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Lipoprotein(a) and the risk of type I cardiorenal syndrome in patients with coronary artery disease: A retrospective clinical study

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ABSTRACT

Objective: The present study aimed to investigate the correlation between lipoprotein(a) (Lp-a) and coronary artery disease (CAD) complicated by type I cardiorenal syndrome (CRS).

Methods: We conducted a retrospective analysis of patients diagnosed with CAD admitted to the Department of Cardiovascular Medicine at Shaoxing Central Hospital from January 2021 to December 2022, with chief complaints of "chest distress and dyspnea." Patient demographic data, biochemical indicators (including blood lipid levels and serum creatinine), cardiac function markers (such as pro-brain natriuretic peptide, pro-BNP), echocardiography, and coronary angiography results were collected. Patients were categorized into two groups based on estimated glomerular filtration rate (e-GFR): the CRS group (e-GFR $<$ 60 mL/min/1.73 m^2) and the simple heart failure group (SHF group, e-GFR $\geq$ 60 mL/min/1.73 m^2). A comparative analysis of baseline characteristics, lipid profiles, ejection fraction (LVEF), left atrial size (LA), end-diastolic interventricular septal thickness (IVSd), left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD) between the two groups was performed. Multivariable logistic regression analysis was applied to assess the association between serum lipoprotein(a) (Lp-a) levels and the occurrence of CRS.

Results: A total of 269 patients were included, comprising 149 males and 120 females with an average age of 76.0 $\pm$ 11.4 years. Significant differences were observed between the CRS and SHF groups in terms of age, history of hypertension, diabetes, myocardial infarction, serum triglycerides, Lp-a, and creatinine (all $P < 0.05$). Spearman's correlation analysis revealed an inverse relationship between Lp-a and e-GFR ($r = -0.588$, $P < 0.05$). Multivariable logistic regression analysis indicated that Lp-a (OR = 1.980, 95 % CI: 1.269–2.992, P = 0.027) and age (OR = 1.584, 95 % CI: 0.955–1.913, P = 0.006) were positively associated with the development of CRS.

Conclusion: Serum Lp-a levels are positively correlated with the occurrence of CRS, potentially serving as an independent risk factor for CRS.

1. Introduction

Cardiovascular diseases and renal disorders are closely intertwined, often complicating each other's clinical course[1,2]. The intricate relationship between the heart and kidneys has led to the concept of cardiorenal syndrome (CRS), a clinical condition where dysfunction of one organ exacerbates the dysfunction of the other. Among its various types, type I CRS, characterized by acute worsening of heart failure leading to acute kidney injury, poses a significant therapeutic challenge. The pathophysiological interplay between the heart and kidneys in this setting is complex and multifactorial, often rooted in conditions such as acute coronary syndrome and subsequent cardiogenic shock or acute heart failure[3–6].

Coronary artery disease (CAD), a prevalent form of cardiovascular disease, frequently coexists with traditional risk factors like dyslipidemia, hypertension, and diabetes mellitus[1]. These factors not only contribute to the development and progression of CAD but also play a pivotal role in the pathogenesis of heart failure. Within this context, lipoprotein(a) [Lp(a)] has emerged as a potentially modifiable risk factor. Lp(a) is a unique lipoprotein particle, structurally similar to low-density lipoprotein (LDL), yet with distinct biological properties. It has been implicated in the pathogenesis of atherosclerotic vascular disease, and recent evidence suggests a role in the development of CRS[7,8].

This study aims to explore the association between Lp(a) levels and the occurrence of type I CRS in patients with CAD. We hypothesize that elevated Lp(a) levels may serve as a novel biomarker for the early

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identification of patients at risk for CRS, potentially guiding more targeted therapeutic interventions. By investigating this relationship, we seek to enhance our understanding of the pathophysiological mechanisms underlying CRS and to identify potential therapeutic targets that could mitigate its impact on patient outcomes.

Our research is designed to provide valuable insights into the role of Lp(a) in the cardiorenal axis. The findings may have significant implications for clinical practice, offering a rationale for the assessment of Lp (a) levels in patients with CAD and possibly influencing treatment strategies to prevent or manage CRS. Through this investigation, we aim to contribute to the growing body of knowledge on cardiorenal interactions and their implications for patient care.

