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ORIGINAL RESEARCH

Association Between Vascular Adhesion Protein-1 (VAP-1) and MACE in Patients with Coronary Heart Disease: A Cohort Study

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Background: Vascular adhesion protein-1 (VAP-1), an inflammation-inducible endothelial cell molecule, was reported to be implicated in a variety of cardiovascular diseases. However, the clinical significance of circulating VAP-1 levels in patients with coronary heart disease (CHD) remains less studied.

Patients and Methods: We retrospectively analyzed clinical data of 336 hospitalized patients in the Second Affiliated Hospital of Soochow University from May 2020 to September 2022, 174 of which were diagnosed with CHD. Serum VAP-1 was measured by enzyme-linked immunosorbent assay at enrollment. The primary end point of this study was the occurrence of major adverse cardiovascular events (MACE). The coronary stenosis and clinical manifestations of CHD were assessed and recorded from medical records or follow-up calls. The relevant results were obtained, and the reliability of the conclusions was verified through regression analysis, curve fitting, and survival curve.

Results: After adjusting for potential confounders, higher serum VAP-1 level was associated with increased risk of MACE in patients with CHD [(HR = 5.11, 95% CI = 1.02–25.59), (HR = 5.81, 95% CI = 1.16–29.11)]. The results of curve fitting and survival analysis were consistent with those of regression analysis. However, no significant association was observed between VAP-1 and MACE in the entire study population [(HR = 5.11, 95% CI = 0.41–1.93), (HR = 1.17, 95% CI = 0.52–2.62)]. Furthermore, the level of VAP-1 did not show a significant correlation with coronary stenosis and the clinical manifestations of CHD.

Conclusion: These findings suggested that CHD patients with higher serum levels of VAP-1 are at a higher risk of adverse cardiovascular outcomes.

Keywords: vascular adhesion protein-1, atherosclerosis, coronary heart disease, major adverse cardiovascular events

Introduction

Coronary heart disease (CHD) is among the leading causes of death worldwide. Atherosclerotic plaque formation and plaque rupture are the main pathogenesis of coronary heart disease. Although current management strategies have demonstrated benefits for patients with CHD,[1,2] there is still a high residual risk after such treatments in both chronic stable coronary artery disease and acute coronary syndrome. A certain proportion of CHD patients will suffer from heart failure, malignant arrhythmia, recurrent myocardial infarction and sudden cardiac death. Therefore, the identification of novel diagnostic and/or prognostic biomarkers for CHD has important clinical significance and may lead to new drug targets for CHD.

CHD is characterized by inflammation and fatty deposits in the sub-endothelial space of the coronary arteries. Inflammatory processes play a key role in both the initiation and promotion stages of atherosclerosis, and multiple

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inflammatory mediators are involved, such as pro-inflammatory cytokines, cell adhesion molecules, acute-phase proteins, complement and autoantibodies. Novel regulators and their diagnostic or therapeutic value for CHD need to be identified to facilitate clinical intervention.[3] Vascular adhesion protein-1 (VAP-1), encoded by the AOC3 (amine oxidase copper-containing 3) gene, is a pro-inflammatory and versatile molecule belonging to semicarbazide-sensitive amine oxidase (SSAO) family.[4,5] VAP-1 is expressed on a variety of cell types (eg, vascular endothelial cells, smooth muscle cells, leukocytes, pericytes, adipocytes and chondrocytes), it can be cleaved from the membrane by matrix metalloproteinase (MMP) and released into the circulation, both the transmembrane form and the soluble form exhibit versatile biological functions.[4] VAP-1 functions as an adhesion molecule, facilitating leukocyte extravasation, thereby promoting inflammation.[6] It is also able to catalyze the oxidation of primary amines, producing several cytotoxic substances including ammonium, formaldehyde, methylglyoxal, and hydrogen peroxide.[6] Moreover, VAP-1 was reported to play a role in regulating glucose and lipid metabolism.[7,8] Through the above-mentioned mechanisms, VAP-1 was found to take part in the pathogenesis of diverse human diseases or pathological states involving multiple systems, notably, the soluble VAP-1 (sVAP-1) level was suggested to be a potential diagnostic or prognostic biomarker in several different human pathologies.[4]

Current studies have shown that sVAP-1 level was associated with various cardiovascular disorders,[9–12] such as atherosclerosis, stroke, myocardial ischemia, heart failure, and the incidence of major adverse cardiovascular events (MACE) as well as cardiovascular mortality in different population.[13,14] There is considerable evidence that sVAP-1 may have a potential use in assisting the clinical diagnosis or predicting the prognosis of atherosclerotic cardiovascular diseases.[9] sVAP-1 level and activity were demonstrated to be correlated with the onset and progression of atherosclerosis reflected by different assessments including intima-media thickness, carotid plaque, arterial stiffness, and calcific aortic valve stenosis.[15–17] Some basic researches showed that the intervention of VAP-1 could reduce atherosclerosis in different animal models.[18,19] By now, very few studies have investigated the relationship between VAP-1 and CHD. Wang et al have found an elevation in plasma VAP-1 levels in CHD patients, and they also reported a positive association between plasma VAP-1 concentrations and the extent of CAD measured by coronary angiography.[19] To our knowledge, no other studies provided evidence linking VAP-1 and CHD, and no clinical studies have been taken to investigate the association of sVAP-1 level with the prognosis in patients with CHD.

Therefore, the present retrospective cohort study aims to explore the correlation between sVAP-1 level and the occurrence of MACE in patients with CHD and investigate its association with the clinical manifestations as well as coronary lesions of CHD.

Materials and Methods

Study Design and Participants

In this retrospective cohort study, we included patients who were hospitalized in the Department of Cardiology of the Second Affiliated Hospital of Soochow University between May 2020 and September 2022 (Figure 1). The inclusion criteria are as follows: (1) >18 years old, (2) CHD was defined as having at least one major epicardial coronary artery with stenosis of 50% or more in diameter determined by coronary angiography, (3) Angina pectoris (AP) included stable angina and unstable angina, which were diagnosed according to the corresponding 2023 AHA and ESC guidelines,[1,2] (4) The diagnosis of acute myocardial infarction (AMI) met the fourth universal definition of myocardial infarction (MI).[20] AMI included ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). The exclusion criteria were as follows: valvular heart diseases (moderate or severe insufficiency or stenosis of the mitral or aortic valves), end-stage renal failure, malignant tumors, severe pulmonary infection (Figure 1).

