BMC Cardiovascular Disorders

RESEARCH Open Access

A-kinase anchoring protein 1: an independent predictor of coronary artery disease

Wei Yan[1], Yun-Lang Dai[2] and Jun-Xia Han[3*]

Abstract

Introduction Coronary artery disease (CAD) is the leading cause of death worldwide. A-kinase anchoring protein 1 (AKAP1), thought to regulate the function and structure of mitochondria, is enriched in the heart, where it plays a protective role. However, data on the serum AKAP1 concentration levels in patients with CAD are currently lacking. To address this, the serum levels of AKAP1 in patients with CAD were quantified and their predictive ability for CAD was evaluated in this study.

Methods A total of 255 patients referred for coronary angiography were included in this study and classified into two groups (CAD and non-CAD group). A comparative analysis of clinical data and serum AKAP1 concentration levels was performed between the two groups. The patients were then divided into quartiles according to AKAP1 levels. A multivariate logistic regression model was used to assess the independent association of AKAP1 with CAD.

Results The CAD group showed a lower AKAP1 concentration than the non-CAD group ($P<0.01$). The AKAP1 level was correlated with a history of CAD ($P<0.001$). The receiver operator characteristic (ROC) curve analysis showed a low ability of AKAP1 in predicting CAD (area under the ROC curve = 0.649). Finally, in the multivariate logistic regression model with the highest quartile as the reference, the lowest quartile of AKAP1 remained significantly associated with an increased risk for CAD (odds ratio (OR) = 5.677, 95% confidence interval [CI] 1.704 to 18.912, $P=0.005$).

Conclusions Our results confirmed that serum AKAP1 levels are inversely associated with CAD and may therefore be used as a marker for CAD prediction. But additional studies are needed to confirm and further elucidate our results.

Keywords A-kinase anchoring protein 1, Coronary artery disease, Cardioprotective roles

Introduction

Coronary artery disease (CAD) is a kind of heart disease caused by coronary artery atherosclerosis or spasm, resulting in stenosis or occlusion of the lumen, thereby causing myocardial ischemia, hypoxia and even necrosis. It is the most common cause of mortality and morbidity, affecting 126 million people worldwide (about 17.2% of the global population) according to the Global Burden of Disease Study (2021) [1]. CAD is a chronic, progressive disease characterized by the accumulation of atherogenic lipoproteins, inflammatory cells, and fibrillar collagen in focal areas of arteries, which result in the formation and

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progression of atherosclerotic plaques [2]. The lingering incidences of cardiovascular events, including cardiovascular death, myocardial infarction and stroke, and heart failure, impose significant socioeconomic burdens and negatively impact the quality of patients' life [3, 4]. Therefore, it is urgent to explore biomarkers to distinguish the severity of CAD.

A-kinase anchoring protein 1 (AKAP1) is a family of mitochondrial A-kinase anchoring proteins encoded by Akap1 gene and responsible to maintain mitochondrial homeostasis and cell viability [5]. It is a scaffold protein that recruits protein kinase A (PKA), other signaling proteins, as well as RNA to the outer mitochondrial membrane. The mitochondria play an essential role in supporting the high-energy demand for cardiomyocyte contractions. In acute cardiac injuries, mitochondrial ability to regulate cellular reactive oxygen species (ROS) generation and sequestration affects the survival rate of cardiomyocytes [6, 7]. AKAP1 is considered a cardioprotective scaffolding protein of PKA. Cardiac AKAP proteins, namely mAKAP and AKAP1, can enhance cardiomyocyte survival against hypoxia-caused damage by adaptively regulating the level of mitochondria-mediated oxidative respiration and maintaining the mitochondrial integrity and function [8, 9]. Moreover, mitochondrial AKAP1 in endothelial cells (ECs) plays an essential role in the regulation of nitric oxide (NO) -dependent vascular relaxation and blood pressure by increasing endothelial NO synthase (eNOS) phosphorylation levels through the phosphatidylinositol 3-kinase-Akt signaling pathway [5]. Thus, evidence indicates that mitochondrial AKAP1 is potential therapeutic targets for the treatment of endothelia dysfunctions in CAD [10]. Recent reports collectively highlight the importance of AKAP1 in cardiovascular health and elucidate its role in the pathogenesis of cardiac injury and CAD [9, 11]. Although previous studies have showed that AKAP1 may play an important role in the occurrence and development of CAD, little is known about the role of the serum levels of AKAP1 protein in patients with CAD.

