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ORIGINAL ARTICLE
Ischemic Heart Disease

Clinical Determinants and Prognostic Significance of Circulating Angiopoietin-Like Protein 3 Levels in Patients With Chronic Coronary Syndrome

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Background: Although angiopoietin-like protein 3 (ANGPTL3) has emerged as a novel therapeutic target for lipid modulation, its prognostic significance in chronic coronary syndrome (CCS) remains unclear. This study aimed to evaluate the clinical determinants and prognostic value of circulating ANGPTL3 levels in patients with CCS.

Methods and Results: We prospectively enrolled 264 consecutive patients with CCS (median age 74 years; 73% male) undergoing cardiac catheterization. Serum ANGPTL3 levels were measured using an enzyme-linked immunosorbent assay. The primary endpoint was major adverse cardiovascular events (MACE). Female sex, elevated C-reactive protein and B-type natriuretic peptide, low high-density lipoprotein cholesterol levels, and absence of statin use were independently associated with higher ANGPTL3 levels. During follow up, 35 patients experienced MACE. In multivariable Cox regression models, ANGPTL3 remained an independent predictor of MACE. Receiver operating characteristic analysis identified 90.7 ng/mL as the optimal cut-off value for event discrimination. Kaplan-Meier curves demonstrated significantly higher event rates among patients with ANGPTL3 >90.7 ng/mL. In patients with CCS with low-density lipoprotein cholesterol (LDL-C) <70 mg/dL, elevated ANGPTL3 levels were also associated with increased MACE risk.

Conclusions: Circulating ANGPTL3 levels independently predict adverse cardiovascular outcomes in CCS, including those in patients who achieve LDL-C targets, and may help identify residual cardiovascular risk not captured by traditional lipid parameters.

Key Words: Angiopoietin-like protein 3; Chronic coronary syndrome; Residual cardiovascular risk

Chronic coronary syndrome (CCS) is a broad spectrum of coronary artery diseases that are distinct from acute coronary syndrome (ACS) with respect to temporal progression, clinical manifestations, and functional characteristics.[1] With an aging population, CCS increasingly coexists with multiple comorbidities, resulting in a complex prognostic landscape in which residual cardiovascular risk often persists despite guideline-directed medical therapy.[2,3]

Lipid-lowering therapies, including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors, remain the cornerstone of CCS management, having consistently demonstrated robust efficacy in reducing cardiovascular events.[4–6] Nonetheless, several patients fail to achieve the recommended lipid targets.[7,8] Recently, novel agents targeting alternative lipid regulators have emerged,[9] including angiopoietin-like protein 3 (ANGPTL3), which has garnered increasing attention due to its multifaceted role in lipid metabolism.[10]

ANGPTL3 loss-of-function mutations are associated with familial hypolipidemia, which is characterized by reduced levels of triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), and a reduced burden of atherosclerosis.[11] Accordingly, therapeutic strategies targeting ANGPTL3, including monoclonal antibodies and RNA interference (RNAi), have been developed, demonstrating promising lipid-lowering effects.[12,13]