The ethics committee of the Second Affiliated Hospital of Soochow University has reviewed and approved the present study (JD-LK-2022-125-01). All data were anonymized before analysis. The study complied with the tenets of the Helsinki Declaration (as revised in 2013). Owing to the retrospective design of the study, the need for individual consent for this study was waived.

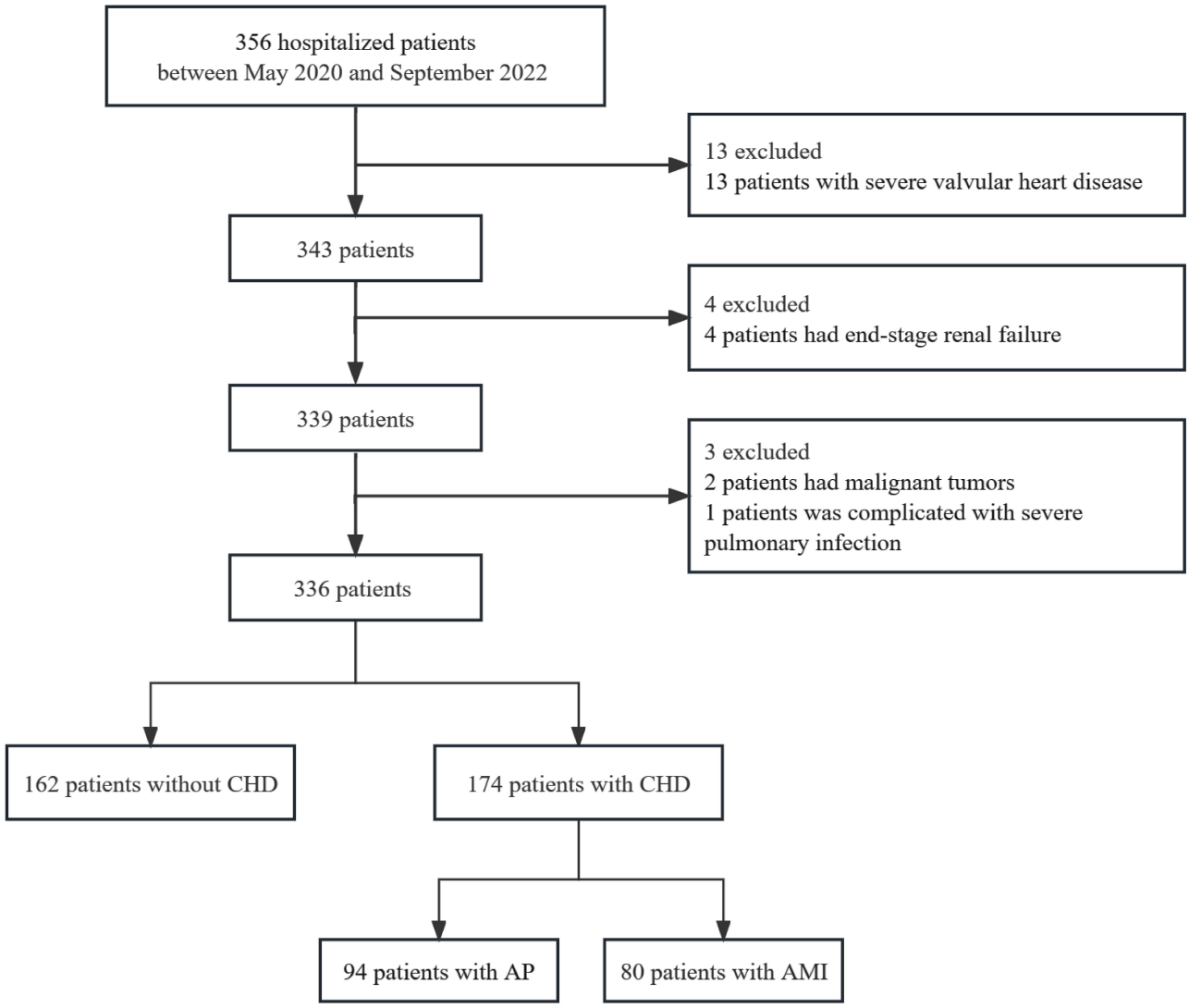

Figure 1 Flowchart of participant selection.
Abbreviations: VAP-1, vascular adhesion protein-1; CHD, coronary heart disease; AP, angina pectoris; AMI, acute myocardial infarction.

Measurement of sVAP-1 Concentration

The plasma used for VAP-1 testing was the remaining sample from the patient's laboratory testing. At the time of admission, all patients signed a consent form agreeing to allow the use of the remaining samples for medical research, provided that the law was not violated. Plasma samples were collected from patients who had fasted overnight and stored in a refrigerator at −80 °C. The VAP-1 Human ELISA Kit (BMS259TEN, Invitrogen, USA) was used in this study. Its principle is to measure the target binding between matched antibody pairs by human VAP-1 solid-phase sandwich enzyme-linked immunosorbent assay (ELISA). The VAP-1 concentration in the samples is measured accordingly. In brief, target-specific antibodies had been precoated in the provided microplate. Samples, standards, and controls were added to these wells and bound to immobilized capture antibodies. Streptavidin-horseradish peroxidase was added to form a sandwich structure. Next, the substrate solution was added to develop color, which reacts with the enzyme-antibody-target complex to produce a measurable signal. The intensity of this signal is proportional to the concentration of the target in the original sample. Finally, the wavelength of the automatic microplate reader (BioTek ELx800, USA) was adjusted to 450/630nm to determine the optical density of the sample, then the concentration of VAP-1 in the measured samples could be calculated.

