (HR) is linearly related to myocardial oxygen consumption, and is an indicator of the cardiac workload[7]. Ejection fraction (EF) increases with myocardial contractility, and can be considered a parameter which includes vascular pressure and blood flow, and affects the cardiac workload[8]. We have proposed a new biomarker cardiac load index (CLI), which is calculated by  $SBP \times HR / \text{left ventricular EF (LVEF)}$ . In this study, we tested our hypothesis that CLI is associated with CAD and may be used as a new predictor for CAD.

## Methods

## Subjects and methods

This is a single-center, retrospectively, case-control study which included 4145 consecutive patients with suspected stable CAD treated at the Chengde Medical University Affiliated Hospital from December 2011 to June 2017. CAD was diagnosed according to coronary computed tomography angiography showing a left main, left anterior descending, circumflex, right coronary, or main branch stenosis  $\geq 50\%$ [9]. All patients were divided into the CAD (n=2914) and the NCAD groups (n=1231) and were assigned into the male and female subgroups. We excluded patients with age  $\leq 18$  years, severe valvular heart disease, aortic dissection, constrictive pericarditis, hypertrophic cardiomyopathy, pregnancy, or malignancy.

We collected all patients' data including baseline demographics (including age, sex, body mass index (BMI), and smoking), CAD-related risk factor diseases (type 2 diabetes, hypertension, dyslipidemia, ischemic stroke), routine blood test results, and biochemistry. We performed echocardiography to measure the LVEF, left atrial diameter, and left ventricular end-diastolic diameter within three days of admission. The resting HR and right brachial artery blood pressure were measured by resident cardiac physicians within 1 hour of admission. We then calculated the CLI values of all patients, where  $CLI = SBP \text{ (mmHg)} \times HR \text{ (bpm)} / EF \text{ (\%)}$ . The normal range of SBP is 90-140 mmHg; of HR, 60-100 bpm; and of EF is 53-70%. The normal range of CLI should be 77-264, according to the normal ranges of SBP, HR, LVEF. The quartiles of CLI between 77 and 264 were 125, 171, and 217, respectively.

## Statistical methods

Continuous variables are expressed as median and interquartile range, in accordance with the results of the Shapiro-Wilk test for normality, and the relationship between the two groups was examined using the Mann-Whitney U test. Categorical variables are presented as numbers and percentages, and the relationships between the two groups were examined using Fisher's exact test. The CLI were converted to binary variables according to the cut-off values of 77, 125, 171, 217, and 264. The optimal CLI cut-off value of 100.5 obtained with the Youden Index is not in line with clinical practice. We therefore performed receiver operating characteristic (ROC) diagnostic test analysis with  $CLI \geq 77$ ,  $CLI \geq 125$ ,  $CLI \geq 171$ ,  $CLI \geq 217$ , and  $CLI \geq 264$ . Subsequently,  $CLI \geq 77$ ,  $CLI \geq 125$ ,  $CLI \geq 217$ , and  $CLI \geq 264$  were compared with  $CLI \geq 171$ , and we obtained the NRI values. Univariate regression analysis was performed to explore the relationship of CLI with the CAD risk factors. Multivariate logistic regression models were established to determine the risk factors of CAD, CAD in males, and CAD in females. P values  $\leq 0.05$  were considered significant. Data were analyzed using Statistical Package for Social Sciences software, version 19 (IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA)).

## Results

### Clinical characteristics of the study

In this study, there were 2490 (60.1%) males, with the median age of 60 years. The prevalence of hypertension, type 2 diabetes, ischemic stroke, and the proportions of male gender, smoking, alcohol

consumption, and chest pain were significantly higher in the CAD than in the NCAD group (all  $P < 0.001$ ). The median values of age, HR, SBP, left atrial diameter, and left ventricular end-diastolic diameter were higher in the CAD than in the NCAD group; however, the median values of LVEF were higher in the NCAD than in the CAD group ( $P < 0.001$ ). The levels of leukocytes, low-density lipoprotein cholesterol (LDL-C), uric acid, blood urea nitrogen, and creatinine were significantly higher in the CAD than in the NCAD group, whereas the levels of high-density lipoprotein cholesterol were lower in the CAD than in the NCAD group (all  $P < 0.001$ ) (Table 1). The CLI is significantly higher in the CAD than in the NCAD group, and is higher in the male than the female subgroup ( $P < 0.001$ ) (Figure1).