To investigate this issue, we quantified the serum levels of AKAP1 in patients undergoing coronary angiography, who were categorized into CAD and non-CAD groups. And then we evaluated the association between AKAP1 and CAD. The primary objective of this study is to explore a biomarker that can differentiate the severity of CAD and explore a potential therapeutic target for patients with CAD.

Materials and methods

Patients

A total of 255 patients who received coronary artery angiography (CAG) for the first time in the Cardiology Department of the First Affiliated Hospital of Soochow University (Suzhou, China) between January 2021 and May 2021 were included in our study. Subjects with either previous myocardial infarction, malignant tumors, severe liver or kidney damage (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), acute complications, pregnancy, and lactation were excluded.

Coronary angiograms were assessed by two cardiologists blinded to the diagnoses of the patients. Patients with > 50% stenosis in at least one epicardial coronary artery were categorized as patients with CAD. The control group was composed of patients without CAD. Of the 255 patients, 188 (73.7%) and 67 (26.3%) patients were included in the CAD and non-CAD groups, respectively. To determine the CAD severity, patients were divided into three subgroups based on the number of significantly affected stenotic vessels (1 vascular disease (VD) < 2VD < 3VD) [12].

The study protocol was approved by the Ethics Committee according to the principles of the Helsinki Declaration. All patient records were anonymized before analysis and informed consent was obtained from all patients.

Data collection

Electronic medical records were used to obtain the demographic variables, clinical data, laboratory values, echocardiographic parameters, and information on patients' past medical history and medications. Blood samples were acquired to perform biochemical analysis after 12 h of fasting. A Hitachi 7600 automatic biochemical analyzer was used to determine the biochemical markers and lipid profiles. A high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA) was used to determine glycosylated hemoglobin (HbA1c), while AKAP1 concentration was evaluated using ELISA kit (Raybiotech, USA). The diagnosis of diabetes mellitus (DM) was made based on the 1999 World Health Organization diagnostic criteria [13]. Body mass index (BMI) was determined using the following equation: weight (kilograms) divided by the square of height (meters). After sitting for 15 min, the blood pressure of the subjects was measured twice on their right upper arm. Systolic blood pressure and diastolic blood pressure were determined by the mean level of the two measurements.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 25.0). Normally distributed data were expressed as the mean ± standard deviation (SD), whereas non-normal distributed data were expressed as median (interquartile range). Discrete variables are expressed as frequencies and percentages. The continuous variables were compared between the CAD and non-CAD groups using Student's t-test and

the Mann-Whitney U test for variables with normal and skewed distributions, respectively. The continuous variables were compared using analysis of variance and Kruskal-Wallis tests for those with normal and skewed distributions for three or more groups, respectively. The discrete variables were compared between the CAD and non-CAD groups using the Chi-square test. A Spearman correlation test was employed to study the continuous variables related to AKAP1 levels. Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminative ability of AKAP1 and left ventricular ejection fraction (LVEF) for CAD, and the optimal cut-off of the two values were determined using the Youden index. Multivariate logistic regression models were used to analyze the association between the quartiles of AKAP1 and CAD. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The variables for which $P<0.1$ was obtained in the univariate analysis were considered for use in the multivariate model along with age and gender. $P<0.05$ was considered statistically significant. The flowchart of the research process is showed in Fig. 1.

Results

Biochemical and anthropometric parameters

A preliminary analysis of biochemical and anthropometric parameters obtained from the CAD and non-CAD groups is presented in Table 1. Patients with CAD were more likely to have DM and undergo antidiabetic therapy. HbA1c and c-reactive protein levels were higher, and high-density lipoprotein, LVEF and AKAP1 levels were lower in patients with CAD than in the controls.