Covariates

Data on demographic characteristics, comorbidities, personal history, vital signs, laboratory tests and outcomes were collected from medical records or follow-up telephone calls. The demographic characteristics included gender and age. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The comorbidities and personal history included atrial fibrillation (Af), heart failure (HF), high blood pressure (HBP), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), smoking and drinking history. Comorbidities are medical conditions that coexist alongside the primary diagnosis, CHD. The above-mentioned comorbidities were diagnosed according to the corresponding clinical practice guidelines.[21–25] The vital signs collected were systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). The laboratory test results from the first day of admission were required, which included white blood cells (WBCs), the counts of neutrophil, lymphocyte, monocyte and platelet (PLT), hemoglobin (Hb), C-reactive protein (CRP), serum creatinine (Scr), blood urea nitrogen (Bun), serum uric acid (UA), eGFR (estimated glomerular filtration rate), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), very low-density lipoprotein cholesterol (VLDL), low-density lipoprotein cholesterol (LDL), fasting blood-glucose (FBG), glycated hemoglobin A1c (HbA1c), serum glutamic pyruvic transaminase (ALT), serum glutamic oxalacetic transaminase (AST), total bilirubin (TBil), indirect bilirubin (IBil), serum albumin (ALB), sodium, potassium, chlorine, creatine kinase (CK), cardiac troponin T (CTnT), N terminal brain natriuretic peptide precursor (NT-proBNP), D dimer, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVDD). The echocardiographic measurements were acquired with Model GE Vivid E9, using an M5S phased array transducer with a transmission frequency of 2.0–4.5 MHz. Images were taken of the parasternal view with patients lying in the left decubitus position. LVEF was calculated using the modified Simpson method from the apical 4- and 2-chamber views.[26] All echocardiographic measurements were obtained by one experienced echocardiographer.

Outcomes

The primary outcome was major adverse cardiovascular events (MACE) including cardiovascular death, myocardial infarction, non-myocardial infarction, acute coronary syndrome, stroke or acute decompensated heart failure. In addition, the relationships between VAP-1 and the clinical manifestations as well as coronary artery stenosis of CHD were also investigated. Coronary stenosis was defined as a stenosis of 50% or more in the coronary artery determined by coronary angiography. The coronary arteries here referred to the right coronary artery (RCA), the left anterior descending coronary artery (LAD), and the left circumflex coronary artery (LCX), including their major branches. Subjects were divided into four groups as 0-vessel, 1-vessel, 2-vessel and 3-vessel disease according to the number of stenosed coronary arteries. The number of coronary stenosis was labeled 0 when patients had undergone a previous percutaneous coronary intervention (PCI) and now had no coronary artery stenosis.

Statistical Analysis

The population data are presented according to the VAP-1 tertiles or clinical manifestations of CHD (non-CHD, angina and myocardial infarction). Categorical variables were presented as absolute numbers and proportions (%). Normally distributed continuous variables were presented as mean and standard deviation (SD). Non-normally distributed continuous variables were presented as median and interquartile range (IQR). The chi-square test was used to compare categorical variables, whereas rank sum test and one-way ANOVA were used for non-normally and normally distributed continuous variables, respectively.

Multivariable Cox regression analyses were used to explore the independent associations between VAP-1 and MACE in CHD patients. Both non-adjusted and multivariate-adjusted models were applied. The selection of covariates in the regression model was based on clinical judgment. Covariates that were identified as significant in the univariate analysis or causing a >10% alteration in initial regression coefficients were included. In most of these multivariable regression analyses, Model I was adjusted for age, gender and BMI. Model II was adjusted for age, sex, BMI, and other significant covariates in the univariate analysis. Model III considered statistical significance and clinical practice. The relationship

between VAP-1 and the occurrence of MACE was also described using smooth curves. Kaplan–Meier and log-rank analyses were used to plot survival curves to compare the cumulative rates of death.

For those continuous variables with missing values less than 6%, the missing values were substituted with median or mean values. The comparison of baseline information before and after interpolation was not statistically different (Supplementary Tables 1 and 2).

For all analyses, the statistical software packages Free Statistics software versions 1.8 and R 4.3 (http://www.R-project.org, The R Foundation) were used. A two-sided $P < 0.05$ was considered statistically significant.

Results

Characterization of Clinical Cohort

Of the 356 participants, we excluded 13 patients with severe valvular heart disease, 4 with baseline end-stage renal failure, and 3 with cancer or severe lung diseases (Figure 1). Finally, 336 patients were included for analysis. Of these patients, 174 had CHD, and 98 of them were further diagnosed with angina pectoris, while the rest of them were diagnosed with myocardial infarction according to the corresponding guidelines (Figure 1). The baseline characteristics of the included CHD patients are shown in Table 1. At baseline, the mean age of these CHD patients was 66.1 ± 11.9 years, and 77.6% were male. These patients were divided into three groups based on the tertiles of VAP-1. The participants in the group with the highest VAP-1 levels were older and more likely to have comorbidities including HF and DM. Compared to the patients in the Q1 and Q2 group, patients in the Q3 group had higher levels of NT-proBNP,