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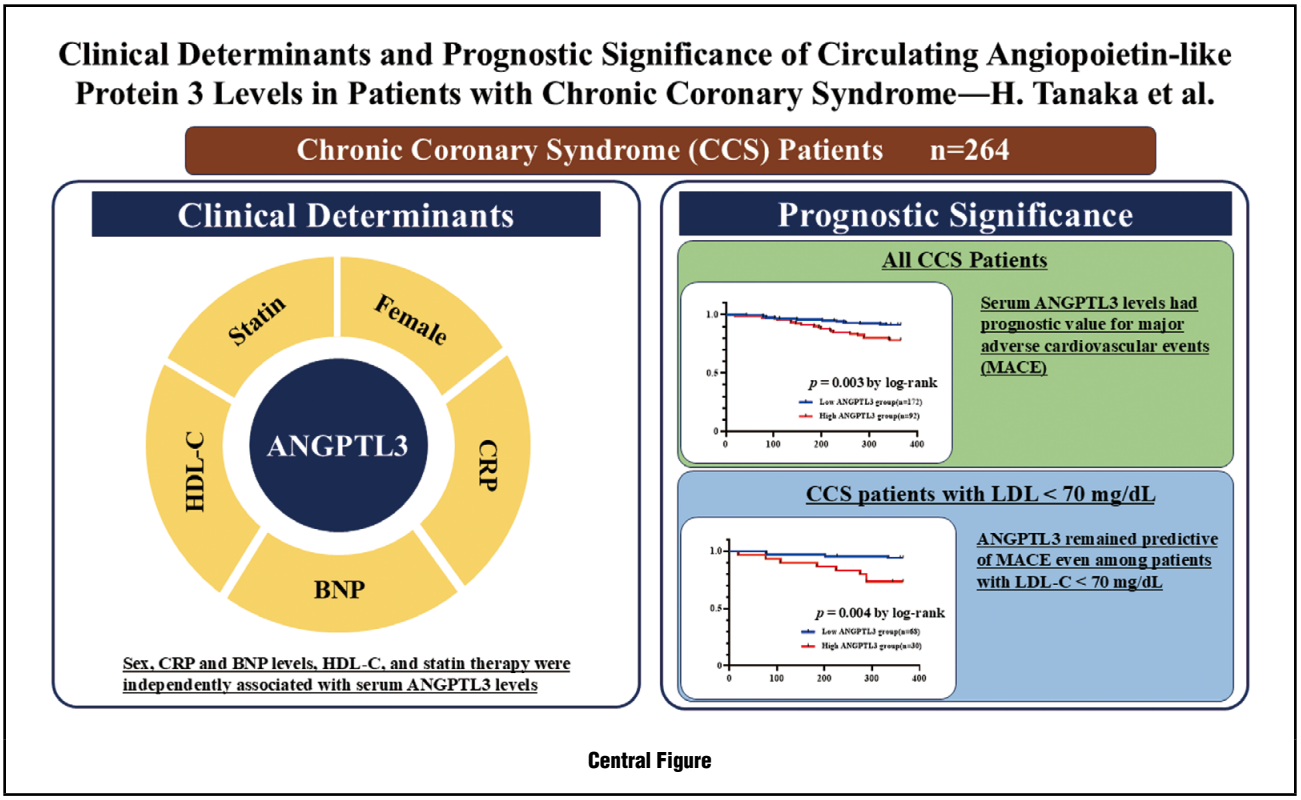

Central Figure

In addition to lipid metabolism, circulating ANGPTL3 levels have been associated with liver function, inflammatory status, and sex differences in health-checkup populations,[14] suggesting a broader pathophysiological role. However, the clinical significance of ANGPTL3 in CCS remains unclear.

This study aimed to investigate the clinical correlates of circulating ANGPTL3 levels and to assess their prognostic value in patients with CCS.

Methods

Study Population

This prospective observational study consecutively enrolled 264 patients with CCS who underwent cardiac catheterization at Miyazaki University Hospital between January 2022 and December 2023. During the study period, a total of 549 patients underwent cardiac catheterization at our institution. Among them, 268 patients met the criteria for CCS, defined as having at least one of the following: (1) a prior history of myocardial infarction (MI); (2) a history of coronary revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); or (3) >50% stenosis in at least one major epicardial coronary artery on invasive coronary angiography (CAG). Of the 268 eligible patients, 4 were lost to follow up because of inability to make contact with them, leaving 264 patients for the final analysis. Follow up was mainly conducted through regular outpatient visits. When in-person visits were not possible, clinical outcome data were obtained via telephone interviews with the patients or their family members. The Ethics Committee of the University of Miyazaki approved the study protocol (approval no. O-1058). Written informed consent was obtained from all participants, and the study complied with the Declaration of Helsinki.

Clinical Data Collection

All patients underwent comprehensive baseline evaluations, including detailed medical history, current medication use, physical examination, transthoracic echocardiography, and laboratory testing. The collected clinical histories included MI, stroke, peripheral artery disease (PAD), CABG, and PCI. Physical measurements included blood pressure and body mass index (BMI). Echocardiographic assessment was performed to evaluate the left ventricular ejection fraction. Laboratory tests included renal and liver function parameters, complete blood count, C-reactive protein (CRP), B-type natriuretic peptide (BNP), glycated hemoglobin (HbA1c) levels, and lipid profiles. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive agents.[15] Diabetes was identified as a casual plasma glucose level ≥200 mg/dL, fasting plasma glucose level ≥126 mg/dL, or prior diagnosis treated with antidiabetic medications.[16] Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.[17] Liver dysfunction was determined as an aspartate aminotransferase level ≥36 U/L or an alanine aminotransferase level ≥34 U/L in men and ≥26 U/L in women, following previous reports.[18,19] Because of non-normal distributions, the CRP and BNP values were log-transformed (log CRP and log BNP) prior to analysis.

