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Association of low serum albumin concentration and adverse cardiovascular events in stable coronary heart disease

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ABSTRACT

Objective: Coronary heart disease (CHD) is a leading cause of death in developed countries. Exploration of indicators to identify high risk individuals who develop adverse outcomes despite stable baseline condition is important. This study is to evaluate the association between serum albumin concentration and cardiovascular (CV) outcomes in individuals of stable CHD.
Methods: Seven-hundred–thirty-four participants from Biosignature study, a nationwide prospective cohort study aimed to identity risk factors among patients with stable CHD, were enrolled for analysis. They were divided into low serum albumin group (baseline albumin concentration <3.5 g/dL, $n = 98$) and normal albumin group (baseline albumin concentration ≥3.5 g/dL, $n = 636$). The relations between baseline albumin and adverse CV outcomes within 18 months of follow-up were analyzed.
Results: Compared baseline characteristics with normal albumin group, subjects in low albumin group are older, having more diabetic patients, lower hemoglobin level, lower estimated glomerular filtration rate, lower total cholesterol level, lower left ventricular ejection fraction, and higher blood glucose. While there is no significant difference of total CV events between two groups, low serum albumin concentration is associated with an increased risk of all-cause mortality (10.2% vs. 0.5%, $p < 0.001$) and hard CV events (7.1% vs. 1.4%, $p < 0.001$). The association remains significant after adjustments for confounders (all-cause mortality, HR: 6.81, 95% CI: 1.01–45.62; hard CV events, HR: 3.68, 95% CI: 1.03–13.19).
Conclusions: Low serum albumin concentration (<3.5 g/dL) worsens prognosis of patients with stable CHD.

1. Introduction

Coronary heart disease (CHD) is a leading cause of death in developed countries. Patients with stable CHD are known to have an increased risk of the future cardiovascular (CV) events, thus identifying risk factors among them is warrant for therapeutic prevention [1]. Several biomarkers have been investigated for risk stratifications. Proposed biomarkers usually reflect important pathophysiological states of atherosclerosis: inflammatory process, such as C-reactive protein (CRP), vulnerability of the atheromatous plague, such as myeloperoxidase and soluble CD40 ligand, and hypercoagulable state, such as fibrinogen [2].

Serum albumin, a major protein found in extracellular fluid compartment, contributes to maintain diverse physiological functions [3].

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It has been studied to be associated with atherosclerosis with possible mechanisms including response to inflammation [4–6], fibrinolysis and hemostasis [7], possible inhibition of platelet aggregation [8], the capacity of antioxidant [9], the tendency of blood hyperviscosity [10], and the relation of nutritional status [6]. Epidemiologic studies reported that low serum albumin concentration predicted adverse outcomes in general population [11–15], acute coronary syndrome [16–18], stroke [19], heart failure [20], renal failure [21], elderly [22–24], and malignancy [25]. In current interventional era, serum albumin concentration is also an important predictor of no-reflow phenomenon following primary percutaneous coronary intervention and in-stent restenosis rate after bare-metal stent implantation [26,27].

This is a prospective study aimed to investigate the association between serum albumin concentration and CV outcomes in patients with stable CHD.

2. Methods

2.1. Study population

The Biosignature study was a nationwide prospective cohort study to identify risk factors among CHD patients in stable condition at baseline. Nine medical centers in Taiwan participated in this study. Patients with history of significant CHD, as documented by coronary angiogram, a history of myocardial infarction (MI) as evidenced by 12-lead electrocardiography or hospitalization, or a history of angina with ischemic electrocardiographic changes or positive response to stress test, were identified. Among them, those who had received successful percutaneous coronary intervention with either coronary stenting or balloon angioplasty at least once previously and had been stable on medical treatment for at least 1 month were enrolled. Patients were excluded if [1] they had been hospitalized for unstable angina, acute coronary syndrome, acute MI, acute cerebrovascular events, or other acute CV events within the 3 months prior to enrollment, [2] they planned to receive further coronary revascularization or interventional procedures for other CV diseases during the following one year period, [3] they had significant malignancy or tumor diseases requiring advanced medical or surgical therapy or both in the following one year, [4] they had other major systemic diseases requiring hospitalization or operation in the following one year, or [5] they were unable or unwilling to be followed up during the following one year period. Additionally, patients with life expectancy of <6 months (e.g., malignant metastatic neoplasm), and those receiving treatment with immunosuppressive agents were also excluded. In this sub-analysis of albumin, we also excluded patients whose estimated glomerular filtration rate (eGFR) was <15 mL/kg/m^2 or who had been already on regular dialysis. The study complied with the Declaration of Helsinki and was approved by the appropriate Health Authorities, independent Ethics Committees, and Independent Review Boards (IRB) in each hospital as well as the Joint IRB Ethics Committee Review Boards in Taiwan.