### **Receiver operating characteristic curve diagnostic test analysis**

The area under the curve (AUC) of  $CLI \geq 171$  (0.594) is greater than that of  $CLI \geq 125$  (0.547),  $CLI \geq 217$  (0.579), and AUC of  $CLI \geq 264$  (0.544) ( $P < 0.001$ ).  $CLI \geq 125$ ,  $CLI \geq 217$ , and  $CLI \geq 264$  were compared with  $CLI \geq 171$ , indicating that the net reclassification indices (NRI) were -0.090, -0.025, and -0.096, respectively. The ROC diagnostic test of  $CLI \geq 77$  was not statistically significant ( $P = 0.938$ ). Therefore, 171 is the CLI diagnostic cut-off value of this study. The predictive power of  $CLI \geq 171$  for CAD improves after accounting for male sex, age  $\geq 45$  years, smoking, type 2 diabetes, hypertension, ischemic stroke, and  $LDL-C \geq 3.37$  mmol/L (AUC: 0.723 vs. 0.591;  $P < 0.001$ ) (Table 2).

### **Univariate analysis of CLI and CAD risk factors**

All patients were assigned into the high CLI group ( $CLI \geq 171$ ) and the low CLI group ( $CLI < 171$ ). The prevalence of  $BMI \geq 25$  kg/m<sup>2</sup>, dyslipidemia, hypertension, ischemic stroke, and CAD was significantly higher in the high CLI than in the low CLI group ( $P < 0.05$ ).  $BMI \geq 25$  kg/m<sup>2</sup>, dyslipidemia, hypertension, ischemic stroke, and CAD are associated with CLI, with odds ratios (OR) of 1.198, 1.140, 1.993, 1.370, and 2.165, respectively ( $P < 0.05$ ) (Table 3).

### **Multivariate logistic regression models of CAD**

Univariate logistic regression analysis was performed to screen those variables with  $P < 0.05$ , following which multivariate logistic regression models were created to identify risk factors for CAD, CAD in males, and CAD in females. In addition to the classic risk factors include male sex, age  $\geq 45$  years, smoking, type 2 diabetes, hypertension, ischemic stroke, and  $LDL-C \geq 3.37$  mmol/L were independent risk factors for CAD (all  $P < 0.001$ ).  $CLI \geq 171$  is a new independent risk factor for CAD ( $P < 0.001$ ) and is an independent risk factor for CAD in males and in females, with an OR of 1.966 and 1.866, respectively (both  $P < 0.001$ ) (Table 4).

## **Discussion**

This study was the first to provide the concept of  $SBP \times HR / LVEF$  representing CLI. The SBP and HR product is an indirect index of cardiac work, which can predict cardiac function, morbidity, and mortality in patients with cardiovascular disease[10]. LVEF is a valuable diagnostic and prognostic tool for

cardiovascular disease, and reflects cardiac function and remodeling[11]. Elevated CLI may promote inflammation and oxidative stress, activate the vascular smooth muscle and leukocyte infiltration, facilitate cardiac and vascular remodeling, and, furthermore, may accelerate the occurrence of atherosclerosis and the development of CAD[12,13].

In this study, multivariate logistic regression analysis indicated that in addition to the classic risk factors of CAD,  $CLI \geq 171$  is also an independent risk factor for CAD and has a higher risk for CAD than do smoking and hypertension. Myocardial ischemia is associated with disorders of cardiac function. Elevated  $SBP \times HR$  implies increasing myocardial oxygen consumption, and decreased LVEF indicates the myocardial in ischemic state and insufficient vascular pressure. Elevated HR is known to induce myocardial ischemia and cardiovascular events in patients with CAD[14]. Increased HR leads to endothelial oxidative stress, inflammation, and thrombosis and is conducive to atherosclerosis and plaque rupture, and eventually to adverse outcomes[15]. Hypertension is a known common pathogenic factor in CAD in developing countries. Elevated SBP promotes atherosclerosis and has a stronger predictive value for coronary heart disease, myocardial infarction, stroke, and cardiovascular mortality[16]. Ischemic heart disease is the most common cause of LVEF reduction, accounting for approximately 60% of all cases[17]. Previous studies have reported that CAD-induced cardiac failure with reduced LVEF accounts for the largest proportion of patients with cardiac failure[18]. Atherosclerosis is the most common pathophysiological mechanism for CAD; as atherosclerosis deteriorates, the stiffness of the vessel wall increases and the elasticity decreases, and coronary artery stenosis and occlusion occur, thereby reducing the blood flow and oxygen supply[19]. Elevated CLI indicates aggravated coronary inflammation and cardiovascular remodeling, which exacerbate the development of CAD and promote the occurrence of adverse cardiovascular events.