The number of diseased coronary vessels identified on CAG, number and proportion of PCI and CABG procedures performed during the post-CAG follow-up period,

Table 1. Baseline Characteristics in Patients With or Without an Incidence of Event

Variable	All patients (264)	Without event (229)	With event (35)	P value
Age (years)	74 [67–80]	74 [67–80]	73 [67–80]	0.819
Male (%)	192 (72.7)	167 (72.9)	25 (71.4)	0.853
BMI (kg/m^2)	24.0±4.1	24.2±3.9	22.7±4.6	0.049
LVEF (%)	58 [47–62]	58 [49–63]	55 [36–61]	0.092
Hypertension (%)	211 (80.0)	183 (80.0)	28 (80.0)	0.990
Diabetes (%)	134 (50.8)	121 (52.8)	13 (37.1)	0.084
History of stroke (%)	57 (21.6)	47 (20.5)	10 (28.6)	0.295
PAD (%)	74 (28.0)	63 (27.5)	11 (31.4)	0.634
Hemodialysis (%)	39 (14.8)	27 (11.8)	12 (34.3)	0.002
Smoking (%)	165 (62.5)	144 (62.9)	21 (60.0)	0.743
eGFR (mL/min/1.73 m^2)	52.5 [35.8–70.5]	54.8 [39.5–71.7]	31.0 [7.8–49.3]	<0.001
AST (U/L)	21 [17–25]	21 [17–25]	21 [14–25]	0.355
ALT (U/L)	16 [12–22]	16 [12–23]	15 [9–20]	0.051
Hb (g/dL)	12.8±2.0	13.0±1.9	11.4±2.1	<0.001
Plt count (×10^4/μL)	20.7±6.3	20.9±6.2	19.0±7.1	0.101
CRP (mg/dL)	0.10 [0.04–0.27]	0.08 [0.04–0.23]	0.24 [0.11–0.63]	0.001
Log CRP	−0.93±0.64	−0.97±0.64	−0.66±0.64	0.007
BNP (pg/mL)	54 [18.0–188.9]	48.9 [16.7–149.9]	233.6 [54.7–534.7]	<0.001
Log BNP	4.10±1.45	3.95±1.37	5.09±1.56	<0.001
HbA1c (%)	6.2 [5.7–6.8]	6.2 [5.8–6.9]	5.9 [5.3–6.6]	0.036
TG (mg/dL)	106 [73–150]	95 [76–147]	107 [72–151]	0.687
LDL-C (mg/dL)	78 [62–102]	77 [62–103]	82 [59–102]	0.808
HDL-C (mg/dL)	44 [36–51]	44 [37–52]	40 [31–50]	0.040
ANGPTL3 (ng/mL)	80.1 [62.8–101.9]	77.5 [60.4–98.3]	96.4 [73.1–121.2]	0.001
Medication				
Antiplatelet agents (%)	189 (71.6)	167 (72.9)	22 (62.9)	0.229
Statin (%)	190 (72.0)	170 (74.2)	20 (57.1)	0.043
Ezetimibe (%)	75 (28.4)	69 (30.1)	6 (17.1)	0.098
β-blocker (%)	138 (52.2)	120 (52.4)	18 (51.4)	0.915
ACEi/ARB (%)	127 (48.1)	113 (49.3)	14 (40.0)	0.301
ARNI (%)	40 (15.2)	33 (14.4)	7 (20.0)	0.406
CCB (%)	121 (45.8)	107 (46.7)	14 (40.0)	0.455
SGLT2i (%)	69 (26.1)	62 (27.1)	7 (20.0)	0.375
MRA (%)	51 (19.3)	42 (18.3)	9 (25.7)	0.318
CCS subtype				
Type i (%)	55 (20.8)	44 (19.2)	11 (31.4)	0.112
Type ii (%)	120 (45.5)	105 (45.9)	15 (42.9)	0.740
Type iii (%)	245 (92.8)	210 (91.7)	35 (100.0)	0.018

Baseline clinical, laboratory, and medication characteristics are shown for all patients and stratified by the presence or absence of clinical events. Values are presented as mean ± SD, median [interquartile range], or n (%). P values indicate comparisons between patients with and without clinical events using the unpaired t-test or Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ANGPTL3, angiopoietin-like protein 3; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; CCS, chronic coronary syndrome; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PAD, peripheral artery disease; Plt, platelet; SGLT2i, sodium-glucose cotransporter 2 inhibitor; TG, triglyceride.

and details of discharge medications are presented in **Supplementary Table 1**.