Based on the affected stenotic vessels (1VD, 2VD, and 3VD), the serum levels of AKAP1 in patients with CAD with 1VD, 2VD, and 3VD and patients without CAD were compared. AKAP1 level was lower in the CAD group, including the 1VD, 2VD, and 3VD subgroups, than in the non-CAD group ($P<0.05$) (Table 2). Moreover, AKAP1 level was significantly lower in the 3VD patient subgroup than in the 1VD patient subgroup ($P<0.05$).

Correlation between AKAP1 and CAD

The correlations between AKAP1 and all the variables and characteristics are presented in Tables 3 and 4. AKAP1 levels were found to be negatively correlated with BMI and HbA1c. In addition, AKAP1 levels were also correlated with a history of DM and CAD and the use of statins and antidiabetic therapy.

Discriminative ability of AKAP1 and LVEF for CAD

The ROC curve of AKAP1 concentration as a predictive factor for CAD highlighted the limited ability of AKAP1 to predict CAD. The area under the curve was 0.649 (95% CI 0.579–0.719, $P<0.001$). The optimal cut-off level for AKAP1 to predict CAD was found to be 0.42 ng/mL (High AKAP1 levels (>0.42 ng/mL) were associated with the high risk of CAD), with a specificity of 77.6% and sensitivity of 47.3%. The ROC curve of AKAP1 and LVEF levels as predictive factors for CAD were showed in Fig. 2.

Effects of AKAP1 quartiles on CAD

The patients were categorized on the basis of AKAP1 levels into the quartile 1 (<0.32ng/mL), quartile 2 (0.32–0.50ng/mL), quartile 3 (0.50–0.77ng/mL) and quartile 4 (≥0.77ng/mL) groups. Age, sex, HbA1c, high-density lipoprotein, LVEF, DM and statins and antidiabetic therapy were included in the logistic regression model. In the multivariate analysis with the highest quartile as the reference, the lowest AKAP1 quartile remained significantly associated with CAD (OR = 5.677, 95%CI 1.704 to 18.912, $P=0.005$) In the fully adjusted Model 5. No difference was observed between the other quartiles in the risk of CAD (Table 5).

Discussion

Our study showed that the CAD group exhibited a lower AKAP1 concentration than the non-CAD group. This result highlights the potential cardioprotective roles of AKAP1. Our data showed that the serum AKAP1 levels in the 3VD patient subgroup was significantly lower than that in the 1VD and non-CAD subgroups. This implies that the serum AKAP1 levels are inversely associated with CAD severity. AKAP1 levels were found to be negatively correlated with BMI and HbA1c. In addition, AKAP1 levels were also correlated with a history of DM and CAD and the use of statins and antidiabetic therapy. In this study, AKAP1 displayed a low discriminative ability for CAD (area under the ROC curve = 0.649), implying the overt gray zone with regard to AKAP1 between CAD and non-CAD patients. Lastly, in the multivariate analysis with the highest quartile as the reference, the lowest AKAP1 quartile remained significantly associated with CAD, highlighting the potential unique association between AKAP1 and CAD.

Cardiomyocytes rely on proper mitochondrial function to support the high-energy demand required for contraction. AKAP1 is localized in the mitochondrial outer membrane and plays key roles in the regulation of mitochondrial function. AKAP1 is enriched in the heart and play crucial roles in the cardiovascular system under both physiological and pathological conditions [8]. Similar to our study on cardiovascular disease, Fang et al. demonstrated that AKAP1 reduced ROS-induced lipid peroxidation ferroptosis through the inhibition of ubiquitination of NADH-ubiquinone oxidoreductase 75 kDa subunit (NDUFS1) by mitochondrial damage in model of renal patients with acute heart failure, indicating a novel