2. Materials and methods

2.1. Study design and patient enrollment

This retrospective cohort study was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Shaoxing Central Hospital, and written informed consent was obtained from all individual participants included in the study. We meticulously curated a group of patients who were hospitalized in the Department of Cardiovascular Medicine at Shaoxing Central Hospital between January 2021 and December 2022, presenting with symptoms of "chest distress and shortness of breath." The study's objective was to investigate the relationship between lipoprotein(a) [Lp(a)] and the incidence of type I cardiorenal syndrome in patients with coronary artery disease.

Inclusion criteria for the study were strictly defined to ensure a homogeneous study population. Patients were included if they were 18 years or older, irrespective of gender. They had to fulfill the diagnostic criteria for acute heart failure as per the 2018 Chinese Guidelines for the Diagnosis and Treatment of Heart Failure, which include clinical signs of heart failure, echocardiographic evidence of left ventricular dysfunction, and elevated levels of natriuretic peptides. Additionally, all participants had to have undergone either coronary angiography or coronary computed tomography angiography (CCTA), demonstrating the presence of significant coronary artery stenosis ($\geq$50 % luminal narrowing) or a documented history of myocardial infarction.

Exclusion criteria were applied to rule out patients with confounding factors that could potentially skew the results. Patients were excluded if they had a previous diagnosis of chronic kidney disease, chronic renal insufficiency, or any malignant tumors. We also excluded patients with immune system disorders, as these conditions could influence both cardiac and renal function. Furthermore, individuals with dilated cardiomyopathy, hypertrophic cardiomyopathy, rheumatic heart disease, or acute myocarditis were not considered eligible for this study, as these conditions could independently affect heart and kidney function.

2.2. Data collection and management

Comprehensive data collection was performed for each patient, ensuring that all relevant clinical information was meticulously recorded. This included demographic information such as age, gender, and body mass index (BMI), as well as detailed medical history, including the presence of comorbidities like hypertension, diabetes, and a history of smoking. Past medical history, specifically relating to cardiovascular events like myocardial infarction, and family history of cardiovascular diseases were also documented.

A thorough review of each patient's medical records was conducted to extract relevant clinical data. This included information on the current admission, such as symptoms at presentation, clinical signs, and results of initial laboratory investigations. We also recorded data on concomitant medications, particularly those related to cardiovascular and renal therapy, such as diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, and statins.

2.3. Laboratory assessments

Blood samples were collected from each patient after an overnight fast to measure various biochemical parameters. The lipid profile, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), was assessed using a Beckman Coulter AU5800 analyzer. The levels of lipoprotein(a) [Lp(a)], apolipoprotein A (Apo-A), and apolipoprotein B (Apo-B) were also determined [9–12]. Additionally, serum creatinine [13,14] and brain natriuretic peptide (BNP) [15,16]levels were quantified to assess renal function and cardiac stress, respectively.

2.4. Echocardiographic evaluation

Transthoracic echocardiography was performed on all patients using a state-of-the-art Philips EPIQ-7 ultrasound system. This non-invasive imaging modality provided valuable insights into cardiac structure and function. The left atrial diameter (LA), interventricular septal end-diastolic thickness (IVSd), left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD) were measured according to the American Society of Echocardiography guidelines. The left ventricular ejection fraction (LVEF), a key indicator of cardiac systolic function, was calculated using the modified Simpson's biplane method [17,18].

2.5. Coronary angiography

Coronary angiography was conducted in a catheterization laboratory equipped with advanced imaging systems. At least two experienced interventional cardiologists independently interpreted the angiograms, assessing the severity and nature of coronary artery lesions. The left coronary artery was visualized in multiple 5–6 views, and the right coronary artery was visualized in 2–3 views to ensure comprehensive evaluation of the coronary vasculature [19–21].

2.6. Renal function assessment

The glomerular filtration rate (e-GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which provides a more accurate estimation of renal function compared to older formulas [22–24]. Patients were categorized into two groups based on their e-GFR values: the CRS group, with e-GFR less than 60 mL/min/1.73 m^2, and the simple heart failure group (SHF group), with e-GFR greater than or equal to 60 mL/min/1.73 m^2.