Clinical Outcomes

The clinical endpoint was a composite of all-cause mortality, non-fatal MI, hospitalization for heart failure, and ischemic stroke as major adverse cardiovascular events (MACE). Patients were followed up prospectively for up to 1 year or until the occurrence of any event that comprised the composite outcome.

Measurement of Serum ANGPTL3 Levels

Fasting venous blood was obtained on the morning of CAG after fasting for ≥8 h. Samples were centrifuged at

Table 2. Univariate and Multivariable Analyses of Clinical Determinants of Serum ANGPTL3 Levels

	Univariate				Multivariable			
	Unstandardized coefficients		Standardized coefficients		Unstandardized coefficients		Standardized coefficients	
	B	SE	β	P value	B	SE	β	P value
Age (years)	0.344	0.170	0.124	0.044	−0.041	0.162	−0.015	0.801
Male	−7.872	2.084	−0.227	<0.001	−7.110	2.073	−0.205	<0.001
BMI (kg/m²)	−0.592	0.470	−0.078	0.209	–	–	–	–
Diabetes	1.133	1.905	0.037	0.552	–	–	–	–
Hypertension	−0.839	2.378	−0.022	0.725	–	–	–	–
CKD	5.842	1.910	0.186	0.003	1.019	1.980	0.032	0.607
Liver dysfunction	1.340	2.775	0.030	0.630	–	–	–	–
Log CRP	13.990	2.834	0.292	<0.001	9.062	2.752	0.189	0.001
Log BNP	7.025	1.248	0.329	<0.001	4.124	1.397	0.193	0.004
Hb (g/dL)	−3.857	0.936	−0.247	<0.001	−1.410	1.007	−0.090	0.163
LDL-C (mg/dL)	0.142	0.055	0.158	0.010	0.042	0.058	0.047	0.463
HDL-C (mg/dL)	−0.291	0.140	−0.127	0.039	−0.296	0.130	−0.129	0.024
TG (mg/dL)	0.061	0.032	0.117	0.057	–	–	–	–
Statin therapy	−8.443	2.056	−0.246	<0.001	−6.320	2.145	−0.184	0.004

Univariate and multivariable linear regression analyses were performed to identify clinical factors associated with serum ANGPTL3 levels. Variables with a P value <0.05 in univariable analyses were included in the multivariable model. Results are presented as B with corresponding SE, β and P values. In the multivariable analysis, sex, CRP and BNP levels, HDL-C levels, and statin therapy were independently associated with ANGPTL3 levels. CKD, chronic kidney disease; SE, standard error. Other abbreviations as in Table 1.

3,000 rpm for 15 min at 4°C, and the serum sample was stored at −30°C until analysis. ANGPTL3 concentrations were measured in duplicate using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Statistical Analysis

Statistical analyses were performed using JMP Pro version 18.0.2 (SAS Institute, Cary, NC, USA) and GraphPad Prism version 10.4.1 (GraphPad Software, La Jolla, CA, USA). Continuous variables are presented as either median with interquartile range (IQR), or mean±standard deviation, as appropriate. Group comparisons were performed using the Mann-Whitney U test or unpaired Student's t-test, as applicable. Categorical variables are expressed as counts and percentages and compared using the chi-square or Fisher's exact test. Univariate and multivariable linear regression analyses were performed to determine the clinical determinants of serum ANGPTL3 levels. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of ANGPTL3 for the composite endpoint. Event-free survival was estimated using the Kaplan-Meier method and compared between groups using the log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) of adverse outcomes. Subgroup analyses were performed according to LDL-C levels (<70 vs. ≥70 mg/dL), and potential effect modifications were evaluated by including multiplicative interaction terms in Cox models (P for interaction). Statistical significance was set at P<0.05.

Results

Among the 264 enrolled patients, 35 experienced a MACE during follow up, comprising 13 deaths (6 cardiac and 7 non-cardiac), 2 non-fatal MI, 16 heart-failure hospitalizations, and 4 ischemic strokes. ANGPTL3 levels were measured in all patients, with a median value of 80.1 ng/mL, as shown in the **Supplementary Figure**.