Table 1 Baseline Characteristics of Patients with CHD

Variables	VAP-1 (ng/mL)				P value
	Total	Q1 (≤715)	Q2 (715–1100)	Q3 (≥1100)	
	(n = 174)	(n = 58)	(n = 58)	(n = 58)	
CHD, n (%)					0.488
AP	94 (54.0)	30 (51.7)	29 (50)	35 (60.3)	
AMI	80 (46.0)	28 (48.3)	29 (50)	23 (39.7)	
Number of coronary stenosis, n (%)					0.263
0	8 (4.6)	4 (6.9)	2 (3.4)	2 (3.4)	
1	53 (30.5)	23 (39.7)	14 (24.1)	16 (27.6)	
2	64 (36.8)	20 (34.5)	25 (43.1)	19 (32.8)	
3	49 (28.2)	11 (19)	17 (29.3)	21 (36.2)	
Gender (female), n (%)	135 (77.6)	45 (77.6)	44 (75.9)	46 (79.3)	0.906
Age (years)	66.1 ± 11.9	57.8 ± 13.7	69.2 ± 9.6	71.2 ± 6.5	< 0.001
BMI (kg/㎡)	24.7 ± 3.1	25.7 ± 2.9	24.5 ± 2.9	24.1 ± 3.2	0.023
Af, n (%)	32 (18.4)	6 (10.3)	10 (17.2)	16 (27.6)	0.054
HF, n (%)	81 (46.6)	19 (32.8)	26 (44.8)	36 (62.1)	0.006
HBP, n (%)	118 (67.8)	42 (72.4)	36 (62.1)	40 (69)	0.478
DM, n (%)	65 (37.4)	15 (25.9)	22 (37.9)	28 (48.3)	0.044
COPD, n (%)	11 (6.3)	4 (6.9)	1 (1.7)	6 (10.3)	0.181
Smoke, n (%)	90 (51.7)	36 (62.1)	32 (55.2)	22 (37.9)	0.028
Drink, n (%)	37 (21.3)	17 (29.3)	10 (17.2)	10 (17.2)	0.186
SBP (mmHg)	133.5 ± 21.7	134.5 ± 21.8	127.8 ± 19.5	138.2 ± 22.8	0.036
DBP (mmHg)	78.4 ± 12.8	81.9 ± 13.0	76.8 ± 11.2	76.3 ± 13.5	0.033
HR (beats per minute)	79.4 ± 13.1	82.3 ± 13.5	77.5 ± 13.7	78.5 ± 11.8	0.128
WBC ($\times 10^9$/L)	7.9 ± 2.6	8.8 ± 2.9	7.5 ± 2.4	7.5 ± 2.4	0.016
Neutrophil ($\times 10^9$/L)	5.7 ± 2.5	6.3 ± 2.7	5.5 ± 2.3	5.5 ± 2.4	0.147
Lymphocyte ($\times 10^9$/L)	1.5 ± 0.6	1.6 ± 0.6	1.4 ± 0.6	1.5 ± 0.5	0.139
Monocyte ($\times 10^9$/L)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.282

(*Continued*)

Table 1 (Continued).

Variables	VAP-1 (ng/mL)				P value
	Total	Q1 (≤715)	Q2 (715–1100)	Q3 (≥1100)	
	(n = 174)	(n = 58)	(n = 58)	(n = 58)	
Hb (g/L)	134.5 ± 16.2	140.5 ± 15.9	132.1 ± 15.1	130.6 ± 15.9	0.002
PLT (×10^9/L)	205.6 ± 56.8	231.2 ± 54.0	203.1 ± 55.4	183.7 ± 51.8	< 0.001
CRP (mg/L)	5.7 ± 2.2	5.7 ± 2.5	5.3 ± 1.3	6.0 ± 2.5	0.328
Scr (umol/L)	80.8 ± 28.3	73.7 ± 22.9	76.9 ± 24.5	92.8 ± 33.8	< 0.001
Bun (mmol/L)	6.0 ± 2.3	5.2 ± 1.9	6.0 ± 1.9	6.9 ± 2.8	< 0.001
UA (umol/L)	358.6 ± 103.6	357.2 ± 101.2	352.6 ± 96.0	366.5 ± 115.1	0.779
eGFR (mL/min)	88.5 ± 29.2	99.4 ± 26.5	91.2 ± 25.5	75.5 ± 30.8	< 0.001
TG (mmol/L)	1.2 (0.9, 1.8)	1.4 (1.2, 2.0)	1.2 (0.9, 1.7)	1.0 (0.9, 1.3)	0.004
TC (mmol/L)	3.9 ± 1.1	4.0 ± 0.9	4.0 ± 1.1	3.6 ± 1.1	0.06
HDL (mmol/L)	1.1 ± 0.2	1.0 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	0.489
VLDL (mmol/L)	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.4 (0.2, 0.6)	0.3 (0.2, 0.5)	0.451
LDL (mmol/L)	2.4 ± 1.0	2.5 ± 0.9	2.5 ± 1.0	2.2 ± 1.0	0.067
FBG (mmol/L)	6.2 ± 1.7	6.1 ± 1.7	6.2 ± 1.6	6.4 ± 1.9	0.726
HbA1c (%)	6.3 ± 1.0	6.0 ± 0.8	6.2 ± 1.0	6.8 ± 1.0	< 0.001
ALT (U/L)	23.0 (15.0, 40.0)	26.0 (17.0, 43.0)	20.0 (15.0, 37.0)	22.0 (15.0, 32.5)	0.316
AST (U/L)	26.0 (18.0, 57.0)	26.0 (18.0, 63.2)	24.5 (17.0, 94.5)	26.0 (18.0, 40.0)	0.811
TBIL (mmol/L)	12.4 ± 5.5	12.3 ± 4.9	12.3 ± 5.7	12.6 ± 6.1	0.933
IBIL (mmol/L)	5.0 (3.7, 6.3)	4.8 (3.7, 6.1)	5.0 (3.7, 6.2)	5.0 (3.7, 6.8)	0.63
ALB (g/L)	39.6 ± 3.7	40.7 ± 3.9	39.0 ± 3.5	39.0 ± 3.6	0.021
Sodium (mmol/L)	140.7 ± 3.5	141.0 ± 3.2	140.8 ± 3.4	140.3 ± 3.9	0.542
Potassium (mmol/L)	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	4.0 ± 0.4	0.034
Chlorine (mmol/L)	104.3 ± 3.0	104.2 ± 2.7	104.4 ± 3.2	104.2 ± 3.2	0.875
CK (U/L)	115.5 (70.8, 427.2)	135.0 (79.0, 682.0)	122.0 (72.0, 541.0)	101.0 (65.8, 252.8)	0.341
CTnT (pg/mL)	46.0 (6.0, 1148.0)	63.8 (5.0, 1769.6)	58.5 (5.0, 1559.9)	34.0 (10.0, 235.5)	0.683
NT-proBNP (pg/mL)	636.0 (114.0, 2436.0)	212.0 (65.2, 1012.2)	672.0 (129.0, 2182.5)	1819.0 (220.0, 5579.0)	< 0.001
D dimer (ug/mL)	0.3 (0.2, 0.6)	0.3 (0.2, 0.4)	0.4 (0.2, 0.6)	0.5 (0.3, 0.8)	0.03
LVEF (%)	53.0 ± 13.4	56.3 ± 11.3	54.0 ± 13.5	48.8 ± 14.4	0.009
LVDD (mm)	51.8 ± 7.3	50.3 ± 6.4	51.8 ± 6.4	53.2 ± 8.6	0.107
Time of MACE (weeks)	30.0 (17.0, 35.0)	32.0 (22.2, 36.0)	30.5 (18.0, 34.8)	18.0 (11.2, 32.8)	< 0.001
MACE, n (%)	38 (21.8)	7 (12.1)	12 (20.7)	19 (32.8)	0.025