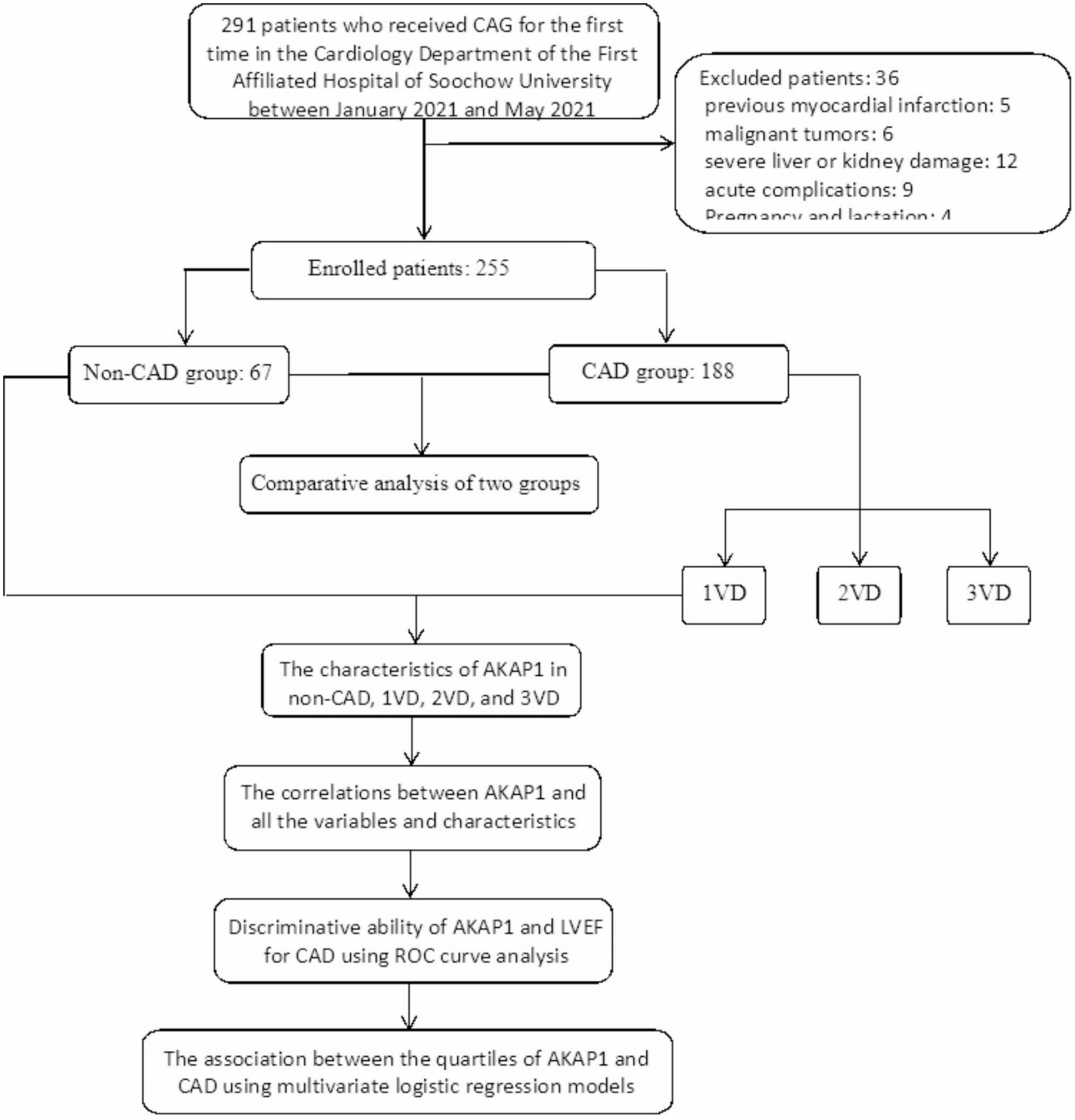

Fig. 1 Flowchart of the research process

target for heart failure treatment [14]. Moreover, Qi et al. showed that AKAP1 deficiency exacerbated diabetic cardiomyopathy by impeding mitochondrial translocation of NDUFS1 to induce mitochondrial dysfunction and cardiomyocyte apoptosis, suggesting that AKAP1 upregulation has therapeutic potential for myocardial injury in individuals with diabetic cardiomyopathy [15]. For CAD, a previous study in 2016 revealed that under the condition of myocardial ischemia, Akap1 genetic deletion resulted in mitochondrial morphological abnormalities, increased cardiomyocyte mitophagy and myocardial infarct size, contributing to a decrease in heart function and survival [9]. Over the last decade, despite several studies demonstrating an association between AKAP1 and cardiovascular disease, few have focused on individuals with CAD as our study. In recent years, the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (SS) has significantly improved angiographic risk stratification [16]. Recent research has suggested percutaneous coronary