2.7. Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics software, version 20.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD) and were analyzed using parametric tests such as one-way ANOVA, with post hoc comparisons made using the least significant difference (LSD) test. Non-parametric data were presented as medians with interquartile ranges and were compared using the Kruskal-Wallis test. Categorical variables were expressed as frequencies and percentages and were analyzed using the chi-square test or Fisher's exact test, where appropriate. Multivariable logistic regression analysis was conducted to assess the association between Lp(a) levels and the occurrence of CRS, adjusting for potential confounders. A two-tailed p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. The patient cohort was divided into two groups: The CRS group and the SHF group, with a total of 269 patients enrolled in the study

Table 1 delineates the baseline characteristics of the study population, highlighting a significant disparity in age between the CRS group and the SHF group, with the latter exhibiting a notably younger demographic profile($P = 0.000$).

Upon comparison of the two groups, significant disparities were noted in the prevalence of traditional cardiovascular risk factors. Specifically, the CRS group exhibited a higher incidence of hypertension, diabetes mellitus, and a history of myocardial infarction, aligning with the expected complexities in patient profiles where renal compromise is evident. These observations were substantiated by statistical significance, with a $P < 0.05$.

The echocardiographic evaluations provided a comprehensive assessment of cardiac structure and function. While there were no significant differences in the left ventricular ejection fraction (LVEF) between the two groups(all $P > 0.05$).

3.2. Laboratory assessments unveiled a striking association between Lp(a) levels and the CRS group

Patients within this cohort demonstrated elevated serum levels of Lp (a), which were quantifiably higher than those in the SHF group ($P = 0.010$). (Fig. 1). In the realm of lipid profiles, our study revealed significant differences between the groups. Notably, the levels of triglycerides (TG) were markedly higher in the CRS group compared to the SHF group. This discrepancy was statistically significant, with a $P = 0.000$.(Table 1).

Table 1
Comparison of Clinical Characteristics of Patients.

Item	Simple heart failure group(SHF) (n = 110)	cardiorenal syndrome group(CRS) (n = 159)	*P Value*
Demographic Characteristics			
Gender (Male, %)	58 (52.7 %)	91 (57.2 %)	0.272
Age (years)	68.5 ± 12.2	80.7 ± 9.2	0.000
BMI (kg/m^2)	23.9 ± 3.2	23.6 ± 2.7	0.122
Underlying Diseases			
Hypertension (n, %)	61 (55.5)	112 (70.4)	0.008
Diabetes Mellitus(n, %)	32 (29.1)	65(40.9)	0.007
History of myocardial infarction (n, %)	14 (12.7)	35 (22.0)	0.036
Biochemical Indicators			
TG (mmol/L)	0.94 (0.63,1.05)	1.36 (0.82,1.58)	0.000
TC (mmol/L)	4.23 ± 1.17	4.36 ± 1.06	0.075
HDL-C (mmol/L)	1.17 ± 0.40	1.25 ± 0.37	0.093
LDL-C (mmol/L)	2.34 (1.78,2.80)	2.41 (1.79,2.97)	0.077
apo-A (mmol/L)	1.12 (0.94,1.26)	1.06 (0.69,1.03)	0.191
apo-B (mmol/L)	0.88 ± 0.27	0.74 ± 0.31	0.148
Lp-a (mg/L)	19.0 (6.35,22.95)	26.9 (9.3,35.5)	0.010
Scr (μmol/L)	67.9 ± 19.8	113.0 ± 81.5	0.000
BNP(ng/ml)	573.8 (371.4, 944.6)	652.7(355.9, 1052.7)	0.226
Echocardiographic			
LVEF (%)	47.1 ± 15.0	49.1 ± 12.5	0.219
LA (mm)	40.0 ± 9.6	40.1 ± 9.5	0.917
IVSd (mm)	10.4 ± 1.75	10.4 ± 2.1	0.212
LVESD (mm)	36.5 ± 8.3	34.3 ± 10.3	0.448
LVEED (mm)	52.7 ± 9.8	51.9 ± 7.3	0.173

TG, Triglycerides; TC, Total Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; apo-A, Apolipoprotein A-I; apo-B, Apolipoprotein B; Scr, Serum Creatinine; BNP, B-type Natriuretic Peptide.