Risk factors for CAD differ between males and females due to differences in the genes carried by the X and Y chromosomes and in the sex hormones.[20,21]. Women display greater cardiac strength values than men, but male myocardia fibers are more sensitive to calcium than are female fibers[22]. There are differences in the degree of vascular wall stiffness, HR dynamics, and HR variability between males and females[23,24]. We found that CLI was higher in the male than the female subgroup, that  $CLI \geq 171$  was an independent risk factor for CAD in both the male and female subgroups, and the risk for CAD in males is slightly higher than in females.

In addition, CLI is associated with  $BMI \geq 25 \text{ kg/m}^2$ , dyslipidemia, hypertension, and ischemic stroke. These variables are known risk factors for CAD and influence the occurrence and development of atherosclerosis. Patients with one or more of these risk factors may develop higher CLI; moreover, higher CLI may aggravate the development of overweight, dyslipidemia, hypertension, and ischemic stroke and promote the development of CAD.

This study explores the potential of CLI as a new biomarker, which can be used to predict CAD along with other clinical risk factors. Exploring new risk factors and predictors improves the diagnosis and prevention of CAD.

This study has several limitations. This study is a single-center case-control study evaluating retrospective data. Further studies are required to elucidate whether the findings are applicable to other populations.

In conclusion, CLI is a novel risk indicator in patients with CAD and may be used as a predictor for the prevalence of CAD. Furthermore, this novel index differs between male and female patients, the risk for CAD in males is slightly higher than in females.

## **Abbreviations:**

CLI, cardiac load index; CAD, coronary artery disease; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

## **Declarations**

### **Ethics approval and consent to participate**

We conducted this study according to the standards of the Declaration of Helsinki on medical research, and the study protocol was approved by the Institutional Review Boards of the Affiliated Hospital of Chengde Medical University. All subjects provided written informed consent.

### **Consent for publication**

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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### **Authorship contributions**

YS contributed to the design of the study, performed the research, analyzed the data, and wrote the paper. JL, CH and XJ performed the research and collected the data. WF,TL performed the research. LS analyzed and interpreted the data and critically revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript for publication.

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## Tables

### Tables

<b>Table 1 Clinical characteristics of all subjects</b>					
Variables	Total (n=4145)	NCAD group (n=1231)	CAD group (n=2914)	$\chi^2/Z$	P
Male (%)	2490(60.1)	514(41.8)	1976(67.8)	244.955	<0.001
Age (year)	60(53, 68)	57(51, 63)	62 (55, 71)	-14.366	<0.001
BMI (kg/m <sup>2</sup> )	25.2(23.1, 27.5)	25.4(23.4, 27.6)	25.1(23.0, 27.4)	-1.589	0.112
Smoking (%)	1783(40.0)	341 (27.7)	1442(49.5)	167.542	<0.001
Chest pain (%)	2355(57.9)	518(42.7)	1837(64.3)	162.848	<0.001
Hypertension (%)	2356(56.8)	587 (47.7)	1796 (60.7)	59.821	<0.001
Type 2 diabetes (%)	787(19.7)	173(14.3)	614(22.1)	31.700	<0.001
Dyslipidemia (%)	1215(30.3)	346(28.6)	869(31.1)	2.425	0.119
Ischemic stroke (%)	487(11.7)	85(6.9)	402(13.8)	39.628	<0.001
HR (bpm)	72(64, 80)	70(64, 78)	72(64, 80)	-3.524	<0.001
SBP (mmHg)	130(120, 150)	130(120, 144)	135(120, 150)	-4.555	<0.001
DBP (mmHg)	80(76, 90)	80(75, 90)	80 (76, 90)	-0.806	0.420
LVEF (%)	60(55, 65)	62(58, 66)	58 (54, 63)	-18.156	<0.001
Left atrial diameter (mm)	34(30, 37)	33(30, 35)	34(31, 38)	-5.975	<0.001
Left ventricular end-diastolic diameter (mm)	50(46, 54)	49(46, 52)	50(47, 55)	-11.478	<0.001
Leukocytes (10 <sup>9</sup> /L)	6.65(5.446, 8.04)	6.40(5.35, 7.68)	6.74(5.50, 8.18)	-5.414	<0.001
TC (mmol/L)	4.21(3.58, 4.95)	4.24(3.61, 4.90)	4.20(3.57, 4.98)	-0.291	0.771
TG (mmol/L)	1.50(1.05, 2.23)	1.51(1.06, 2.22)	1.50 (1.04, 2.25)	-0.083	0.934
HDL-C (mmol/L)	1.04(0.87, 1.26)	1.09(0.92, 1.33)	1.03(0.86, 1.24)	-6.610	<0.001
LDL-C (mmol/L)	2.35(1.80, 2.95)	2.30 (1.75, 2.81)	2.38(1.81, 3.01)	-3.715	<0.001
Uric acid (mmol/L)	310(257, 370)	294(247, 347)	317(262, 376)	-7.729	<0.001
Blood urea nitrogen	5.57(4.58	5.17(4.30,	5.70(4.70,	-11.025	<0.001