Table 1 Demographic and clinical characteristics of CAD-, CAD+

Variable	CAD-	CAD+	*P* value
Male	46 (68.7%)	139 (73.9%)	0.406[1]
Age, yrs	63 (55, 69)	65 (56, 71)	0.539[2]
Smoking	13 (19.4%)	56 (29.8%)	0.100[1]
Hypertension	55 (82.1%)	148 (78.7%)	0.557[1]
Diabetes mellitus	13 (20.1%)	79 (42.0%)	< 0.01[1]
Hyperlipidemia	25 (37.3%)	86 (45.7%)	0.232[1]
Body mass index, kg/m^2	24.82 ± 3.61	25.03 ± 2.63	0.662[3]
Systolic blood pressure, mmHg	130 (121, 142)	133 (120, 145.5)	0.907[2]
Diastolic blood pressure, mmHg	80 (74, 90)	80 (72, 88)	0.350[2]
Alanine transaminase, U/L	19.00 (15.00, 31.00)	20.40 (14.00, 29.95)	0.943[2]
Creatinine, mg/dL	69.00 (57.00, 78.40)	69.40 (61.35, 79.85)	0.198[2]
Fasting blood-glucose, mmol/L	5.22 (4.75, 5.79)	5.19 (4.51, 6.57)	0.918[2]
Glycosylated hemoglobin, %	6.0 (5.7, 6.3)	6.3 (5.8, 7.3)	0.004[2]
Total cholesterol, mmol/L	4.20 (3.27, 4.96)	4.31 (3.64, 5.00)	0.179[2]
Triglyceride, mmol/L	1.46 (0.93, 1.81)	1.49 (1.07, 2.06)	0.424[2]
High-density lipoprotein, mmol/L	1.07 (0.96, 1.20)	0.95 (0.82, 1.17)	0.002[2]
Low-density lipoprotein, mmol/L	2.65 (2.03, 3.15)	2.50 (1.96, 3.28)	0.755[2]
C-reactive protein, mg/L	0.33 (0.21, 1.34)	1.43 (0.42, 5.17)	< 0.01[2]
LVEF, %	68.00 (62.75,73.00)	62.00 (56.00,68.00)	< 0.01[2]
AKAP1, ng/mL	0.62 (0.44,0.88)	0.42 (0.29,0.73)	< 0.01[2]
Aspirin	18 (26.9%)	65 (34.6%)	0.248[1]
Statins	14 (20.9%)	61 (32.4%)	0.075[1]
Antihypertensive medication	43 (64.2%)	123 (65.4%)	0.854[1]
Antidiabetic therapy	6 (9.0%)	62 (33.0%)	< 0.01[1]

Continuous variables are expressed as mean ± SD or median (interquartile range); categorical variables are presented as numbers and percentage. LVEF, left ventricular ejection fraction. [1]P are obtained using the Chi-square test, [2]P are obtained using the Mann-Whitney U test and [3]P are obtained using Student's t-test

Table 2 The characteristics of AKAP1 in CAD + subjects with 1VD, 2VD, and 3VD

Variable	CAD-	1VD[a]	2VD[a]	3VD[ab]	*P* value
AKAP1, ng/mL	0.62 (0.44,0.88)	0.45 (0.32,0.74)	0.43 (0.27,0.84)	0.36 (0.27,0.62)	<0.01

Compared with CAD- group: [a]$P < 0.05$; compared with the 1VD group: [b]$P < 0.05$

Table 3 Spearman correlation coefficients for AKAP1

Variable	AKAP1	*P* value
Age	0.081	0.200
Body mass index	-0.129	0.039
Systolic blood pressure	-0.110	0.080
Diastolic blood pressure	-0.023	0.720
Alanine transaminase	0.067	0.286
Creatinine	-0.029	0.647
Fasting blood-glucose	-0.109	0.082
Glycosylated hemoglobin	-0.159	0.011
Total cholesterol	-0.005	0.932
Triglyceride	-0.037	0.556
High-density lipoprotein	0.011	0.864
Low-density lipoprotein	0.052	0.409
C-reactive protein	-0.010	0.875
Left ventricular ejection fraction	0.056	0.388