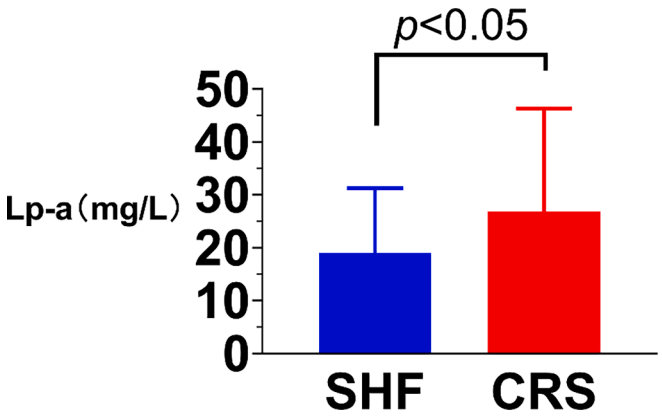

Fig. 1. Comparison of Lipoprotein(a) Levels Between Two Groups SHF,Simple heart failure group; CRS,cardiorenal syndrome group.

3.3. Medication use comparison

Table 2 outlines the medication usage between the cardiorenal syndrome (CRS) group and the simple heart failure (SHF) group. In the SHF group, 83.6 % of patients were on statins, compared to 86.1 % in the CRS group($P > 0.05$).The use of antiplatelet drugs, beta-blockers, lipid-lowering drugs other than statins, RAAS inhibitors, diuretics, and MRAs was also documented, showing similar rates of usage between the two groups(all $P > 0.05$).

3.4. The correlation between Lp(a) and renal function, as estimated by the e-GFR, was further interrogated using Spearman's rank correlation coefficient

A robust inverse correlation was identified ($r = -0.588$, $P < 0.001$), suggesting that as Lp(a) levels increase, renal function, as reflected by the e-GFR, declines.(Fig. 2).

3.5. In the multivariable logistic regression analysis, Lp(a) emerged as a significant predictor of CRS, with an odds ratio of 1.980 (95 % CI: 1.269–2.992, P = 0.027)

This model accounted for age, gender, and the presence of traditional cardiovascular risk factors, reaffirming Lp(a) as an independent

Table 2
Comparison of Medication Use of Patients.

Item	Simple heart failure group(SHF) (n = 110)	cardiorenal syndrome group (CRS) (n = 159)	*P Value*
Antiplatelet drugs			
Aspirin	92(83.6)	125(78.6)	0.058
Indobufen	9(8.18)	20(12.6)	0.253
Clopidogrel	12(10.9)	18(11.3)	0.916
Ticagrelor	17(15.5)	19(11.9)	0.407
Beta-blockers			
Metoprolol	47(42.7)	55(34.6)	0.176
Bisoprolol	24(21.8)	47(29.6)	0.157
Lipid-lowering drugs			
Statins	92(83.6)	137(86.1)	0.567
Fibrates	17(15.5)	32(20.1)	0.193
Ezetimibe	13(11.8)	22(13.8)	0.629
RAAS inhibitors			
ACEI	35(31.8)	57(35.8)	0.493
ARB	16(14.5)	15(9.43)	0.197
ARNI	37(33.6)	57(35.8)	0.708
Diuretics	85(77.2)	132(83.0)	0.241
MRA	35(31.8)	64(40.2)	0.159

ACEI, Angiotensin-Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; ARNI, Angiotensin-Neprilysin Inhibitors; MRA, Mineralocorticoid Receptor Antagonist.

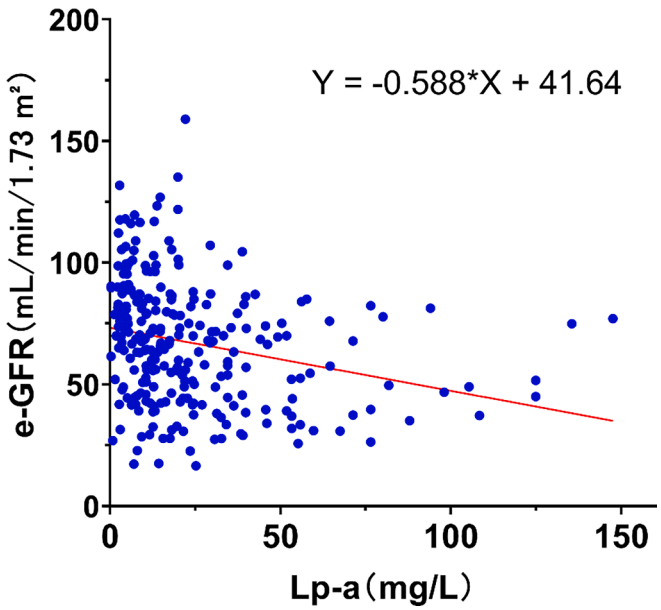

Fig. 2. Linear Relationship Graph between Lp(a) and e-GFR.