Baseline Characteristics of Patients With or Without MACE

As summarized in **Table 1**, the overall study cohort had a median age of 74 years (IQR 67–80) and consisted predominantly of males (72.7%), with a mean BMI of 24.0 kg/m². Diabetes and hypertension were observed in 50.8% and 80.0% of patients, respectively. Compared with patients without MACE, those who experienced MACE had significantly higher log CRP (P=0.007), log BNP (P<0.001), and ANGPTL3 levels (P=0.001), but significantly lower BMI (P=0.049), eGFR (P<0.001), hemoglobin (P<0.001), HbA1c (P=0.036), and HDL-C (P=0.040). Statin use was also significantly less frequent in the MACE group (P=0.043). The 2 groups showed no significant differences in age, sex, transaminase levels, triglycerides, or LDL-C. Details of medication use, including statins and other cardiovascular agents and the distribution of CCS subtypes (i–iii, not mutually exclusive) are summarized in **Table 1**. Because the CCS subtype classification (types i–iii) allows overlap among categories, some patients were classified into more than one subtype. Among them, type iii was the most prevalent subtype and was observed in the majority of patients.

Clinical Determinants of Serum ANGPTL3 Levels

Table 2 presents the results of the univariate and multivariable analyses of the clinical determinants associated with serum ANGPTL3 levels. In univariate linear regression analysis, serum ANGPTL3 levels were significantly associated with age (standardized β=0.124, P=0.044), sex (β=−0.227, P<0.001), CKD (β=0.186, P=0.003), log CRP (β=0.292, P<0.001), log BNP (β=0.329, P<0.001), hemoglobin (β=−0.247, P<0.001), LDL-C (β=0.158, P=0.010), HDL-C

Table 3. Multivariable Cox Regression Analyses of MACE Across Different Adjustment Models

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	–	–	–	–	–	–
BMI (kg/m^2)	0.95 (0.87–1.03)	0.226	0.97 (0.89–1.05)	0.495	–	–
Sex, male	–	–	–	–	–	–
CKD	3.40 (1.30–8.89)	0.005	–	–	1.66 (0.58–4.78)	0.329
Hb (g/dL)	–	–	0.70 (0.58–0.85)	<0.001	0.75 (0.62–0.90)	0.002
Log CRP	1.53 (0.91–2.54)	0.111	1.42 (0.88–2.28)	0.148	–	–
Log BNP	–	–	–	–	1.36 (1.02–1.82)	0.033
Statin therapy	–	–	–	–	–	–
ANGPTL3 (per 10 ng/mL)	1.11 (1.01–1.22)	0.025	1.13 (1.03–1.24)	0.014	1.11 (1.01–1.22)	0.032

	Model 4		Model 5		Model 6	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	–	–	–	–	1.01 (0.98–1.04)	0.619
BMI (kg/m^2)	–	–	–	–	–	–
Sex, male	–	–	–	–	1.23 (0.58–2.60)	0.584
CKD	2.40 (0.89–6.49)	0.061	3.51 (1.35–9.16)	0.003	–	–
Hb (g/dL)	0.73 (0.61–0.89)	0.001	–	–	–	–
Log CRP	1.42 (0.87–2.30)	0.156	1.55 (0.92–2.57)	0.102	–	–
Log BNP	–	–	–	–	–	–
Statin therapy	–	–	0.65 (0.33–1.29)	0.228	–	–
ANGPTL3 (per 10 ng/mL)	1.12 (1.01–1.23)	0.026	1.12 (1.01–1.22)	0.029	1.19 (1.09–1.30)	<0.001

Multivariable Cox proportional hazards regression models were constructed to assess the independent predictors of MACE. Variables were entered into sequential models based on clinical relevance and statistical significance in univariable analyses. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events. Other abbreviations as in Tables 1,2.

(β=−0.127, P=0.039), and statin use (β=−0.246, P<0.001). In the multivariable model, sex (β=−0.205, P<0.001), log CRP (β=0.189, P=0.001), log BNP (β=0.193, P=0.004), HDL-C (β=−0.129, P=0.024), and statin use (β=−0.184, P=0.004) remained independently associated with serum ANGPTL3 levels.

Univariate and Multivariable Cox Proportional Hazards Analyses for Clinical Determinants of MACE Incidence

In univariate analysis, the following variables were significantly associated with MACE: BMI, CKD, log CRP, log BNP, hemoglobin, HDL-C, statin therapy, and ANGPTL3 (**Supplementary Table 2**). Notably, each 10 ng/mL increase in ANGPTL3 was associated with an HR of 1.18 (95% CI 1.09–1.29; P<0.001).