Table 4 Comparison of AKAP1 levels between the different characteristics

Characteristics	AKAP1 (ng/mL)	*P* value
Gender		0.307
Male	0.52 (0.32, 0.81)	
Female	0.43 (0.31, 0.64)	
Smoking		0.233
Yes	0.52 (0.33, 0.87)	
No	0.46 (0.32, 0.75)	
Hypertension		0.109
Yes	0.45 (0.31, 0.73)	
No	0.61 (0.33, 0.99)	
Diabetes mellitus		0.001
Yes	0.37 (0.25, 0.68)	
No	0.58 (0.36, 0.85)	
Hyperlipidemia		0.382
Yes	0.48 (0.32, 0.72)	
No	0.52 (0.32, 0.86)	
Coronary artery disease		< 0.001
Yes	0.42 (0.29, 0.73)	
No	0.62 (0.44, 0.88)	
Use of aspirin		0.124
Yes	0.42 (0.29, 0.79)	
No	0.53 (0.34, 0.76)	
Use of statins		0.002
Yes	0.41 (0.28, 0.61)	
No	0.58 (0.34, 0.88)	
Antihypertensive medication		0.471
Yes	0.46 (0.31, 0.76)	
No	0.56 (0.32, 0.84)	
Antidiabetic therapy		< 0.001
Yes	0.32 (0.23, 0.57)	
No	0.58 (0.36, 0.86)	

intervention is a favorable alternative for patients with a low SS, but coronary artery bypass grafting is indicated for those with a high SS [17]. Low endothelial progenitor cell counts or activity, as well as attenuated nitric oxide synthase, have been associated with poor endothelial function in patients with high SS [18]. Wang et al., in contrast, have found that the atherogenic index of plasma is associated with the SS and may help prevent CAD in the Chinese population [19]. Therefore, these findings suggest that novel surrogate markers like AKAP1 for SS in CAD severity prediction might be developed.