contributor to the development of CRS. Age was also identified as an independent risk factor, associated with an increase in the likelihood of CRS (OR = 1.584, 95 % CI: 0.955–1.913, P = 0.006). (Table 3) .

4. Discussion

Coronary artery disease (CAD) is a prevalent cardiovascular condition, characterized by high incidence, disability, and mortality rates, and has emerged as a significant cause of heart failure [1]. The early occurrence of cardiorenal syndrome (CRS) during the treatment of acute heart failure is a critical factor associated with poor patient prognosis [25,26]. There is a dearth of research, both domestically and internationally, on the relationship between lipoprotein(a) [Lp(a)] levels and patients with type I CRS. This study aimed to analyze the relationship between Lp(a) and the comorbidity of CRS in patients with CAD and heart failure, with the hope of providing a theoretical basis and potential novel targets for the prevention and treatment of CRS, thereby reducing the incidence of major adverse cardiovascular and cerebrovascular events (MACE).

Research by Matsushita [7] suggests that elevated levels of Lp(a) are predictive of coronary plaque rupture and are strongly correlated with the occurrence of major adverse cardiovascular events in patients with CAD. Our retrospective case study found that the incidence of myocardial infarction was significantly higher in the group with abnormal Lp(a) levels compared to the group with normal levels. The majority of patients with CAD in this study were regularly taking Lipid-lowering drugs, and there was no significant difference in total cholesterol and low-density lipoprotein levels between the simple heart failure (SHF) and CRS groups. However, there was a statistically significant difference in triglyceride and Lp(a) levels, possibly because statins primarily reduce total cholesterol and LDL-C, with less impact on triglycerides and Lp(a) [27,28].

Table 3
Multivariable logistic regression analysis of cardiorenal syndrome (CRS).

Factor	β-value	SE	OR value (95 % CI)	P-value
Age	0.124	0.017	1.584 (0.955 ~ 1.913)	0.006
HTN	0.590	0.295	0.946 (0.530 ~ 1.688)	0.852
DM	0.590	0.305	1.804 (0.992 ~ 3.280)	0.053
MIH	0.561	0.364	0.980 (0.280 ~ 1.164)	0.123
TG	0.441	0.233	1.554 (0.984 ~ 2.453)	0.059
LP-a	0.020	0.006	1.980 (1.269 ~ 2.992)	0.027

HTN, Hypertension; DM, Diabetes Mellitus; MIH, History of myocardial infarction; TG, Triglycerides.

Our study reveals a significant association between elevated serum lipoprotein(a) [Lp(a)] levels and the occurrence of type I cardiorenal syndrome (CRS) in patients with coronary artery disease (CAD). The mechanistic links between Lp(a) and CRS are multifaceted and can be discussed from several perspectives.

One of the primary mechanisms by which Lp(a) may contribute to CRS is through the activation of the renin-angiotensin-aldosterone system (RAAS). Lp(a) has been shown to stimulate the production of angiotensin II, a potent vasoconstrictor that promotes inflammation and fibrosis in the renal microvasculature. This can lead to a reduction in renal perfusion and a decline in glomerular filtration rate (GFR), which are hallmarks of CRS. The activation of RAAS by Lp(a) thus provides a plausible mechanism for the development of CRS in patients with CAD [29–31].

Furthermore, Lp(a) promotes the formation of atherosclerotic plaques, which can narrow or block the renal arteries. This process can impair renal function by reducing the blood supply to the kidneys, leading to ischemia and fibrosis. The resulting decline in renal function can further exacerbate heart failure, as the kidneys play a crucial role in volume and pressure regulation. Thus, the pro-atherogenic effects of Lp(a) may contribute to the vicious cycle of cardiorenal dysfunction characteristic of CRS [32].