Notes: Percentage calculated from the total population; some factors total <100% due to missing data. Coronary stenosis was defined as a stenosis of 50% or more in the coronary artery determined by coronary angiography. The coronary arteries here referred to the right coronary artery (RCA), the left anterior descending coronary artery (LAD), and the left circumflex coronary artery (LCX), including their major branches. Subjects were divided into four groups as 0-vessel, 1-vessel, 2-vessel and 3-vessel disease according to the number of stenosed coronary arteries. The number of coronary stenosis was labeled 0 when patients had undergone a previous percutaneous coronary intervention (PCI) and now had no coronary artery stenosis.

Abbreviations: VAP-1, Vascular adhesion protein-1; CHD, coronary heart disease; AP, angor pectoris; AMI, acute myocardial infarction; BMI, Body Mass Index; Af, atrial fibrillation; HF, heart failure; HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; Scr, serum creatinine; Bun, blood urea nitrogen; UA, serum uric acid; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; FBG, fasting blood-glucose; HbA1c, Glycated hemoglobin A1c; ALT, serum glutamic pyruvic transaminase; AST, serum glutamic oxalacetic transaminase; TBil, total bilirubin; IBil, indirect bilirubin; ALB, serum albumin; CK, creatine kinase; CTnT, cardiac troponin T; NT-proBNP, N terminal brain natriuretic peptide precursor; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; MACE, major adverse cardiovascular events.

D dimer and lower LVEF. In addition, some differences existed between groups with respect to other covariates (Age, BMI, Smoke, SBP, DBP, WBC, Hb, PLT, Scr, BUN, eGFR, TG, HbA1c, ALB, Potassium). Notably, during a median follow-up of 30 months (IQR, 17–35), the incidence of MACE was positively correlated with the level of VAP-1 (P = 0.025) in CHD patients, the time to MACE and death were also shorter in the group of higher VAP-1 levels.

Association Between Serum VAP-1 Level and MACE in CHD Patients

Univariate and multivariate analyses were performed to identify the predictors of MACE among the clinical, demographic, biochemical and radiographic data for patients with CHD (Tables 2 and 3). In univariate analysis, we found a statistically significant correlation between MACE risk and VAP-1 levels as well as other factors including CHD types, age, HF, BMI, Smoke, SBP, DBP, WBC, Hb, PLT, Scr, BUN, eGFR, TG, HbA1c, ALB, Potassium (Table 2). Multivariate analyses were subsequently used to further evaluate the independent correlation between MACE and

Table 2 Univariate Cox Regression Analysis of Risk Factors Associated with MACE in Patients with CHD

Variables	HR (95% CI)	P value
CHD (AP)	0.31 (0.14, 0.69)	0.004
The number of coronary stenosis		0.135
0	Ref.	
1	0.33 (0.09, 1.26)	0.106
2	0.39 (0.11, 1.39)	0.145
3	0.74 (0.21, 2.59)	0.642
VAP-1	1.0013 (1.0008, 1.0018)	< 0.001
Gender (female)	1.46 (0.61, 3.5)	0.394
Age (years)	1.04 (1.01, 1.08)	0.008
BMI (kg/m^2)	0.81 (0.72, 0.9)	< 0.001
Af (no)	2.5 (1.17, 5.34)	0.018
HF (no)	3.53 (1.74, 7.15)	< 0.001
HBP (no)	1.71 (0.82, 3.55)	0.151
DM (no)	2.75 (1.43, 5.3)	0.002
COPD (no)	0.7 (0.09, 5.19)	0.729
Smoke (no)	0.63 (0.33, 1.21)	0.164
Drink (no)	0.61 (0.26, 1.46)	0.269
SBP (mmHg)	0.9908 (0.974, 1.0079)	0.289
DBP (mmHg)	0.99 (0.96, 1.01)	0.306
HR (beats per minute)	1.004 (0.977, 1.0316)	0.776
WBC ($\times 10^9$/L)	0.84 (0.72, 0.97)	0.015
Neutrophil ($\times 10^9$/L)	0.89 (0.77, 1.03)	0.127
Lymphocyte ($\times 10^9$/L)	0.43 (0.22, 0.82)	0.01
Monocyte ($\times 10^9$/L)	0.67 (0.15, 3.07)	0.607
Hb (g/L)	0.97 (0.95, 0.99)	0.003
PLT ($\times 10^9$/L)	0.991 (0.9843, 0.9977)	0.009
CRP (mg/L)	1.11 (1, 1.23)	0.051
Scr (umol/L)	1.01 (1, 1.02)	0.014
Bun (mmol/L)	1.31 (1.16, 1.48)	< 0.001
UA (umol/L)	1.0014 (0.9981, 1.0047)	0.406
eGFR (mL/min)	0.98 (0.97, 0.99)	0.001
TG (mmol/L)	0.61 (0.35, 1.06)	0.081
TC (mmol/L)	0.68 (0.48, 0.97)	0.031
HDL (mmol/L)	1.08 (0.28, 4.19)	0.907
VLDL (mmol/L)	1.21 (0.31, 4.64)	0.784
LDL (mmol/L)	0.73 (0.5, 1.07)	0.11
FBG (mmol/L)	1.06 (0.89, 1.27)	0.503
HbA1c (%)	1.3 (0.96, 1.76)	0.089
ALT (U/L)	0.9978 (0.9793, 1.0166)	0.814
AST (U/L)	0.9928 (0.9852, 1.0005)	0.067
TBIL (mmol/L)	1.07 (1.01, 1.14)	0.021

(*Continued*)

Table 2 (Continued).