As shown in **Table 3**, ANGPTL3 consistently remained an independent determinant of MACE across all sequential multivariable models (HR range 1.11–1.19 per 10 ng/mL; all P<0.05). Moreover, CKD, hemoglobin, and log BNP levels retained significance in Models 1 and 5, Models 2–4, and Model 3, respectively. Conversely, the association between statin therapy, log CRP levels, and MACE was not significant after multivariable adjustment.

Prognostic Cut-Off Value of Serum ANGPTL3

ROC curve analysis identified 90.7 ng/mL as the optimal cut-off value of serum ANGPTL3 for predicting MACE (AUC 0.67; 95% CI 0.57–0.77; P=0.001). Patients with ANGPTL3 levels above this threshold were more likely to be female and to exhibit CKD, anemia, elevated CRP and BNP levels, and lower statin use (**Supplementary Table 3**); however, the association between ANGPTL3 and MACE did not depend on these differences, as shown in **Table 3**.

Association Between Serum ANGPTL3 Levels and Clinical Outcomes: Stratified Analysis by LDL-C Levels

A stratified analysis by LDL-C levels (<70 vs ≥70 mg/dL; **Supplementary Table 4**) revealed that patients in the low-LDL-C group demonstrated lower levels of log CRP, triglycerides, and hemoglobin, and were more likely to receive antiplatelet agents, β-blockers, statins, and ezetimibe (all P<0.05). Overall, Kaplan-Meier analysis showed that patients with ANGPTL3 levels >90.7 ng/mL had a significantly higher incidence of MACE than did those below 90.7 ng/mL (log-rank P=0.003; **Figure A**). In the subgroup analysis, higher ANGPTL3 levels (>90.7 ng/mL) were associated with a significantly higher incidence of MACE (log-rank P=0.004; **Figure B**) in patients with LDL-C <70 mg/dL. In contrast, no significant difference in MACE incidence was observed among those with LDL-C ≥70 mg/dL (log-rank P=0.115; **Figure C**). Cox proportional hazards analysis yielded a hazard ratio of 2.65 (95% CI 1.36–5.19; P=0.004) in the overall cohort; this value was 5.01 (95% CI 1.51–16.63; P=0.009) and 1.91 (95% CI 0.84–4.33; P=0.122) in patients with LDL-C <70 mg/dL and LDL-C ≥70 mg/dL, respectively. The P value for the interaction in our analysis indicated that the association between ANGPTL3 and MACE did not significantly differ across LDL-C strata (P for interaction 0.389; **Table 4**).