(mmol/L)	6.77)	6.15)	7.10)		
Creatinine ( $\mu\text{mol/L}$ )	68(58, 80)	63(55, 74)	70(60, 82)	-11.782	<0.001

NCAD, non-coronary artery disease; CAD, coronary artery disease; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Variables	AUC	P	SE(%)	SP(%)	PPV(%)	NPV(%)	NRI
CLI $\geq$ 77	0.501 (0.482-0.520)	0.938	70.3	44.4	99.8	0.3	0.503
CLI $\geq$ 125	0.547 (0.527-0.566)	<0.001	72.6	43.6	88.7	20.6	-0.090
CLI $\geq$ 217	0.579 (0.561-0.597)	<0.001	88.4	33.7	22.8	92.9	-0.025
CLI $\geq$ 264	0.544 (0.525-0.562)	<0.001	92.8	31.7	10.7	98.1	-0.096
CLI $\geq$ 171	0.591 (0.573-0.610)	<0.001	79.0	36.5	49.2	69.0	
CLI with CAD risk factors	0.723 (0.705-0.740)	<0.001					

ROC, receiver operating characteristic; CLI, cardiac load index; CAD, coronary artery disease

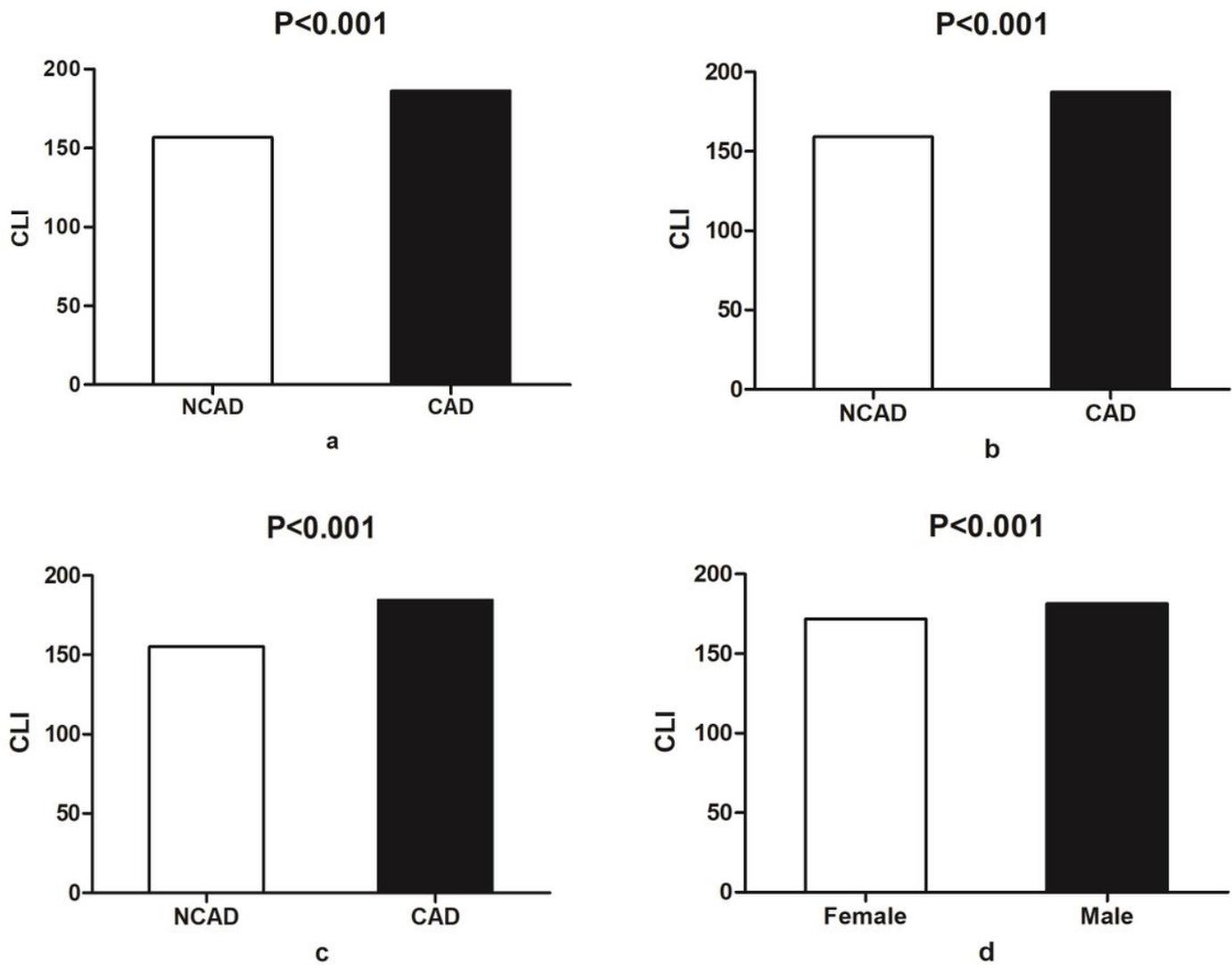
<b>Table 3 Univariate analysis of CLI and CAD risk factors</b>				
Variables	High CLI group	Low CLI group	OR	P
BMI $\geq$ 25kg/m <sup>2</sup>	734 (42.8)	601 (38.5)	1.198	0.011
Dyslipidemia	557 (45.8)	1190 (42.6)	1.140	0.057
Hypertension	1202 (51.0)	614 (34.3)	1.993	<0.001
Type 2 diabetes	414 (52.6)	1329 (41.5)	1.563	<0.001
Ischemic stroke	247 (50.7)	1569 (42.9)	1.370	0.001
CAD	1435 (79.0)	1479(63.5)	2.165	<0.001

CLI, cardiac load index; CAD, coronary artery disease; BMI, body mass index