Variables	HR (95% CI)	P value
IBIL (mmol/L)	1.28 (1.16, 1.41)	< 0.001
ALB (g/L)	0.94 (0.86, 1.03)	0.219
Sodium (mmol/L)	0.97 (0.89, 1.06)	0.495
Potassium (mmol/L)	0.89 (0.32, 2.5)	0.823
Chlorine (mmol/L)	0.89 (0.79, 1)	0.052
CK (U/L)	0.9993 (0.9985, 1)	0.041
CTnT (pg/mL)	0.9997 (0.9994, 0.9999)	0.018
NT-proBNP (pg/mL)	1.0001 (1.0001, 1.0001)	< 0.001
D dimer (ug/mL)	1.41 (0.79, 2.53)	0.243
LVEF (%)	0.95 (0.93, 0.98)	< 0.001
LVDD (mm)	1.11 (1.07, 1.16)	< 0.001

Notes: Coronary stenosis was defined as a stenosis of 50% or more in the coronary artery determined by coronary angiography. The coronary arteries here referred to the right coronary artery (RCA), the left anterior descending coronary artery (LAD), and the left circumflex coronary artery (LCX), including their major branches. Subjects were divided into four groups as 0-vessel, 1-vessel, 2-vessel and 3-vessel disease according to the number of stenosed coronary arteries. The number of coronary stenosis was labeled 0 when patients had undergone a previous percutaneous coronary intervention (PCI) and now had no coronary artery stenosis.

Abbreviations: VAP-1, Vascular adhesion protein-1; MACE, major adverse cardiovascular events; CHD, coronary heart disease; AP, angina pectoris; BMI, Body Mass Index; Af, atrial fibrillation; HF, heart failure; HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; Scr, serum creatinine; Bun, blood urea nitrogen; UA, serum uric acid; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; VLDL, very low density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; FBG, fasting blood-glucose; HbA1c, Glycated hemoglobin A1c; ALT, serum glutamic pyruvic transaminase; AST, serum glutamic oxalacetic transaminase; TBil, total bilirubin; IBil, indirect bilirubin; ALB, serum albumin; CK, creatine kinase; CTnT, cardiac troponin T; NT-proBNP, N terminal brain natriuretic peptide precursor; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension.

Table 3 Multivariate Cox Regression Analysis of Risk Factors Associated with MACE in Patients with CHD

Variable		Non-Adjusted Model HR (95% CI)	Model I HR (95% CI)	Model II HR (95% CI)	Model III HR (95% CI)
VAP-1 (ng/mL)	Q1 (≤715)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Q2 (715–1100)	2.52 (0.97~6.54)	2.13 (0.74~6.09)	5.63 (1.29~24.5)	5.11 (1.02~25.59)
	Q3 (≥1100)	3.45 (1.45~8.24)	2.83 (1.07~7.47)	5.05 (1.12~22.68)	5.81 (1.16~29.11)

Notes: data presented are HR and 95% CIs. Non-adjusted Model: We did not adjust any covariates. Model I: Adjusted for Gender, Age, BMI. Model II: Adjusted for the variables in Model I plus The number of coronary stenosis, Af, HBP, DM, COPD, SBP, DBP, HR, WBC, Lymphocyte, PLT, CRP, eGFR, CK, CTnT, LVEF. Model III: Adjusted for the variables in Model II plus LVDD, Neutrophil, Bun, UA, HbA1c, ALT, AST, TBIL, D dimer. In each case, the model is not adjusted for the variable itself.

Abbreviations: VAP-1, Vascular adhesion protein-1; MACE, major adverse cardiovascular events; CHD, coronary heart disease; BMI, Body Mass Index; Af, atrial fibrillation; HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; Bun, blood urea nitrogen; UA, serum uric acid; eGFR, estimated glomerular filtration rate; ALT, serum glutamic pyruvic transaminase; AST, serum glutamic oxalacetic transaminase; TBil, total bilirubin; CK, creatine kinase; CTnT, cardiac troponin T; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension.

VAP-1. As shown in Table 3, the risk of MACE tended to increase with elevated VAP-1 levels in the unadjusted model, and the result remained stable and statistically significant as more covariates were adjusted [(Q2 VS Q1: HR = 5.11, 95% CI = 1.02–25.59), (Q3 VS Q1: HR = 5.81, 95% CI = 1.16–29.11)]. Similarly, the incidence of MACE was positively correlated with the VAP-1 level in patients with CHD according to the curve fitting (P = 0.994, Figure 2). Consistently, Kaplan–Meier survival curves showed that during 30 months of follow-up, patients with serum VAP-1 in the highest tertile had a significantly lower rate of survival than subjects in other tertiles (P = 0.006, Figure 3).