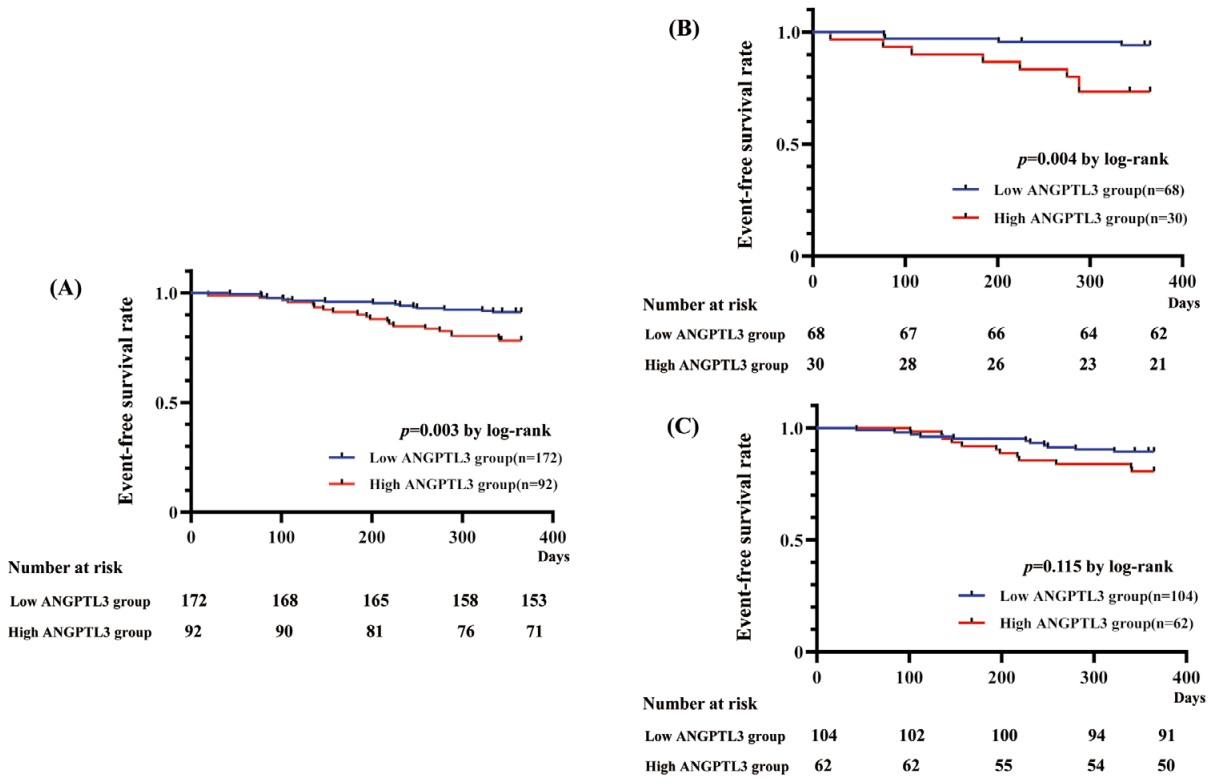

Figure. Kaplan-Meier curves for major adverse cardiovascular events (MACE) incidence stratified by serum angiopoietin-like protein 3 (ANGPTL3) levels. (**A**) In the overall cohort, patients with higher serum ANGPTL3 levels (>90.7 ng/mL; red line) had significantly lower event-free survival compared with those with lower levels (≤90.7 ng/mL; blue line; log-rank P=0.003). (**B**) Among patients with low-density lipoprotein (LDL-C) <70 mg/dL, higher ANGPTL3 levels were also significantly associated with a worse prognosis (log-rank P=0.004). (**C**) In the subgroup with LDL-C ≥70 mg/dL, no significant difference in event-free survival was observed between the 2 ANGPTL3 groups (log-rank P=0.115). The number of patients at risk at each time point is shown below each panel.

Table 4. Discrimination of MACE by ANGPTL3 Levels >90.7 ng/mL in the Overall and LDL-C Levels Strata

Subgroup	HR (95% CI)	P value	P for interaction
All patients	2.65 (1.36–5.19)	0.004	
LDL-C <70 mg/dL	5.01 (1.51–16.63)	0.009	0.389
LDL-C ≥70 mg/dL	1.91 (0.84–4.33)	0.122	

Hazard ratios were derived using Cox proportional hazards models to assess the association between serum ANGPTL3 levels (>90.7 ng/mL) and incidence of MACE. Analyses were performed in the overall cohort and stratified by LDL-C levels (<70 or ≥70 mg/dL). P for interaction evaluates whether the association differs significantly between strata. Abbreviations as in Tables 1,3.

Discussion

This study yielded the following key findings: (1) sex, CRP and BNP levels, HDL-C, and statin therapy were independently associated with serum ANGPTL3 levels; (2) ANGPTL3 was a consistent independent clinical determinant of MACE; and (3) among patients with LDL-C levels <70 mg/dL, serum ANGPTL3 levels could discriminate patients at higher risk for MACE.

Several non-lipid factors appear to modulate ANGPTL3 levels in CCS. The positive association with CRP suggests that the fibrinogen-like domain of ANGPTL3 binds integrin $\alpha v\beta 3$ and amplifies inflammatory signaling,[20] aligning with prior population data linking ANGPTL3 to low-grade inflammation.[14] Similarly, female sex was associated with higher ANGPTL3 levels, consistent with earlier reports.[21] Because our cohort was comprised of 70% male participants, lower overall ANGPTL3 concentrations may have increased the sensitivity for detecting disease-related perturbations, highlighting the need for sex-stratified analyses in future studies. ANGPTL3 is synthesized in hepatocytes and is transcriptionally regulated by the liver X receptor (LXR).[22] Statins suppress LXR activity and can therefore downregulate ANGPTL3 expression,[23] which is confirmed

by our finding that statin therapy predicts lower ANGPTL3 levels. Contrary to observations in health-check cohorts,[14] ANGPTL3 was not associated with transaminase levels, possibly because widespread statin use and other unmeasured hepatic factors blunted this association.