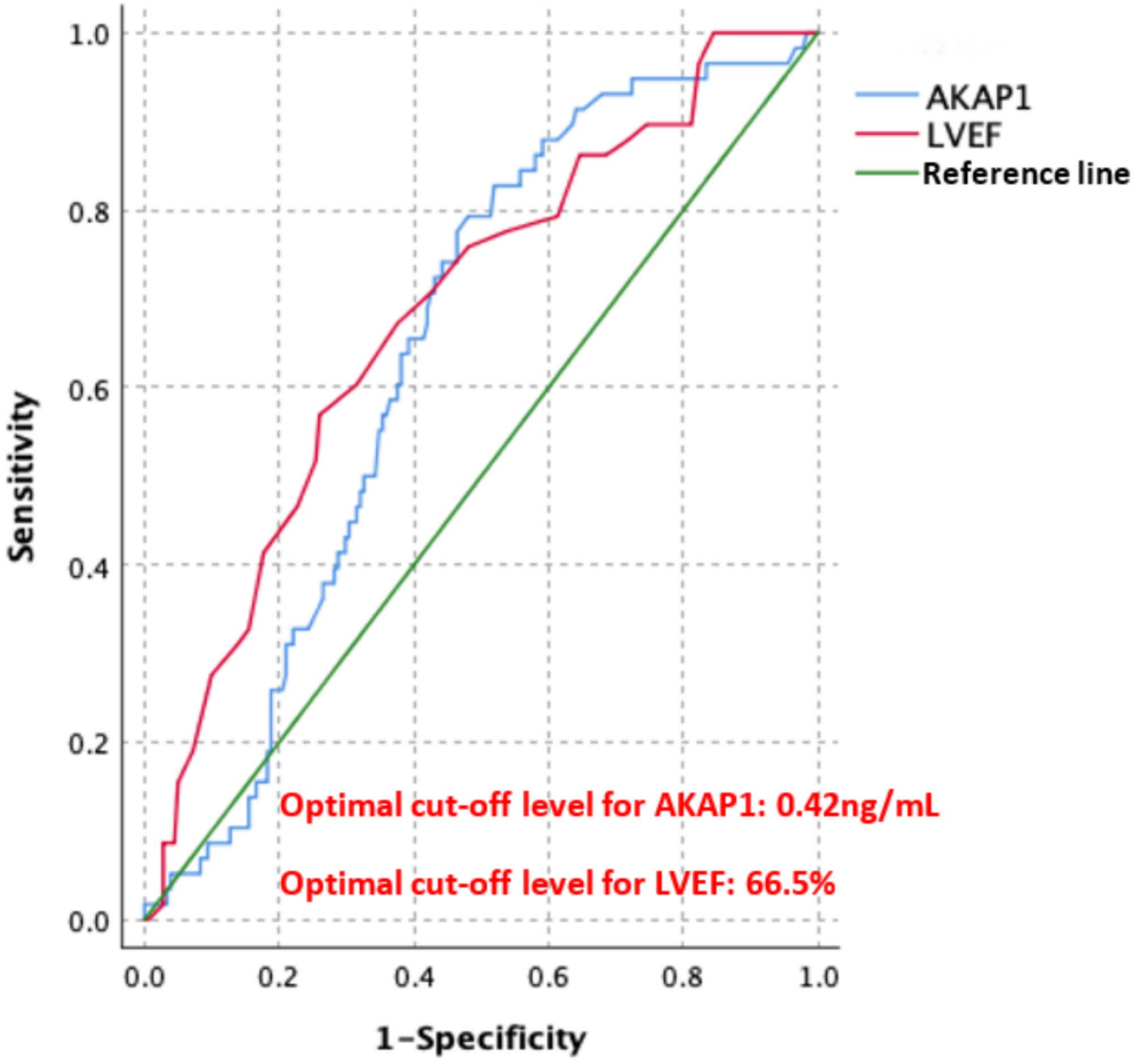

Fig. 2 ROC curve based on a univariate model examining the power of AKAP1 and LVEF to predict CAD. The optimal cut-off level for AKAP1 to predict CAD was found to be 0.42 ng/mL, with a specificity of 77.6% and a sensitivity of 47.3%. The area under the curve was 0.649 (95%CI 0.579–0.719, $P < 0.001$). The optimal cut-off level for LVEF to predict CAD was found to be 66.5%, with a specificity of 74.0% and a sensitivity of 56.9%. The area under the curve was 0.685 (95%CI 0.608–0.762, $P < 0.001$)

In CAD, AKAP1 has been shown to play cardioprotective roles by decreasing sensitivity to myocardial infarction and cardiomyocyte mitophagy, adapting oxidative respiration quickly to hypoxia, regulating balance of mitochondrial fission and fusion, and modulating function of endothelial cells (ECs) [20, 21]. In hypoxic cells, AKAP1 is rapidly degraded through the ubiquitin-proteasome pathway. The hypoxia-induced E3-ubiquitin ligase Siah2 is responsible for binding and ubiquitylation of AKAP1. The Siah2-mediated AKAP1 proteasomal degradation causes a significant decrease in mitochondrial respiration and metabolic activity [22, 23]. This regulatory mechanism adapts more rapidly to low oxygen microenvironment than the hypoxia inducible factor-1α-activated transcriptional regulation in attenuating oxidative metabolism in ischemic tissue. At the same time, hypoxia-Siah2-induced AKAP1 degradation not only reduces mitochondrial oxidative respiration but also disturbs the balance of mitochondria fission and fusion, causing cardiomyocytes apoptosis [11, 24]. Mitochondria are the major cellular energy source, and the enhanced mitochondrial fragmentation under hypoxia ultimately

Table 5 Effects of AKAP1 quartiles on CAD in multivariate logistic regression analysis

AKAP1 quartile	Model 1 (OR, 95%CI)	*P*	Model 2 (OR, 95%CI)	*P*	Model 3 (OR, 95%CI)	*P*	Model 4 (OR, 95%CI)	*P*	Model 5 (OR, 95%CI)	*P*
Q1	8.134 (2.616, 25.297)	< 0.001	8.134 (2.616, 25.297)	< 0.001	6.520 (1.978, 21.492)	0.002	6.520 (1.978, 21.492)	0.002	5.677 (1.704, 18.912)	0.005
Q2	1.833 (0.847, 3.964)	0.124	1.833 (0.847, 3.964)	0.124	1.602 (0.669, 3.836)	0.291	1.602 (0.669, 3.836)	0.291	1.554 (0.647, 3.735)	0.324
Q3	0.898 (0.439, 1.834)	0.767	0.898 (0.439, 1.834)	0.767	0.918 (0.407, 2.068)	0.836	0.918 (0.407, 2.068)	0.836	0.879 (0.390, 1.980)	0.756
Q4	Ref		Ref		Ref		Ref		Ref	