2.2. Serum albumin and baseline data collection

After enrollment, trained study nurses and qualified doctors collected all data prospectively whenever feasible. Baseline characteristics including risk factors such as history of hypertension, diabetes, smoking habit, as well as medications history were collected. Variable medications and dosage information were collected by chart review and structured questionnaire. Biochemical profiles including blood glucose, lipid profile (total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) and kidney function were recorded. Left ventricular ejection fraction (LVEF) measured by echocardiography, nuclear image or angiography was also recorded. Albumin level was determined at initial enrollment. Patients were divided into two groups based on serum albumin concentration with a cut-off value of 3.5 g/dL. Those with serum albumin <3.5 g/dL were categorized as low serum albumin group and the others (with serum albumin ≥3.5 g/dL) were categorized as normal serum albumin group.

2.3. Clinical follow up for adverse events

Each patient with initially stable conditions under medical treatment was prospectively and regularly followed up. After enrollment, follow-up data collection was at the time of outpatient clinic visit, and approximately every 3 months for the first year and every 6 months starting from the second year after enrollment.

The primary outcome of this study was the first occurrence of death or hard CV events, a composite of CV death, nonfatal MI, and nonfatal stroke. The secondary outcome was the first occurrence of any CV events, including CV death, nonfatal MI, nonfatal stroke, hospitalization for refractory or unstable angina, and hospitalization for other causes including heart failure, and peripheral arterial disease (PAD). MI was confirmed if ischemic symptoms presented with elevated serum cardiac enzyme levels and/or characteristic electrocardiographic changes. Coronary revascularization procedures with either percutaneous coronary intervention or coronary artery bypass grafting surgery were confirmed by medical record review. Stroke was confirmed if there was a new neurologic deficit lasting for at least 24 h with definite imaging evidence of cerebrovascular accident.

2.4. Statistics

Baseline characteristics and cardiovascular outcomes of the two groups were compared. Quantitative variables were expressed as mean and standard deviation in the presence of normal distribution. Qualitative variables were presented in both absolute frequencies (number of patients) and relative frequencies (percentage). Comparisons of continuous variables between groups were performed by ANOVA test. The primary and secondary outcomes were described by an overall percentage and expressed by means of proportions with a confidence interval (CI) of 95%. Event-free survival rate was calculated using the Kaplan–Meier method, with the significance evaluation using log–rank tests. For regression models, hazard ratio for the regression of Cox proportional hazards was used, along with the corresponding standard error, a CI of 95%, and p value. Independent baseline variables with a p-value of <0.05 in the univariate analyses and proposed associated confounders, including high sensitivity-CRP (hs-CRP), smoking and previous MI, were included in the multivariate analyses. P values were reported up to three decimals while those below 0.001 are reported as $p < 0.001$. In all the tests, the two-tailed alpha significance level was 0.05.

3. Results

3.1. Albumin and baseline patient characteristics

Among the 734 subjects with stable CHD and had baseline albumin measurements, 84% of them were men and the mean age was 62.1 years old. The low albumin group had 98 patients, with a mean albumin concentration of 3.2 ± 0.3 g/dL; the rest 636 patients were in normal albumin group, with a mean albumin concentration of 4.1 ± 0.3 g/dL. Table 1 showed the baseline characteristics of study patients. In low albumin group, the patients were older, lower in average hemoglobin level, eGFR, LVEF, and total cholesterol, while higher in serum

Table 1
Baseline characteristics of patients according to serum albumin concentration.