The independent correlation between ANGPTL3 and BNP levels is a novel finding. Although BNP is influenced by age, adiposity, renal function, and overt inflammation,[24,25] the correlation persisted after adjustment for these variables, implying that ANGPTL3 may index subclinical myocardial stress or inflammation not captured by CRP alone.

Furthermore, a significant inverse correlation was observed between serum ANGPTL3 and HDL-C levels in our cohort. ANGPTL3 suppresses endothelial lipase (EL) activity and is positively associated with HDL-C levels.[26] This discrepancy with findings from previous reports may stem from our cohort's characteristics, which consisted of patients with CCS, many of whom received statin therapy. Statins influence both ANGPTL3 expression and EL activity, thereby potentially mediating the observed association in our study.[23,27,28] Consistent with prior population-based data,[29] circulating ANGPTL3 levels were not significantly correlated with triglyceride levels in our cohort. Notably, recent evidence indicates that the ANGPTL3/ANGPTL8 complex, rather than ANGPTL3 alone, exhibits a robust positive association with triglyceride levels.[30] Simultaneous measurement of ANGPTL3 and ANGPTL8 in CCS patients may help clarify the precise relationship between ANGPTL3 biology and triglyceride metabolism.

Previous studies have linked ANGPTL3 with adverse outcomes in ACS, particularly in patients with obstructive sleep apnea.[31] Our study extends the prognostic value of this finding to CCS, a clinical condition with distinct pathophysiology. Similar to the results of a previous report,[32] 65% of events in our cohort comprised heart-failure admissions or non-cardiovascular deaths, which are outcomes that are less influenced by lipid burden; however, ANGPTL3 retained strong predictive power. The absence of a correlation with LDL-C underscores the likelihood that ANGPTL3 may reflect systemic vulnerability (e.g., frailty, renal dysfunction, and chronic inflammation) rather than plaque instability.

Although ANGPTL3 regulates lipid metabolism,[33] no significant interaction with LDL-C was observed in predicting outcomes, suggesting that its association with cardiovascular risk is consistent across LDL-C strata. In patients with LDL-C <70 mg/dL – who achieved the management target with high statin use – ANGPTL3 continued to capture residual cardiovascular risk. In contrast, in the LDL-C ≥70 mg/dL subgroup, the overall cohort-derived cut-off failed to discriminate outcomes, whereas an optimized threshold of 108.9 ng/mL effectively predicted adverse events, implying that a higher cut-off may be required when LDL-C remains elevated. These findings identify ANGPTL3 as a prognostic and residual risk marker independent of LDL-C levels, warranting validation in larger populations.

In clinical settings, measuring ANGPTL3 may enhance risk stratification in a heterogeneous CCS population, particularly when LDL-C goals are achieved but residual risk persists. Whether therapeutic targeting of ANGPTL3 via monoclonal antibodies or RNA interference translates into event reduction beyond lipid-lowering warrants dedicated trials.

Study Limitations

The findings of this single-center observational study with a relatively small sample size may have limited generalizability, and the 1-year follow up could underestimate long-term risk. Moreover, residual confounding by unmeasured variables (e.g., thyroid status, insulin resistance, arrhythmia burden) cannot be excluded. Liver dysfunction was defined solely by transaminase elevation and may not reflect synthetic capacity. Furthermore, the sample size in the LDL-C strata was modest and statin dosing was heterogeneous, reducing the power to detect interactions. ANGPTL3 was measured only once at baseline; given that the proportion of statin use increased from 72.0% to 88.3% during hospitalization, unmeasured intraindividual changes in ANGPTL3 levels after statin initiation may have attenuated the observed associations. Circulating ANGPTL3 was assessed using a single ELISA platform. In the absence of a standardized assay, inter-assay variability must be considered when comparing results across studies or defining universal cut-off values. Last, frailty, a potent prognostic factor in older CCS patients, was not formally quantified in this study.

Conclusions

Circulating ANGPTL3 independently predicts adverse outcomes in CCS, even when the LDL-C level reaches its optimal target. These findings suggest that ANGPTL3 integrates residual non-lipid cardiovascular risk and may be a valuable biomarker for personalized risk assessments in CCS.

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Disclosures

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IRB Information

The Ethics Committee of the University of Miyazaki approved the study protocol (approval no. O-1058).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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