<b>Table 4 Multivariate logistic regression models of CAD</b>									
Variables	All subjects			Male subgroup			Female subgroup		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Male	2.556	2.112-3.094	<0.001						
Age $\geq$ 45 years	2.205	1.662-2.926	<0.001	2.049	1.459-2.808	<0.001	3.426	1.645-7.134	0.001
Smoking	1.708	1.399-2.084	<0.001	1.556	1.262-1.943	<0.001	2.337	1.375-3.970	0.002
Type 2 diabetes	1.730	1.409-2.124	<0.001	1.116	0.836-1.491	0.457	2.425	1.832-3.209	<0.001
Hypertension	1.560	1.337-1.82	<0.001	1.277	1.034-1.575	0.023	1.956	1.556-2.458	<0.001
Ischemic stroke	1.914	1.462-2.506	<0.001	2.115	1.424-3.141	<0.001	1.690	1.161-2.461	0.006
LDL-C $\geq$ 3.37mmol/L	1.812	1.437-2.285	<0.001	1.832	1.260-2.665	0.002	1.808	1.339-2.441	<0.001
CLI $\geq$ 171	1.945	1.661-2.276	<0.001	1.966	1.582-2.444	<0.001	1.866	1.481-2.350	<0.001

CLI, cardiac load index; CAD, coronary artery disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

## Figures



**Figure 1**

(a) comparison of CLI between CAD and NCAD groups of all subjects; (b) comparison of CLI between CAD and NCAD groups of male subjects; (c) comparison of CLI between CAD and NCAD groups of female subjects; (d) comparison of CLI between male group and female groups