	All patient $N = 734$	Albumin ≥3.5 $N = 636$	Albumin <3.5 $N = 98$	P
Demographics				
Age, year	62.1 ± 12.4	61.3 ± 12.1	67.4 ± 12.7	<0.001
Gender, male (%)	617(84.1%)	534(84.0%)	83(84.7%)	0.854
Body mass index, kg/m^2	26.6 ± 3.9	26.7 ± 3.9	26.1 ± 4.3	0.189
Medical history, n (%)				
Hypertension	476(64.9%)	411(64.6%)	65(66.3%)	0.742
Diabetes mellitus	262(35.7%)	216(34.0%)	46(46.9%)	0.013
Previous MI	455(62.0%)	387(60.9%)	68(69.4%)	0.105
Previous stroke	21(2.9%)	16(2.5%)	5(5.1%)	0.153
Heart failure	36(4.9%)	29(4.6%)	7(7.1%)	0.27
Current smoking	440(60.0%)	382(60.1%)	58(59.2%)	0.869
Measurement				
Hemoglobin, g/dL	13.8 ± 1.8	14.0 ± 1.8	12.7 ± 1.9	<0.001
Platelet, ×10^3/μL	215.9 ± 60.2	217.0 ± 59.6	207.7 ± 64.1	0.153
Glucose, mg/dL	120.9 ± 45.7	118.6 ± 43.1	136.3 ± 57.9	0.005
eGFR, mL/min/1.73m^2	82.3 ± 31	84.4 ± 31.1	68.6 ± 26.7	<0.001
Albumin, g/dL	40.0 ± 0.5	4.1 ± 0.3	3.2 ± 0.3	<0.001
GOT, u/L	30.7 ± 32.8	29.5 ± 29.5	39.4 ± 49.8	0.081
GPT, u/L	30.5 ± 28.2	30.4 ± 27.4	31.1 ± 33.7	0.855
Total cholesterol, mg/dL	163.6 ± 39.5	164.7 ± 40.3	156.7 ± 32.7	0.032
HDL-cholesterol, mg/dL	41.5 ± 11.0	41.5 ± 10.8	41.1 ± 12.3	0.708
LDL-cholesterol, mg/dL	97.0 ± 32.0	97.6 ± 32.7	93.3 ± 26.4	0.145
Triglyceride, mg/dL	138.6 ± 88.9	141.0 ± 89.8	122.9 ± 81.8	0.062
Hs-CRP, mg/dL	0.39 ± 1.0	0.35 ± 1.02	0.56 ± 0.92	0.191
LVEF, %	56.4 ± 13.5	57.2 ± 13.1	51.5 ± 15.0	<0.001
Angiography, n (%)				
1-vessel disease	135(25.3%)	114(25.1%)	21(26.9%)	0.726
2-vessel disease	178(33.4%)	154(33.9%)	24(30.8%)	0.595
3-vessel disease	185(34.7%)	157(34.5%)	28(35.9%)	0.811
Medication, n (%)				
Anti-platelet	289(39.4%)	256(40.3%)	33(33.7%)	0.215
Beta-blocker	483(65.8%)	423(66.5%)	60(61.2%)	0.305
ACEI	155(21.1%)	132(20.8%)	23(23.5%)	0.540
ARB	289(39.4%)	256(40.3%)	33(33.7%)	0.215
Statin	535(72.9%)	463(72.8%)	72(73.5%)	0.889

Abbreviation: MI: myocardial infarction; eGFR: estimated glomerular filtration rate; GOT: glutamate oxaloacetate transaminase; GPT: glutamate pyruvate transaminase; HDL: high-density lipoprotein; LDL: *low-density lipoprotein;* CRP: *C-reactive protein; LVEF: left ventricular ejection fraction; ACEI:* angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blockers.

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