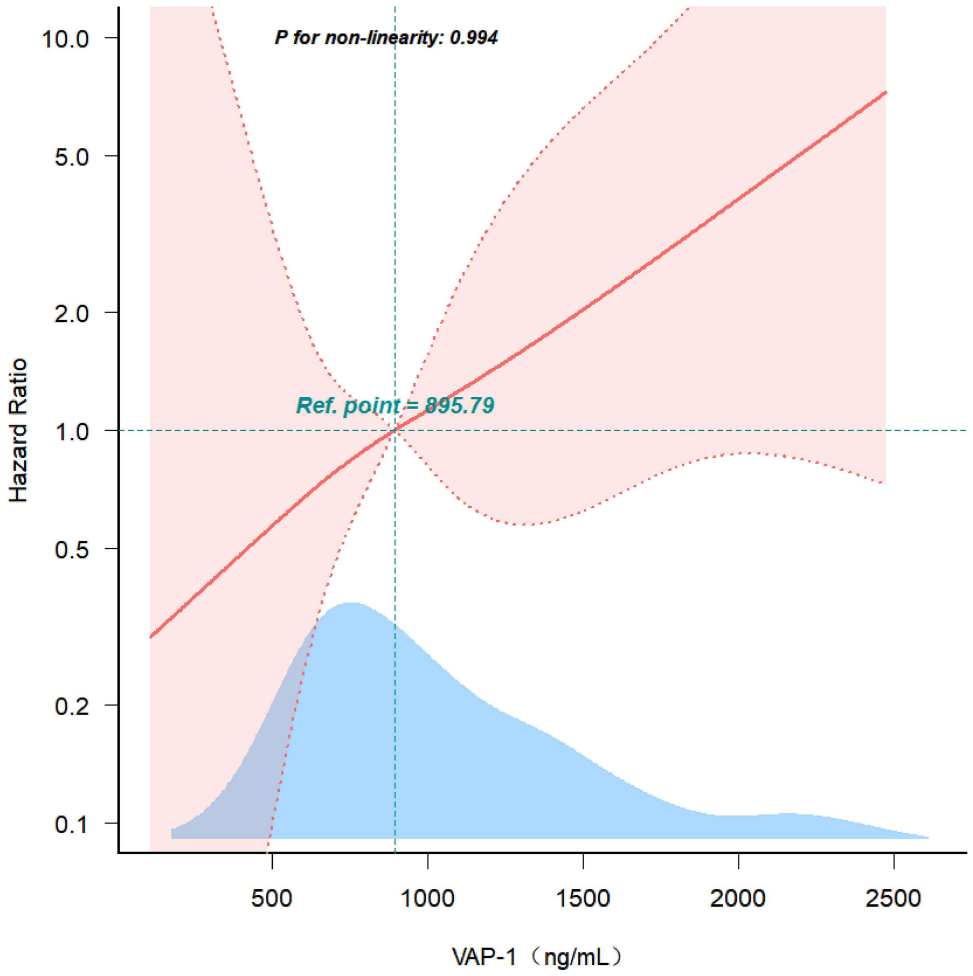

Figure 2 Relationship between VAP-1 and MACE in patients with CHD. Adjusted for Gender, Age, BMI, the number of coronary stenosis, Af, HBP, DM, COPD, SBP, DBP, HR, WBC, Lymphocyte, Neutrophil, PLT, CRP, Bun, UA, eGFR, HbA1c, ALT, AST, TBIL, CK, CTnT, D dimer, LVEF, LVDD.

Abbreviations: VAP-1, vascular adhesion protein-1; MACE, major adverse cardiovascular events; CHD, coronary heart disease; BMI, Body Mass Index; Af, atrial fibrillation; HBP, high blood pressure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WBC, white blood cell; PLT, platelet; CRP, C-reactive protein; Bun, blood urea nitrogen; UA, serum uric acid; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; ALT, serum glutamic pyruvic transaminase; AST, serum glutamic oxalacetic transaminase; TBil, total bilirubin; CK, creatine kinase; CTnT, cardiac troponin T; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension.

In addition, we analyzed the risk factors for MACE in the entire participants, including both non-CHD and CHD patients (Supplementary Tables 3 and 4). The correlation between MACE and VAP-1 in the entire participants, however, did not reach statistical significance after adjusting for covariates [(Q2 VS Q1: HR = 5.11, 95% CI = 0.41–1.93), (Q3 VS Q1: HR = 1.17, 95% CI = 0.52–2.62), (Supplementary Table 5)].

Association Between Serum VAP-1 Level and the Severity of CHD

To explore the association of serum VAP-1 level with the severity of CHD, the participants were divided into three groups, namely non-CHD, AP, and AMI groups, the results exhibited no significant differences between serum VAP-1 levels in different groups (P = 0.501, Supplementary Table 6). After adjusting for confounding variables in the multiple regression analysis, there were still no statistically significant differences observed in VAP-1 levels among the groups (Supplementary Table 7). Finally, the associations of serum VAP-1 levels with the number of diseased coronary vessels were assessed, and the results showed no differences of VAP-1 levels in patients with different numbers of coronary lesions (Supplementary Table 8).