In addition to its effects on RAAS and promotion of atherosclerosis, Lp(a) shares structural homology with plasminogen (PLG) and can competitively inhibit its function, leading to a reduced capacity for fibrinolysis. This disruption in the normal fibrinolytic process can result in the formation of microthrombi within the renal glomeruli, increasing their permeability and contributing to glomerulosclerosis. The subsequent decline in renal function can further strain the heart, as the kidneys play a crucial role in volume and pressure regulation [7,8,33].

Moreover, Lp(a) has been implicated in the induction of inflammation and oxidative stress, both of which are key drivers of CRS. High levels of Lp(a) can trigger the release of pro-inflammatory cytokines and reactive oxygen species (ROS), which can damage the endothelium of renal arterioles and promote vascular dysfunction. This can lead to the progression of renal disease and worsen heart failure, as the heart struggles to compensate for the reduced capacity of the kidneys to regulate fluid balance and electrolyte concentrations. The inflammatory and oxidative effects of Lp(a) thus provide another pathway through which Lp(a) may contribute to the development of CRS [34,35].

In this study, the incidence of hypertension, diabetes, and myocardial infarction in the CRS group was significantly higher than in the SHF group. Hypertension, as the most common chronic non-communicable disease, causes damage to the systemic arterial system, including the renal arteries. Long-term sustained hypertension increases the intracapsular pressure of the glomeruli, leading to glomerular fibrosis, atrophy, and renal arteriosclerosis, causing renal parenchymal ischemia and a continuous reduction in the number of renal units, ultimately leading to an increased incidence of CRS [36–38]. Diabetes, the second most common chronic metabolic disease after hypertension, is a leading cause of diabetic nephropathy, which primarily causes microvascular changes and glomerulosclerosis. With changes in the disease spectrum, it has become the leading cause of chronic kidney disease and end-stage renal disease, ultimately complicating the increase in CRS [39–42]. Prior myocardial infarction (MI) is a significant predictor of cardiorenal syndrome (CRS), exerting its influence through a cascade of pathophysiological mechanisms. The legacy of MI can lead to left ventricular dysfunction, which in turn generates a hemodynamic strain that diminishes renal perfusion. This reduction in renal blood flow can precipitate a decline in glomerular filtration rate (GFR), a key marker of renal function. Moreover, the post-MI milieu is characterized by heightened levels of circulating inflammatory cytokines, which can directly injure the renal tubules and exacerbate interstitial fibrosis. The

resultant renal impairment further amplifies the neurohormonal activation, creating a deleterious feedback loop that augments both cardiac and renal dysfunction. [43–45].

4.1. Limitations

Our study's retrospective and single-center design poses limitations, potentially introducing biases specific to our patient population and healthcare system, and limiting the generalizability of our findings. The reliance on historical data also raises concerns about data completeness and accuracy. Future multicenter, prospective studies with larger samples, incorporating genetic data, and detailed lifestyle information, could provide a more comprehensive understanding of Lp(a)'s role in CRS and its impact on cardiorenal outcomes. Despite these limitations, our study contributes valuable insights into the association between Lp (a) levels and CRS, emphasizing the need for further research and highlighting Lp(a)'s potential role in managing patients with CAD.

4.2. Conclusions

In conclusion, our study sheds light on the role of Lp(a) in the development of CRS in patients with CAD. The significant association between Lp(a) levels and CRS, as demonstrated in our analysis, warrants further investigation into the potential use of Lp(a) as a therapeutic target and biomarker for early identification of CRS risk. This could have important implications for the management of patients with CAD, particularly in the context of preventing or mitigating the impact of CRS. By better understanding the role of Lp(a) in the cardiorenal axis, we may be able to develop more effective strategies for the prevention and treatment of CRS, ultimately improving outcomes for patients with cardiovascular and renal comorbidities.

Ethics statement

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for this study was obtained from the Institutional Review Board of Shaoxing Central Hospital.

Patient consent

Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Zhenhua Jiang: Writing – original draft, Data curation, Conceptualization. **Hailiang Ma:** Methodology, Formal analysis, Data curation. **Jianqiang Meng:** Software, Formal analysis, Data curation. **Dewen Zhu:** Validation, Software, Investigation. **Yuanben Lu:** Investigation, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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