Model 1: crude model

Model 2: adjusted for Age, Gender

Model 3: adjusted for Age, Gender, High-density lipoprotein, Glycosylated hemoglobin, Left ventricular ejection fraction

Model 4: adjusted for Age, Gender, High-density lipoprotein, Glycosylated hemoglobin, Left ventricular ejection fraction, Diabetes mellitus

Model 5: adjusted for Age, Gender, High-density lipoprotein, Glycosylated hemoglobin, Left ventricular ejection fraction, Diabetes mellitus, Statins, Antidiabetic therapy

leads to cardiomyocytes cell death. In addition, AKAP1 is known to modulate the function of ECs via the Akt-eNOS-NO axis, affecting multiple vascular functions. The mitochondria are the major intracellular source of energy and ROS in ECs and modulate their function by controlling the mitochondria-dependent redox balance [25, 26]. Mitochondrial ROS (mtROS) enhances the vascular endothelial growth factor-mediated activation of phosphatidylinositol 3-kinase / Akt signaling in ECs [10]. The phosphorylation of eNOS by Akt is partially regulated by ROS in a dose- and time-dependent manner [27], which determines the endothelium-derived NO synthesis and regulation of vasorelaxation and blood pressure [5]. Previous studies showed that Akap1-/- aortic ECs exhibit an increase in hypoxia-induced mitophagy, mitochondrial dysfunction, ROS production, and apoptosis [5, 28]. Additionally, the global deletion of Akap1 results in a reduction of phosphorylated Akt and phosphorylated eNOS in mesenteric arteries and heart ECs [5]. In Akap1 knockout mice, attenuation of acetylcholine-induced vascular relaxation, delayed post-ischemic neovascularization in skeletal muscles, and increased arterial blood pressure were observed [5].

To the best of our knowledge, this study is the first to investigate the relationship between CAD and AKAP1 in patients referred for CAG. Remarkably, using the highest quartile as the reference, the lowest AKAP1 quartile was found to remain significantly associated with CAD in our study. These findings innovatively suggest that AKAP1 in CAD severity prediction might be developed and AKAP1 upregulation might have therapeutic potential for individuals with CAD.

Study limitations

This study has several limitations. First, as a single-center, observational study with a relatively small sample size, some variables showed nonsignificant correlation with AKAP1. Second, only baseline measurements of AKAP1 were available. Therefore, it was not possible to assess changes in the AKAP1 values over time or the implications of these changes. Third, this study did not establish the causative relationship between CAD and AKAP1. Lastly, we did not comprehensively compare AKAP levels with other indicators, so the results were not comparable. Hence, further studies are needed.

Conclusion

The AKAP1 serum levels exhibit an inverse relationship with CAD. This result indicates that AKAP1 may have cardioprotective properties in cardiovascular disorders, such as CAD. Therefore, heart-enriched AKAP1 could be considered a potential therapeutic target in patients with CAD.

Acknowledgements

The authors thank the other investigators, the staff, and the participants of the studies for their valuable contributions.

Author contributions

(1) Conception and design: Wei Yan, Yun-Lang Dai, Jun-Xia Han; (2) Analysis and interpretation of data: Wei Yan, Yun-Lang Dai, Jun-Xia Han; (3) Drafting of the manuscript: Wei Yan, Yun-Lang Dai; (4) Final approval of the manuscript submitted: All authors.

Funding

The authors did not receive any funding.

Data availability

Availability of data and materialsThe datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 202173) and followed the principles of the Helsinki Declaration. All patient records were anonymized before analysis and informed consent were obtained from all enrolled patients.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Received: 30 April 2024 / Accepted: 27 February 2025
Published online: 07 March 2025

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