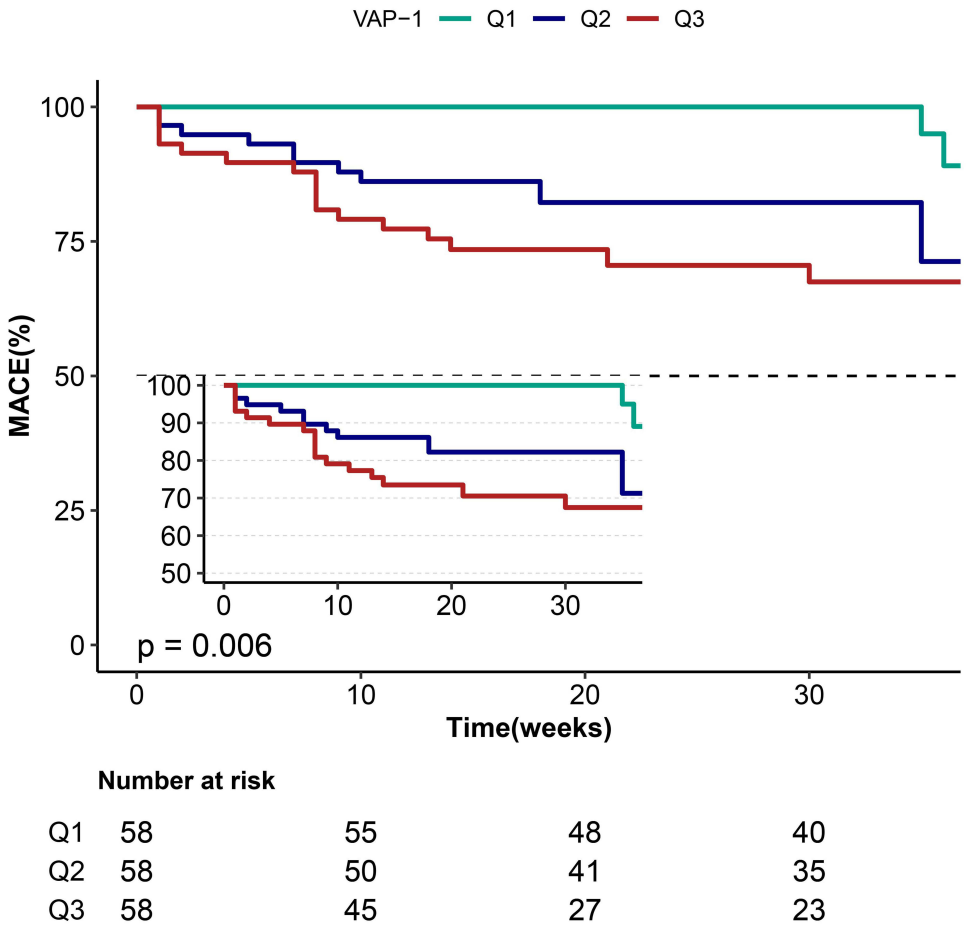

Figure 3 Kaplan–Meier survival curves for MACE of patients with CHD.
Abbreviations: VAP-1, vascular adhesion protein-1; CHD, coronary heart disease; MACE, major adverse cardiovascular events.

Discussion

In this retrospective cohort study, we found that higher levels of soluble VAP-1 were closely related to the increased occurrence of MACE in CHD patients and the correlation remained robust after adjustment for multiple confounders. Nevertheless, there was no significant association between elevated VAP-1 levels and clinical manifestations as well as coronary artery stenosis of patients with CHD. To our knowledge, this is the first clinical study that specifically investigated the relationship between VAP-1 and both the prognosis and clinical manifestations of CHD.

Atherosclerosis is a chronic inflammatory vascular disease that involves endothelial injury, inflammatory cell recruitment and the accumulation of lipids, especially oxidized low-density lipoprotein (ox-LDL), which progresses to increase the risk of acute cardiovascular events.[27] Clinical studies have demonstrated that serum sVAP-1 may serve as a biomarker for atherosclerosis,[12,13] and VAP-1 was regarded as a possible cause of the pre-clinical atherosclerotic process.[4] Mechanistically, VAP-1 may participate in the pathogenesis of atherosclerosis through several different ways. On the one hand, VAP-1 could recruit leukocytes such as monocytes and T cells to the arterial walls, leading to vascular inflammation and plaque formation.[28–31] Second, as an amine oxidase, VAP-1 produces hydrogen peroxide, aldehyde and ammonia, which could assist in the generation of free radicals, promoting the oxidation of LDL and lipid deposition. Atherosclerosis is considered a major cause of CHD, but so far the research on the relationship between VAP-1 and CHD is quite limited. Wang et al found higher plasma VAP-1 levels in CHD patients and reported a positive correlation between VAP-1 concentration and the number of coronary artery lesions.[19] But it is worth pointing out that the sample size and covariates of this cross-sectional study were relatively small,[19] and more studies are needed to confirm and explore the findings. The results of our study were inconsistent with the above conclusion, we found that sVAP-1 levels

did not differ between CHD patients and non-CHD individuals, also, no significant correlation was found between sVAP-1 level and the clinical manifestations of CHD (angina, and myocardial infarction). In addition, our cohort did not observe any correlation between VAP-1 and the number of coronary stenosis as assessed by coronary angiography. Although our findings showed no substantial associations between VAP-1 and coronary stenosis either clinically or radiologically, VAP-1 was closely related to the prognosis of CHD indicated by our study. Clearly further studies are needed to confirm these findings.

Currently, some research has revealed a significant correlation between VAP-1 and the prognosis of specific diseases in different population.[14] In patients with type 2 diabetes, VAP-1 was found to independently predict 10-year all-cause, cardiovascular, and cancer mortality.[14] A recent study reported that sVAP-1 levels could predict the risk of cardiovascular events and mortality in hemodialysis patients.[32] A Finnish study found that VAP-1 was associated with an increased risk of MACE and MACE mortality in individuals aged 50 and above without prior MACE.[13] Our present study showed that sVAP-1 level is positively associated with the incidence of MACE in patients with CHD. The underlying reasons or mechanisms remain obscure. As mentioned above, sVAP-1 level was not correlated with the degree of coronary stenosis in our study. We speculate that the reason why CHD patients with higher levels of VAP-1 are at higher risk of MACE may not primarily because of more severe coronary artery lesions, but through some other indirect mechanisms. As early as 2000, Jaakkola et al have reported that the expression of VAP-1 was significantly higher in coronary vessels surrounding myocardial infarction and was involved in leukocyte infiltration during myocardial ischemia or ischemia reperfusion, which exacerbated myocardial injury, thus affecting the prognosis of patients.[11] The role of VAP-1 in post-myocardial infarction ischemia-reperfusion injury or cardiac remodeling and dysfunction were further confirmed by several researchers.[33,34] Thus, we speculated that high levels of VAP-1 were causally associated with progressive cardiac remodeling and injury, leading to the occurrence of adverse cardiovascular events. It is worth noting that some researchers have shown that blockage of VAP-1 could prevent myocardial inflammation and injury in animal models, which implied its potential as a therapeutic target in ischemic heart disease.[6,33]

Overall, our study demonstrated for the first time that higher VAP-1 levels were associated with an increased incidence of MACE in CHD patients, which may be of great significance in the clinical evaluation of the prognosis of CHD. Nonetheless, our study has certain limitations. First, as a retrospective study, there is bound to be residual confounding. During the study design phase, we included as many covariates as possible and performed multiple model adjustments to ensure the stability of the results. Diseases that have been confirmed to be associated with VAP-1, such as active hepatitis, inflammatory skin diseases, inflammatory retinopathy, and inflammatory neurological diseases, are relatively rare in hospitalized patients in our department and were not included in the study. Second, although the sample size of this study (n = 336) was nearly double that of a previously related study concerning VAP-1 and CHD,[19] further studies with larger sample sizes are still needed. In addition, we did not include all-cause mortality as an end point because of the effects of Corona Virus Disease 2019 (covid-19).

Conclusion

Taken together, our findings indicated that higher VAP-1 levels could significantly increase the risk of MACE in patients with CHD.

Ethical Approval

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (JD-LK-2022-125-01).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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